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(1\textsuperscript{nd} round of prioritization)

HBM4EU Priority Substance Group: Mixtures

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CONTENTS

1. Background Information ........................................................................................................................................ 3
   1.1. Hazardous properties .................................................................................................................................. 3
   1.2. Exposure characteristics ............................................................................................................................... 3
   1.3. Policy relevance ................................................................................................................................................ 4
2. Categorisation of Substances ................................................................................................................................ 5
3. Objectives / Policy-related questions .................................................................................................................... 5
4. Research activities to be undertaken .................................................................................................................... 6
5. References .............................................................................................................................................................. 7
1. Background Information

The phenomenon of mixtures (in the context of HBM) refers to the common occurrence of chemical xenobiotic substances in the body. There is no broadly accepted operational definition of mixtures. In principle, every single substance, once it enters the body, will exhibit its health effects in interaction with a person's genetic makeup and acquired characteristics, and in concert with all other (xenobiotic) substances from previous and simultaneous exposures. These combined and/or simultaneous may come involuntarily or voluntary through different exposures routes from ambient environments, indoor and occupational environments, food, food additives, consumer products, medication, (medical or voluntary) implants, recreational drugs, performance enhancing drugs and food supplements, tattoo ink, etcetera. These mixtures thus form a challenge to (experimental and observational) science, to scientific assessment of risks and to regulation of substances and general risk management policies. The EHBMI project addresses how HBM can contribute to both the science and policy/regulation of dealing with the phenomenon of mixtures. Within the HBM4EU project, the focus for chemical mixtures will be on chemicals with exposure routes through the environment, food, occupation and/or consumer products.

1.1. Hazardous properties

Since a wide range of chemical substances comprise the mixture of chemical substances in the body, and metabolites thereof, all classes of hazardous properties are potentially involved. This poses the challenge to identify where antagonism, addition or synergies in effects come into play, based on modes of action.

Dealing with mixtures in research poses specific challenges e.g. (Kortenkamp 2007, Slama 2015). In toxicological research working mechanisms, mode of action and adverse outcome pathways can be studied in details, but typically only a few permutations of possible mixtures can be assessed. This does not do justice to the wide array of substance to what populations are exposed to. On the other hand, observational studies in humans may capture these multiple substance, but often fall short in characterizing the dynamics of exposure and ADME characteristics (absorption, distribution, metabolism, and excretion) and typically cannot document mechanisms and causality. Developments in modern techniques such as in sensor technologies, and in epigenomics, transcriptomics, metabolomics, as well as development in biostatistics now allow more in depth research of multiple exposures, body burdens and their effects in humans e.g. (Woodruff 2011, Lenters 2015, Agier 2016). To optimally benefit from these developments new forms of cooperation between traditionally separated research communities and projects need to be build. HBM4EU provides an excellent opportunity and platform to build such alliances.

1.2. Exposure characteristics

A central problem in the discussion on mixtures is the virtual absence of adequate exposure data. In many HBM projects, as well as in cohort studies and biobank studies, multiple (groups) of pollutants have been studied; yet the reporting is typically restricted to distributions and central tendency measures of single compounds or groups of compounds. The groups are often clustered on:

- chemical families, e.g. phthlates, bisphenols, dioxins, PCB’s, PAH’s, VOC’s
- exposure routes, e.g. food, household dust
- type application such as plasticisers, flame retardants, pesticides
- supposed working mechanisms e.g. endocrine disruptors, carcinogens, neurotoxins.
In few cases, the distribution of a measure/indicator of cumulative body burdens in individuals is reported. If so, this only summarizes body burdens within the clusters mentioned above and hardly ever overarching indicators are used and reported. Thus, it is largely unknown whether specific profiles of high exposures exist, i.e. individuals high in PCB's are also in pesticides, flame retardants or poly fluorinate compounds or mycotoxins. Meaningful indicators to capture such profiles need to be developed for mixtures in the wider meaning of the word. With such aggregated mixture indicators exposure profiles of concern and potential hotspots or risk groups can then be identified in existing data and in new studies. Therefore, also existing data merit re-evaluation from a mixture perspective.

1.3. Policy relevance

Dealing with mixtures poses substantial regulatory challenges, with numerous pertinent EU and national regulations.

In the European Directive 396/2005 EFSA was appointed to be responsible for establishing the methodology for risk assessment of mixtures. It states among other things “...It is also important to carry out further work to develop a methodology to take into account cumulative and synergistic effects. In view of human exposure to combinations of active substances and their cumulative and possible aggregate and synergistic effects on human health, MRLs should be set after consultation of the European Food Safety Authority....". Since 2005 EFSA has published 4 Opinions and 1 Guidance on how to perform risk assessment for pesticide mixtures. The full methodology was discussed during an EFSA info session or organized to discuss the methodology with the stakeholders1. Also JRC has published several reports on assessment of mixtures, that advocate a new test strategy to define the relevant mixtures2. EFSA takes pesticides as a concrete point of departure to develop strategies for dealing with mixtures.

Such strategies, once developed, will then be generalized to other forms of mixtures. Central in this approach is the grouping of substances into CAG’s, cumulative assessment groups of substance with a common mode of actions. Such CAG’s are developed on the basis of adverse outcomes by organ system, e.g. liver.

