HBM4EU science and policy for a healthy future

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HBM4EU

POLICY BRIEF

JULY 2022

European Human Biomonitoring Initiative

Chemical Mixtures

This policy brief summarizes the mixture related activities in the HBM4EU project. This involves identification of patterns in co-occurrence of multiple chemical substances in European individuals, collection of pesticide suspect screening data for five countries and case studies of health risk assessment.

KEY MESSAGES

- Clusters of co-occurring substances can be identified through network analysis of existing human biomonitoring (HBM) databases. Several of the clusters identified spanned regulatory frameworks, stressing the need to strengthen mixture risk assessment across different sectors.
- Prioritization of clusters of co-occurring substances based on the level of toxicological concern is feasible in principle, but the current limited availability of HBM health-based guidance values hampers wider application.
- The SPECIMEn study revealed a total of 95 pesticide-related markers in urine samples from parent-child pairs in five European countries using suspect screening techniques. A subset of the markers was identified with a high level of confidence; these relate to 30 parent pesticides. Their detection frequency varied substantially between countries. However, consistent strong contributions from agricultural application to detection rates in hotspots or in spraying season were not observed.
- HBM4EU case studies focused on human health effects clearly underline that chemical mixtures are of public health concern, within and across sectors. The case studies demonstrate that assessment of health risks associated with combined exposures is generally possible by using the Hazard Index and/or the Point of Departure Index method. Furthermore, they show the usefulness of the identification of risk drivers that contribute most to the mixture risk.

BACKGROUND: HBM4EU

The European Human Biomonitoring Initiative, HBM4EU, running from 2017 to June 2022, is a joint effort of 28 countries, the European Environment Agency and the European Commission, and co-funded under Horizon 2020. The main aim of the initiative is to coordinate and advance human biomonitoring in Europe. HBM4EU has provided a wealth of improved evidence of the actual exposure of citizens to chemicals and their possible health effects. Human biomonitoring allows us to measure our exposure to chemicals by measuring either the substances themselves, their metabolites or markers of subsequent health effects in body fluids or tissues. Information on human exposure can be linked to data on sources and epidemiological surveys to inform research, prevention, and policy with the objective of addressing knowledge gaps and promoting innovative approaches. If you would like to read more about the project itself, please visit the HBM4EU website.

HBM4EU RESULTS

The HBM4EU project addressed how HBM data can contribute to both the science and policy-making regarding the combined exposure to multiple chemical substances. Here, the focus was on chemicals with exposure routes through the environment, food, occupation and/or consumer products.

Analysis of existing HBM databases from Germany, Belgium, Spain and the Czech Republic revealed some 4 to 10 patterns of co-occurring substances measured in the same individual. Overall, correlations amongst exposure biomarker levels were mostly positive, with few relatively low negative correlations. Where quantitative analysis was explored in one database, some 70% of variance in HBM levels was accounted for by five clusters of associated biomarkers. Existing HBM studies typically have limited numbers of individuals in which the full range of chemical substances has been measured. This limits the ability to identify patterns of co-occurrence and even more so to study the role of determinants. Toxicity weighting of identified clusters of co-occurring substances was explored in one study by calculating hazard quotients based on HBM health-based guidance values (or similar) and combining these in a Hazard Index for separate co-occurrence patterns. In principle, this approach can be used to prioritize clusters based on toxicological concern, but it is severely limited by absence of relative toxicological potency information.

In the SPECIMEn (Survey on PestiCIde Mixtures in Europe) study, pesticide-related HBM levels were assessed in Czech Republic, Hungary, Latvia, Spain and the Netherlands. For each country, this was done in urine samples from parent-child pairs living in hotspot (residences within 250 m of pesticide application sites) or control areas, in the spraying and non-spraying season. In Switzerland pesticides were measured in urine from 300 adults in a different design. Using suspect screening techniques, 95 pesticide-related markers were detected. This number was reduced to 30 markers when focusing on parent pesticides with the highest two confidence levels in identification. We did not observe consistent strong contributions from agricultural application to detection rates in hotspots or in spraying season.

In HBM4EU, different case studies were conducted with the aim to identify methods for the prediction of mixture effects that can be used consistently for human health risk assessments and can inform biomonitoring strategies. This resulted in an advanced decision tree and workflow scheme for assessing hazards from exposure to chemical mixtures. In many cases, it was possible to identify drivers of mixture risks, i.e., chemicals that contribute more strongly to the estimated health risks than other chemicals in the mixtures. In the case studies, the identified risk drivers are regulated under different legislations. Among the risk drivers were several legacy compounds; network analyses showed that these cluster with other newer chemicals. One of the case studies clearly showed the need for repeated measurements in HBM studies, especially for short-lived chemicals. Furthermore, the case studies demonstrated that assessment of risks associated with combined exposures is generally possible by using the Hazard Index and/or the Point of Departure Index method. In the interpretation of results from the Hazard Index in a tiered approach, sufficient attention should be given to the underlying uncertainties in the applied assessment factors for the substance-specific Hazard Quotients used in the Hazard Index.

HBM4EU also laid the foundations for a European HBM Network to monitor human exposure to priority chemicals, including mixtures.

