AN ECHA VIEW

On HBM4EU and it's benefits

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Understanding which chemicals we are exposed to in our work and daily lives remains one of the fundamental challenges regulators face when addressing chemicals of concern.

Human biomonitoring, where chemicals are measured directly from human tissue or blood samples, is one of the most reliable ways to find out whether there is exposure to certain chemicals.

Data from human biomonitoring has proven invaluable in the past for risk management and policy making, but it is not without its shortcomings.

The data is sometimes on a very targeted population, access to data is limited and the substances chosen for monitoring may not always be the most relevant for risk management.

"The HBM4EU project aims to improve this and make human biomonitoring even more effective by harmonising sampling, improving access to data for regulators and by developing a process where regulators and policy makers can actively participate in choosing which substances are prioritised for monitoring. ECHA is actively involved in the project as a member of both the Governing Board and the Policy Board.

The results of the HBM4EU project will not only benefit improved regulatory risk management measures for already known substances, but should also help to identify new emerging substances of concern and to manage the risks from exposure to mixtures of chemicals.

Improvements in non-target screening in the last few years could mean that human and environmental monitoring data could be used to monitor large libraries of chemicals and prioritise relevant substances for further work.

Dr. Bjorn Hansen, Executive Director of European Chemicals Agency - A member of the HBM4EU EU Policy Board

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PHTHALATES

Reflections from Chemical Group Leaders

Phthalates are one of the nine groups of priority substances included in the 1st list of HBM4EU substances. The group of phthalates comprises several single substances used predominately as plasticisers. They are the most common used plasticisers worldwide[1], with some phthalates found in a wide range of consumer products[2]. In the HBM4EU project, we prioritized sixteen of the most common substances, as well as the non-phthalate alternative Hexamoll®DINCH®, which is increasingly used as a substitute.

Some of the phthalate compounds have, or are suspected to have, endocrine disrupting properties, whereby they interfere with the hormone system. One such interference affects the hormonal-driven processes of sexual differentiation. A number of adverse effects have been observed, in particular on the development of the male reproductive system in laboratory animals. These effects have been characterised as "phthalate-syndrome". It is assumed that similar adverse effects are also caused in humans, since there are similarities between phthalate-syndrome and observed testicular dysgenesis syndrome in humans[3]. Unborn and young children are particularly at risk, since their bodies are still in development and, therefore, highly susceptible to these reproductive effects.

This severe toxicological profile and the widespread exposure to phthalates has led to extensive regulatory actions within the European Union (EU) in the past decades. Many phthalates are classified as reproductive toxicants category 1B and have been identified as substances of very high concern (SVHC)[4] under the Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Four of those (DEHP, BBzP, DiBP and DnBP) are already subject to authorisation. Since February 2015, the European Chemicals Agency (ECHA) must grant an authorisation before they can be used within the European Union. In addition, the use of seven phthalates (namely, DEHP, DnBP, DiBP, BBzP, DiNP, DnOP, DiDP) is restricted in concentrations greater than 0.1% in plasticised materials used in toys and childcare articles, and/or in toys and childcare articles that can be placed in the mouth by children[5].

In 2017, ECHA's Committee for Risk Assessment and Committee for Socio-Economic Analysis both supported a proposal by ECHA and Denmark to restrict four phthalates (BBzP, DnBP, DEHP and DiBP) in articles. The recommendation is to restrict phthalates in concentrations greater than 0.1% in articles that cause exposure through the skin or by inhalation, such as flooring, coated fabrics and paper, recreational gear and equipment, mattresses, footwear, office supplies and equipment, and other articles moulded or

1 Ceresana. 2017. Market Study: Plasticizers. 4th Edition
2 European Plasticisers, Orthophthalates
3 HBM (Human Biomonitoring) Commission, 2011. "Stoffmonographie für Phthalate - Neue und aktualisierte Referenzwerte für Monoester und oxidierte Metabolite im Urin von Kindern und Erwachsenen". Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz 54:770-785.

4 European Chemicals Agency, Candidate List of substances of very high concern for Authorisation
5 European Chemicals Agency, Annex XVII to REACH – Conditions of restriction, Entry 51 and Annex XVII to REACH – Conditions of restriction, Entry 52

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coated with plastic[1]. The proposed restriction will apply three years after the amendment of the REACH Annex XVII comes into force.

"HBM4EU will investigate the extent of human exposure to phthalates in Europe, in particular that of vulnerable groups."

