

Position Paper: Preventing risks for people and environment from hazardous chemical mixtures

Rationale for action - Background

Mankind has changed the natural prerequisites for sustainable development of life through innovations of new chemicals (pharmaceuticals, pesticides, polymers, detergents and more) and by refining natural products (e.g. crude oil, wood, natural rubber, fragrances and much more). This has both directly and indirectly influenced and changed human lives, ecosystems and the global environment. While many of the innovations have improved the quality of our lives in many ways, there is also an increased understanding that exposure to many of the chemicals has created a global problem ¹. Several of the UN sustainable development goals (SDGs) are linked to risks from hazardous chemicals and their management. Especially target 3.9 calls for “by 2030, to substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination” ².

As recently reported in Lancet, pollution is currently the biggest cause of non-communicable diseases, and the estimates on disease burden could be the tip of a much larger iceberg ³. Several studies have shown that hazardous chemical exposure has been estimated to contribute substantially to disease and dysfunction across life course, amounting to costs of hundreds of billions of Euros, e.g. for endocrine and neurodevelopment toxicities ⁴. Furthermore, there are strong indications that mixtures of chemicals strongly impact biodiversity in almost half of the European water bodies, already at concentrations that are considered “environmentally protective”, and with taxonomic losses up to 42% ⁵.

¹ Bernhardt E., et al. (2017). Synthetic chemicals as agents of global change. *Front Ecol Environ.* 15(2): 84–90. doi:10.1002/fee.1450.

² UN (2018). United Nations sustainable development knowledge platform. SDGs: SUSTAINABLE DEVELOPMENT GOAL 3 Ensure healthy lives and promote well-being for all at all ages. (<https://sustainabledevelopment.un.org/sdg3>, accessed 4 April, 2018).

³ Landrigan P., et al. (2017). The Lancet Commission on pollution and health. *The Lancet.* Vol. 391, No. 10119.

⁴ Olsson, I. et al (2014). The Cost of Inaction: A Socioeconomic analysis of costs linked to effects of endocrine disrupting substances on male reproductive health. *TemaNord*, ISSN 0908-6692, TemaNord 2014:557 (<http://norden.diva-portal.org/smash/get/diva2:763442/FULLTEXT04.pdf>)

- Bellanger M., et al. Neurobehavioral Deficits, Diseases, and Associated Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. *The Journal of Clinical Endocrinology & Metabolism*, Volume 100, Issue 4, 1 April 2015, Pages 1256–1266. <https://doi.org/10.1210/jc.2014-4323>.

- Grandjean P., and Bellanger M., (2017). Calculation of the disease burden associated with environmental chemical exposures: application of toxicological information in health economic estimation. *Environmental Health.* 2017; 16: 123. doi: 10.1186/s12940-017-0340-3.

- Trasande L, et al. (2016), Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis. *Andrology*, 4, 565–572. doi: 10.1111/andr.12178.

⁵ Beketov, M. A. et al. (2013). Pesticides reduce regional biodiversity of stream invertebrates. *Proceedings of the National Academy of Sciences of the United States of America* 110, 11039-11043, doi:10.1073/pnas.1305618110

- Malaj, E. et al. (2014). Organic chemicals jeopardise freshwater ecosystems health on the continental scale. *Proceedings of the National Academy of Science* 111, 9549-955., doi/10.1073/pnas.1321082111 (2014)

At the same time, the chemical production has increased more than 50-fold since the 1950s ⁶, and was foreseen to triple again by 2015 ⁷. How such chemical pressures affect human and environmental health is still poorly understood, as most studies have dealt with single chemicals. In real life, we are exposed to complex mixtures of man-made chemicals every day.

In the past, EU policies have been successful in limiting pollution and adverse effects from single substances and single exposure routes. However, the challenge remains to reduce the risks from hazardous chemical mixtures and from the total exposure, in single media, across media and across legislations or regulatory sectors. Currently, in EU legislation, there is no mechanism for a systematic and integrated assessment of mixture effects taking into account different routes of exposure and different product types ⁸. Also, chemicals and mixtures that are persistent and bioaccumulative and/or mobile are of special concern, because they accumulate either internally in biota including humans (bioaccumulative substances) or externally in the environment (mobile chemicals) ⁹. Human biomonitoring studies have proved that people in Europe have a considerable number of man-made chemicals in their bodies ¹⁰.

