Prioritised substance group: Mixtures

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Short overview of results of the activities carried out within HBM4EU in 2020 to answer the policy questions with reference to corresponding deliverables.

Policy Question	Short Summary of Results
1. What is the information need of regulatory bodies and stakeholders?	The information needs on mixtures of regulatory bodies and to a lesser degree of other stakeholders was explored through a combined approach of literature review (including policy documents), development of a semi-structured interview protocol, interviews of experts and policy makers and interpretation of the results. The effort also benefited from HBM4EU's participation in the Horizon2020 Joint Mixture Project Cooperation, particularly from the joint meetings where experts and policy makers discussed current issues in research and management. The outcomes of this work are described in detail in D15.1. Focus in this deliverable was on policy makers. Basically, the approach was as follows. For the governance of mixture risks, we formulated a number of 'rational statements' and questions that are relevant to HBM4EU. Subsequently, a set of questions were derived from the statements; these were used for semi-structured interviews with international experts. Second point of departure was to consider mixture risks as a 'systemic risk' problem (this also emerged in the discussion of the Horizon2020 Joint Mixture Projects). Systemic risks in the context of environmental health are complex risks to health embedded in wider environmental, social, economic and political systems (for references see D15.1). Systemic risks require more integrated and possibly precautionary approaches to risk governance. One of the characteristics of systemic risk problems is that systemic risks are under a distributed responsibility: everyone is responsible for a part of the system but no one has the legitimacy to act on the entire system; this is clearly the case for the regulation of mixtures across different regulatory silos. Other characteristics of systemic risks are the inherent substantial uncertainties, complexity and ambiguity of the problems. "Complexity" should here be understood as the difficulty to identify and quantify causal relationships between a variety of potential hazards and the multitude of potential effects following exposure. "Uncertainty" pertains to a situation where the type or nature of any adverse effects, or the likelihood of these effects, cannot be described precisely. "Ambiguity" refers to a situation where several legitimate and meaningful interpretations of accepted risk assessment results coexist. Subsequently, it is quite common to encounter ambiguity about normative values and ethical norms. The conclusions from the literature and interviews were:

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	• Mixture can be viewed as 'systemic risks' given the properties of uncertainty, complexity, and ambiguity and the general 'embeddedness' of chemicals in daily life; risk governance approaches for mixtures should therefore be targeted as such and the contextual aspects may require tailored approaches instead of generic regulation. • The information needs from policy makers and experts is still rather diffuse and unarticulated. • As can be expected from the literature on systemic risks, views on responsibilities and criteria to guide risk reduction strategies vary considerably; this warrant further exploration of views and mental models held by the stakeholders involved. • A broader dialogue on information needs for mixture risk governance with stakeholders is needed, but as yet not planned. Any such exercise, within HBM4EU, should be done in conjunction with Pillar 1. On the basis of the literature and interviews, D15.1 also developed a long list of 'statements' (or positions in terms of argumentation analysis) for future use in exploration of information needs in policy makers and stakeholders. These can be used in further delineation of information needs.
What are common HBM mixture patterns in the European population?	So far, there are insufficient existing HBM mixture data available through the repository to address this question. Statistical scripts and approaches have been developed and tested on a simulated data set. These have been described in AD15.3 and D15.3. The scripts involve a combination of methods, both graphical and analytical, and combine alternative methods. In 2019 the scripts have been successfully applied to real HBM mixture data from the Flemish 'FLEHS' cohort under bilateral agreement. The results have been described in scientific manuscript that was recently submitted for publication. Meanwhile, similar analyses have been initiated for the German 'GerES' cohort and existing data from cohorts from Spain and Czech Republic are being lined up for subsequent analysis and for across country comparisons.
Can we identify hotspots or risk groups with high mixture exposures?	HBM4EU is running a survey of human internal exposure to mixtures of pesticides across five of our partner countries: Hungary, Czech Republic, Spain, Latvia and the Netherlands. Switzerland will also collect urine samples, with a slightly different design. This survey, entitled 'SPECIMEn', explores exposure to pesticides and focusses on residential areas or "hotspots" close to agricultural fields where pesticides are applied. The survey is designed to assess concomitant/combined exposure to multiple pesticides in hotspot and control areas using human biomonitoring. Details of the joint pesticide survey are described in AD15.7. The field work for this survey started in the fall of 2019 and is nearly completed. Urine samples will be collected in 50 parent-child pairs in hotspots (residences within 250 m of agricultural application of pesticides) and 50 parent-child pairs in control areas. Samples and questionnaires will be collected in a non-spraying and a spraying season. Samples will be analysed through pesticide suspect screening in conjunction to CGL Emerging Chemicals (WP16). These suspect screening approaches are built on non-selective analytical workflow and allow the qualitative monitoring of several hundred (up to several thousands) of exposure markers, including various pesticide classes under their parent or metabolite form. This approach will be used to gain insight into the occurrence of extended exposure patterns of pesticide-biomarkers, differences across the countries participating in SPECIMEn, differences between two seasons (spraying season with active application, and non-spraying season with no active application) and/or location (living close to agricultural areas or not). The results obtained will also contribute to the prioritisation of certain substances in terms of further exposure and risk assessment, and to possibly generate early warning information.

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Which sources & pathways contribute most to HBM mixture values?	This policy question could not yet be addressed, but is being worked on in tasks 15.1 and 15.2. Results are expected in 2021.
Which effect markers can we use to assess health risks of mixtures?	This question can be addressed in multiple ways: from the perspective of single chemical families and from the perspective beyond single chemical families. Obviously, the latter is more complex. Within HBM4EU, both perspectives are taken into consideration. Effect biomarkers for oxidative stress, i.e. 8OHdG and 8-isoprostane, are included as an add-on in the joint survey on pesticides 'SPECIMEn'. Further opportunities to include effect biomarkers in the joint survey on pesticides are being explored. Within Task 15.3, case studies are being 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. In four of the five case studies conducted, in cooperation with WP13 and WP14, suggestions for effect biomarkers are expected as additional results of the case study. Additionally, activities on priority chemicals of specific chemical families may provide effect biomarkers of the combined group of chemicals in that family.
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, remain unarticulated. In the long list of 'statements' (or positions in terms of argumentation analysis), several pertain to action perspectives. These were mainly drawn and paraphrased from actual discourse on mixtures, and range from current legislation being sufficiently adequate to protect public health from mixture effects to concrete proposals how to better regulate exposure to mixtures and the associated health effects (see D15.1 for full list). While all these positions have been brought forward in discussions on action perspectives with respect to mixture risk governance, the overall picture as yet is anecdotal; it is unclear to what degree the various options have support in a wider constituency of experts, policy makers or the general public and stakeholders. A more systematic and broader consultation would be needed to gauge support for these (sometimes incompatible) alternative action perspectives to reduce mixture risks in the population. Such an activity is under consideration for the WP15 workshop on policy recommendations on risk assessment of chemical mixtures, which will be organised in conjunction with, among others, Pillar 1.