The differences in exposure within countries will be determined and the main sources of exposure will be identified. A particular focus will be monitoring the success of existing policy actions by means of time trend analysis. At the same time, the extent and potential toxicological impact of exposure to substitutes will be assessed, such as Hexamoll®DINCH®. The possibility of undertaking cumulative risk assessment for phthalates will be explored, with the aim of better protecting human health from exposure to mixtures of phthalates.

Chemical Group Leaders for phthalates:

Rosa Lange , UBA - German Environment Agency

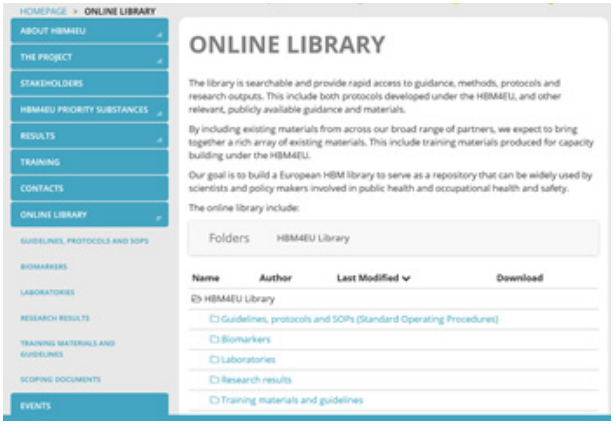
Dr. Marike Kolossa-Gehring, UBA - German Environment Agency

1 European Chemicals Agency, 2017, Restriction proposal on four phthalates and several authorisation applications agreed by RAC and SEAC, ECHA/NA/17/05

ONLINE LIBRARY

The HBM4EU online library, publicly accessible within the HBM4EU website has been launched in December 2017. It aims at collecting common methods, protocols and research output from HBM4EU and is being led by our partners at the Instituto de Salud Carlos III (Spain) under the supervision of Dr. Susana Pedraza- Díaz and Prof. Argelia Castaño.

A concept note establishing criteria for contents and materials was drafted in March 2017 and sent to the Management Board in April 2017. The structure design was agreed shortly after and with the help of our web developers, Formato Verde, it was up and running before the end of 2017.



To include the documents in the library, the contact people provided by the different WPs are invited every 4 months by email (next one due at the end of March) to fill in the data collection fiche providing a short description for each item included in the library. This will enable a quicker search of documents.

Currently, 25 documents are produced by the library. Out of these, 21 HBM4EU and four are materials relevant to the consortium from other sources (COPHES/DEMO-COPHES, German Society for Epidemiology (DGEpi)).

Dr. Joana Lobo Vicente, Project Manager in Chemicals, Environment & Human Health, EEA
Dr. Susana Pedraza-Díaz and Prof. Argelia Castaño, Instituto de Salud Carlos III (Spain), ISCIII

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HEAL

Promoting environmental policy that contributes to good health

Health and Environment Alliance (HEAL) is a member of HBM4EU Stakeholder Forum

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A public health tool to inform the transition towards a toxic-free future

Whereas the use and presence of chemicals in our everyday environment have become evident, significant questions and huge gaps remain about their adverse human health impacts and societal costs. Whether we like it or not, we are exposed to a mixture of chemicals, including potentially hazardous substances, everywhere we go on a daily basis, from the parks and gardens our children play in, to the packaging wrapping we use for our food, and the clothes we wear.

> "From a public health perspective, the real added value and potential success story of the HBM4EU project will rest in its ability to provide comparable data to answer policy questions and trigger new regulations to reduce people's exposure, especially those most vulnerable."

Broadly speaking, these data and results must translate into real health gains, by feeding into impact assessments for new chemical legislation, as well as into the implementation of existing legislation, such as the authorisation of substances under REACH and the authorisation of pesticides under the Plant Protection Products Regulation.

The project has the potential to be highly appealing to the general public, medical and health professionals, and research community across Europe – who are on the front line in responding to the growing concerns from citizens around the health impacts of chemicals and thirst for more information on how we are exposed to them, as shown in a recent European survey[1]. Here it is not only the role of stakeholders like HEAL, but also the role of national hubs to meaningfully engage with stakeholders, researchers and the media to inform, seek input and share developments from the start in 2018.