EXPOSURE & HEALTH EFFECTS

Unintentional chemical mixtures present in the environment are of societal concern as the chemicals contained therein, either singly or in combination, may possess hazardous (toxic) properties for human health.

One particular concern is the potential impact of exposure to mixtures of pesticides arising from dietary and occupational exposure, domestic use or via the wider environment. However, in the absence of real-life mixture exposure data, documentation of actual health risks in the population to date is rather limited and the current regulatory practice is still largely based on considering single chemical substances.

Therefore, a group of scientists from several EU research projects dedicated to study mixture health risks (Bopp et al., 2018) published a Statement on advancing the assessment of chemical mixtures and their risks for human health and the environment (Drakvik et al., 2020).

A European strategy needs to be set for the governance of combined exposure to multiple chemicals and mixtures. Without such a clear strategy, specific objectives and common priorities, research, and policies to address mixtures will likely remain scattered and insufficient.

Figure 1. CHEM Trust, 2022. Chemical cocktails - The neglected threat from toxic mixtures and how to fix it.

Chemical pollutants in the home

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

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

INPUT TO POLICY PROCESSES AND RELEVANT POLICY MEASURES

HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan. These are available in the HBM4EU Science to Policy section.

Chemical mixtures give rise to substantial regulatory challenges due to the various exposure routes from (in) voluntary exposure. Present regulation for chemical mixtures is limited in Europe (Rotter et al., 2018). In terms of human health legislation, CLP Regulation (EC) 1272/2008 has defined classification criteria for mixtures for human health. The pesticide regulation, under the plant protection products and data requirements (Regulation (EC) 1107/2009, Regulation (EU) 283/2013, Regulation (EU) 284/2013), considers mixtures for the constituents of the product but not for mixture assessment from different sources. Regarding biocidal products, Regulation (EU) 528/2012, mixtures are considered for the individual components of the product and if the biocidal product is intended to be authorized for use with other biocidal products. Maximum Residue Limits (MRL), Regulation (EC) 396/2005, cover pesticide residues from pesticide uses and other sources. Regarding dietary exposure regulations, the food law, Regulation (EC) 178/2002, considers cumulative toxic effects for food. Also the EU's Chemicals Strategy for Sustainability expresses the ambition to account for the cocktail effect of chemicals when assessing risks from chemicals, with the overall aim to work towards a zero pollution environment. For REACH, it will be assessed how to best introduce a mixture assessment factor for the chemical safety assessment of substances.

POLICY QUESTIONS

The answers to the policy questions below are summarised. For more details, please see the Substance Reports available on the substance specific page of the HBM4EU website.

1 What are common HBM mixture patterns in the European population?

Existing databases of early HBM studies are useful for the exploration of co-occurring substances in the human body. The number of individuals in which the full range of chemicals of interest is measured, however, is limited and needs to be expanded. Identification of co-occurring substances using HBM data is feasible through network analysis and sparse non-negative matrix under-approximation, each with its own strengths and limitations. Combined application to explore and quantify co-occurrences is recommended.

2 Can we identify hotspots or risk groups with high mixture exposures?

Results obtained from the SPECIMEn study do not suggest a consistent strong contribution from agricultural application to human exposure to pesticides. Broader application of suspect screening is required to obtain a better overview and semi-quantitative evaluation of substance exposures across the EU. This would allow prioritization of substances for targeted analysis and comparison of the suspect screening data with reported substance usage.

3 What are the impacts of chemical mixtures on human health?

The HBM4EU case studies collectively highlight the need to take combined exposures into account in chemical risk assessment. It became evident that a disregard for combined exposures will lead to significant underestimations of the health risks associated with chemical exposures. This is true both for the general population and for more specific exposure scenarios, such as those relevant to occupational settings.

4 What action perspectives are available to reduce mixture levels?

In the exploration of policy needs for mixture risk governance, views on responsibilities and on criteria to guide risk reduction strategies varied considerably. Concrete action perspectives, therefore, remained unarticulated. In policy terms, the mixture risk problem can be seen as a 'wicked problem' due to the nature of the problem, *i.e.,* high uncertainty about risks, high complexity and high ambiguity of values. This implies that (technical) regulations alone cannot bring resolution to the wicked problem. Broader stakeholder involvement and consultation is needed in that respect, in addition to improved mixture risk assessment procedures and practice.

KNOWLEDGE GAPS

HBM4EU has clearly demonstrated the usefulness of HBM data for mixture risk assessment. Therefore, it is recommended that HBM data, particularly data on the common occurrence of chemicals, are more widely utilised. However, in order to assess the actual mixture exposures in the population and co-occurrence in the body, future HBM studies should aim to collect data on the full range of chemicals of interest by targeted analysis in sufficiently large study populations measured in the same individuals. To facilitate and harmonize such studies, a strategy for the measurement of multiple exposure and effect biomarkers in the same subject in HBM programmes needs to be developed, together with an inclusive HBM/exposome infrastructure in Europe. Further research should focus on broadening and refinement of a combination of approaches to identify real-life chemical mixtures of concern to which the population is exposed. This will allow prioritization of mixtures of concern and support policy decisions. This involves data-driven approaches and methodologies to incorporate toxicological potency information and to group substances with common modes of action. Additional conclusions and recommendations for policy development and for further research regarding chemical mixtures have been jointly formulated by partners and stakeholder.

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