Several Member States (MS) also have issues reports and opinions on dealing with mixtures. For instance in the Netherlands, avoidance of cumulative exposures (of all environmental agents, not just substances) is one of the corner stones of modern environmental policy3. In France, the new health law (currently under consideration) indicates that the identification of risks health should be done relying on the Exposome concept, integrating the effects of exposures to all non-genetic factors.

While there is a clear information need articulated from the side of policy makers, there is less insight in the possible action perspectives for policy makers and stakeholders in dealing with mixtures. Moreover, it is difficult to assess “value of information” for HBM data on mixtures: at what point would additional information on HBM and exposure to mixtures (based on HBM data, or the combined knowledge base) lead to other decisions and other/further policy actions? Should exposure to all substances in the mixtures be reduced, or the one with the highest impact on adverse health outcomes, the one with easy and safe alternatives/replacements, or the ones with

1 http://www.efsa.europa.eu/en/events/event/140211
2 http://publications.jrc.ec.europa.eu/repository/handle/JRC37522
the least costs to reduce, or should the cost-benefit ratio of each source/exposure route be taken into account. One can imagine that the cost-benefit ratio to reduce BPA exposure for babies, children, shop personnel, or in medical (emergency) equipment, may vary substantially. Moreover, when mode of action (MoA) and adverse outcome pathways (AOP) are taken as point of departure to assess acceptability of the combined health impacts of exposure to mixtures, there may well be a need to compare across substances emerging from different types of applications, e.g. flame retardants, pesticides, plasticizers, and food additives/contaminants. For HBM data on mixtures to be meaningful for policy development, it is necessary get further insight in and articulation of the expectations and primary policy needs already in the design phase of the research.

2. Categorisation of Substances

Mixtures as a group fall into category C (Very little or no human biomonitoring data and/or information on toxicological/health effects or external exposure is available). While single chemicals, or even chemical family groups such as PCB’s may warrant a category A or B classification, the essence of the mixture issue is the many unknowns about joint and cumulative exposure, combined mode of actions and overall adverse outcomes and health risks and impacts. Data coming available under category D and E would ultimately also fall under the Mixture umbrella.

3. Objectives / Policy-related questions

The overarching objective of the mixture activities in HBM4EU is to improve the efficacy of HBM to inform science, policy/regulatory actions and societal debate with respect to dealing with mixtures.

Some underlying questions include:

▸ What is the information need of regulatory bodies and stakeholders?
▸ What are common HBM mixture patterns in the European population?
▸ Can we identify hotspots or risk groups with high mixture exposures?
▸ Which sources & pathways contribute most to HBM mixture values?
▸ Which effect markers can we use to assess health risks of mixtures?
▸ What action perspectives are available to reduce mixture levels?

The more specific objectives are:

▸ Develop summary indicators to describe the exposure and body burdens of mixtures with an emphasis on defining priority mixtures and drivers of mixture toxicity
▸ Re-evaluate existing HBM mixture data to identify real-life exposure patterns to mixtures
▸ Collect new HBM mixture data in selected European countries
▸ Further develop and apply practical approaches to assess the potential health risks and impacts of mixtures
▸ Inform policy makers, stakeholders and the public at large about mixture exposures, possible health risks and action perspectives
## 4. Research activities to be undertaken

Table 1: Listing of research activities to be carried out to answer the policy questions summed up in 8.3

<table>
<thead>
<tr>
<th>Substance</th>
<th>Available knowledge related to policy question</th>
<th>Knowledge gaps / Activities needed to answer policy question</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>What is the information need of regulatory bodies and stakeholders?</td>
<td>In 2017 preparations started for develop exchange of information and establish cooperation amongst Horizon2020 funded projects on mixtures. To this end, a workshop will be organised mid-2018. HBM4EU will taken part in this effort</td>
</tr>
<tr>
<td>All</td>
<td>What are common HBM mixture patterns in the European population?</td>
<td>In WP15, task 15.1 We will develop summary indicators to describe the exposure and body burdens of mixtures with an emphasis on defining priority mixtures and drivers of mixture toxicity. With these indicators we will re-evaluate existing HBM mixture data to identify real-life exposure patterns to mixtures. In addition to data-driven approaches, we will aggregate HBM mixture data based on MoA/AOP into cumulative assessment groups as an approach tested by EFSA on pesticides. In WP15, task 15.1 we will collect new HBM mixture data in selected European countries</td>
</tr>
<tr>
<td>All</td>
<td>Can we identify hotspots or risk groups with high mixture exposures?</td>
<td>In WP15, task 15.1 and 15.2 will analyse existing and newly generated HBM mixture data to identify possible hotspots and risk groups</td>
</tr>
<tr>
<td>All</td>
<td>Which sources &amp; pathways contribute most to HBM mixture values?</td>
<td>In WP15, in concert with WP12 we will address source attribution to observed HBM mixture data</td>
</tr>
<tr>
<td>All</td>
<td>Which effect markers can we use to assess health risks of mixtures?</td>
<td>In WP15, task 15.3, we will in concert with WP14 address possible effect markers for mixtures</td>
</tr>
<tr>
<td>All</td>
<td>What action perspectives are available to reduce mixture levels?</td>
<td>In WP15, together with WP5, we will evaluate possible action perspectives</td>
</tr>
</tbody>
</table>
5. References