A human biomonitoring project of the scale of HBM4EU is both unique and instrumental in gaining a better understanding of the potential adverse health and environmental effects of chemicals and most importantly, triggering policy responses, and has been on HEAL's wish list for over a decade. Harmonised data on these sometimes complex but widespread substances is something we have not managed to gather at the European level so far. Yet, such knowledge is key to identifying mid and long-term trends in human exposure and relationships with health impacts, in order to set up priorities for regulatory actions at the European and national levels, including informing European and national disease prevention strategies.

1 European Commission, 2017, Special Eurobarometer 456 Report Chemical Safety

Génon K. Jensen, Executive Director of the Health and Environment Alliance (HEAL)

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Providing real-life exposure to drive preventive, protective policies

Policy decisions about chemical groups such as endocrine disruptors[1] or pesticides[2] are increasingly being debated in the public sphere, yet one ingredient is missing – to what extent is the European population contaminated with this chemical? To fill this data gap for one of the most widely used herbicides, glyphosate, online campaign group, Avaaz organised free glyphosate testing for citizens in Brussels during the debate on the renewal of glyphosate last November.

In this context, human biomonitoring is sorely needed and can be an important public health tool through which public health authorities can provide reliable information to citizens about their exposure, enabling citizens to take appropriate measures to reduce their exposure to substances impacting on health.

When the health costs of environmental chemicals - including neurotoxicants or endocrine disruptors - are estimated to be up to 10% of global GDP[3], there is also a strong economic case to justify investments in developing scientific understanding about our exposure to both single chemicals and mixtures of chemicals, and the relationship between exposure and numerous health effects.

A project such as HBM4EU should also allow legislators to gather uniform data about high volume substances to which we are widely exposed, such as the pesticides glyphosate and chlorpyrifos, both of which have been linked to numerous adverse health effects. Other examples are flame retardants, some bisphenols and emerging substances such as nanomaterials.

Another of HEAL's longstanding wishes for HBM is being addressed – building knowledge about our real-life exposure to complex mixtures and resulting health impacts. HBM4EU aims to address this need by integrating existing EU projects such as EDC-MixRisk and convening a joint workshop entitled "Advancing assessment of chemical mixtures and their risks for human health and the environment", to be held on 29 - 30 May at Ispra in Italy.

Citizens across Europe are increasingly asking for better information about the chemicals in their environment, as well as the impacts on health and on our broader society. By bridging policy and science, HBM4EU offers a unique opportunity to respond positively to this demand and guide a true transition towards a toxic-free environment and a clean circular economy. We look forward to further contributing to the development of the initiative and will continue to mobilise our environmental health community to help making HBM4EU a success.

Génon K. Jensen, Executive Director of the Health and Environment Alliance (HEAL)

The Health and Environment Alliance (HEAL) is a leading European not-for-profit organisation addressing how the environment affects health in the EU. With the support of more than 70 member organisations, HEAL brings independent expertise and evidence from the health community to different decision-making processes. Our broad alliance represents health professionals, not-for-profit health insurers, doctors, nurses, cancer and asthma groups, citizens, women's groups, youth groups, environmental NGOs, scientists and public health research institutes. Members include international and Europe-wide organisations as well as national and local groups. Website: www.env-health.org. Follow HEAL on Facebook and Twitter @HealthandEnv.

1 EDC Free Europe, July 2017, EDC-Free campaigners criticize vote on first ever EDC criteria
2 Health and Environment Alliance, November 2017, Glyphosate: future generations to pay the price of reauthorisation of health-harming herbicide
3 Biomedcentral, December 2017, Calculation of the disease burden associated with environmental chemical exposures: application of toxicological information in health economic estimation , Health and Environment Alliance, December 2017, Human exposure to preventable environmental chemicals is resulting in health costs of 10% of global GDP

HBM4EU in 2018

Month	Events
February	Focus group discussion on chemical safety with members of the public in Austria, Vienna, Austria
6 March	Joint meeting of the Management Board and the EU policy Board on prioritisation, Brussels, Belgium
18 - 21 April	HBM4EU will be presented at the 10th Congress of Toxicology in Developing Countries and 12th Serbian Congress of Toxicology, Belgrade, Serbia
29 - 30 May	Joint H2020 Workshop - Advancing the Assessment of Chemical Mixtures and their Risks for Human Health and the Environment, Joint Research Centre, Ispra, IT
27 - 30 May	HBM4EU will be presented at the PPTOX VI Conference, Faroe Islands, Denmark
14 - 15 June	Workshop: Linking HBM and health studies. What are possible opportunities and obstacles? Brussels, Belgium
20 June	Stakeholder workshop on priorities for a future HBM4EU initiative, Brussels, Belgium
18 - 22 June	1st HBM4EU Training Event, Ljubljana, Slovenia
9 - 14 July	HBM4EU will be presented at the ESOF - EuroScience Open Forum, Toulouse, France
26 - 30 August	HBM4EU will be presented at the ISES - ISEET 2018 - The Joint Annual Meeting of the International Society of Exposure Science and the International Society for Environmental Epidemiology, Ottawa, Canada
24 September	Workpackage meetings, Vienna, Austria
25 September	Consortium Meeting, Vienna, Austria
26 September	Meeting of the Stakeholder Forum, Vienna, Austria Meeting of the Advisory Board, Vienna, Austria
27 September	Meeting of the Governing Board, Vienna, Austria
28 September	Stakeholder Conference / Austrian Presidency Event, Vienna, Austria
November	EU Case Study Workshop - workshop with EU policy makers on the interpretation of HBM results
November	2nd HBM4EU Training Event, venue to be confirmed

HBM4EU events External events Annual meetings of key HBM4EU Bodies

REFLECTIONS FROM HELIX

Closing the gap between Exposome Research and HBM

The HELIX Project, coordinated by ISGlobal with 13 European partners, aimed to characterise the early-life exposome by assessing exposure to many environmental hazards during pregnancy and childhood, and linking these to children's molecular omics signatures and to their cardio-metabolic health, respiratory and immune health, and neurodevelopment[1].

"HELIX is the first study to present completely comparable biomonitoring data, geospatial data and omics signatures for many important environmental exposures in mothers and children from six European countries."

Exposures measured by HELIX include air pollutants, noise, green space and urban environment factors, as well as chemical pollutants, and lifestyle and social factors. HELIX officially finished in December 2017.

Human biomonitoring data forms an integral part of the project: blood and urine samples collected from 1,300 mother child pairs were used to measure exposure to organochlorine and brominated compounds, perfluoroalkyl substances, metals, phthalate metabolites, phenols, organophosphate pesticide metabolites and cotinine, during pregnancy and childhood.

In order to ensure comparable biomonitoring data, chemical assays were centralised in the laboratory at the Department of Environmental Exposure and Epidemiology, NIPH, Oslo, or in contracted laboratories for metals, and cotinine.

First results focus on describing the exposome, its correlations and its determinants, highlighting that:

- exposure to many of the chemicals measured was abundant (many chemicals were detected in over 90% of participants)
- there were differences between countries for all exposures measured, so location is a strong determinant of one's exposome; and
- correlations between and within groups of exposures and between mothers and children show complex correlation structures that require advanced statistical modelling in order to disentangle associations with health outcomes.

1 Vrijheid et al., June 2014, The human early-life exposome (HELIX): project rationale and design, Environ Health Perspect.; 122(6):535-44.

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HELIX further quantified the reliability of biomarker measurements of all non-persistent chemicals in panel studies with intensive repeat urine sampling.

These results may be used to correct dose-response relations and to optimize sampling designs in future biomonitoring and Exposome studies, thus limit exposure misclassification.

An important challenge in associating the exposome with health is the simultaneous consideration of many correlated exposures.

HELIX developed a statistical approach to evaluate exposome-health associations in the light of complex correlation patterns, recognising that statistical techniques are often limited in their ability to efficiently differentiate true predictors from correlated covariates[1].

Within this framework, the systematic evaluation of child health risks related to multiple early life exposures is now underway. These results will ultimately help guide public health efforts by allowing us to intervene on those chemical agents or urban and lifestyle exposures that are most likely to be associated with child health. Also, HELIX is developing a catalogue of omics signatures of many environmental exposures, in order to better understand molecular mechanisms and early signs of damage.

With the first Exposome projects drawing to a close, the groundwork has been built for the Exposome and human biomonitoring communities to work closer together on important future directions.

1 Agier et al., 2016, A Systematic Comparison of Linear Regression-Based Statistical Methods to Assess Exposome-Health Associations. Environ Health Perspect. 2016 Dec; 124(12):1848-1856.

These inlude:

- enlarging the scope of exposome research
- integrating toxicological knowledge in human exposome studies
- improving statistical and bioinformatics methods
- improving exposure assessment
- implementing large prospective follow-ups of health effects and
- widening the range of new and unknown chemicals monitored.

Dr. Martine Vrijheid, Research Professor, ISGlobal - Barcelona Institute for Global Health

Project contact & coordination

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