The need to better manage chemical mixtures has been highlighted both by the European Parliament and the Commission⁸. Also the 7th Environment Action Programme calls for strategies on mixtures, pharmaceuticals in the environment, and for a non-toxic environment. The EC is now funding few EU research projects in this field, EDC-MixRisk, EuroMix, EU-ToxRisk, HBM4EU, and SOLUTIONS. Several European Commission services and EU agencies have joined forces with these projects in order to map the achievements and identify remaining gaps in mixture research. Based on the task and discussions so far, we are proposing the following.

Chemical mixtures – moving from a recognized ignorance to action

1. There is a clear need to assess the actual mixture exposures in the European population and ecosystems.

European populations are exposed to mixtures of synthetic chemicals via multiple pathways across their life course. These include exposures during fetal development and through air, food, occupation, cosmetics, consumer products, medication and recreational drug use. Different phases of life are expected to have different patterns of mixture exposures. Hence, e.g. toddlers are expected to have relatively high exposures from indoor sources, including flame retardants, emissions from construction and surface materials and cleaning agents. While exposures for traditional environmental pollutants and some chemical agents have been measured and modelled for specific pathways, comprehensive exposure assessment across multiple sources and pathways in different population subgroups is largely absent. Exposure of aquatic ecosystems to complex mixtures of environmental contaminants including pesticides and biocides, pharmaceuticals, surfactants, industrial chemicals as well as all types of unintended by- and transformation products is caused by point and diffuse sources such as treated and untreated wastewater effluents, urban and agricultural runoff and remobilization of legacy burdens in sediments and dumped waste. While monitoring and assessment of contamination in

⁶ OECD (2001). Environmental Outlook for the Chemicals Industry. Organisation for Economic Co-operation and Development, Paris.

⁷ OECD (2012). OECD Environmental Outlook to 2050. The consequences of inaction. Organisation for Economic Co-operation and Development, Paris.

⁸ EC (2012). Communication from the Commission to the Council – the combination effects of chemicals. Chemical mixtures, COM(2012),10.

⁹ EEA (2018), Chemicals for a sustainable future, Report of the EEA Scientific Committee Seminar, Copenhagen, 17 May 2017. Luxembourg: Publications Office of the European Union.

¹⁰ Knudsen L., Merlo F. (ed.) (2012). Biomarkers and Human Biomonitoring Vol. 1: Ongoing Programs and Exposures. Vol 2: Selected Biomarkers of Current Interest. RSC Publishing, Cambridge, UK.

many cases is limited to few priority substances, most of them legacy pollutants, the vast majority of the chemicals in daily use occurring in complex mixtures remain unconsidered.

- Assessment of actual mixtures exposures in the population and in ecosystems is central as the corner stone of any risk assessment. Source apportionment of actual mixture exposures should deliver the insights needed for effective mixture risk management strategies.

2. Solutions-oriented monitoring is required to link ecological degradation to causative chemical mixtures and their sources

European water bodies support biodiversity and provide important ecosystem goods and services for human welfare. Monitoring and assessment of this unique heritage (according to the Water Framework Directive) is unique in the world and provides a comprehensive picture on the quality status of water bodies on a continental scale. However, existing monitoring framework is still quite limited with respect to the identification of causes of ecological degradation as a requirement for successful and cost-efficient management. Among other stressors, chemical mixtures may play a key role in the impairment of the ecological status of our water bodies, but are not covered by priority substance-based monitoring and assessment. At the same time, this approach does provide strong links to sources of impairment and thus to management solutions.

- New approaches involving effect-based and more holistic chemical monitoring providing chemical and toxicity fingerprints are required to prioritize contaminant mixtures and abatement options. Mixture monitoring approaches should be complemented with emission-based exposure and risk modelling in order fill data gaps, reduce uncertainty and allow for more targeted management.

3. There is a need for legal mandates for performing Mixture Risk Assessments (MRAs)

Requirements for taking mixture toxicity into account have been partly established for specific types of mixtures and specific protection goals under some few pieces of EU chemicals legislation. For instance, according to the plant protection product regulation (PPPR) the mixture toxicity of the PPP as technical mixture has to be considered in the human health and ecological risk assessment. Again, mixtures in the environment resulting from the simultaneous or sequential application regime of several PPP are only implicitly addressed by the PPPR. In general, however, legal requirements for MRAs for human health as well as for ecosystems are missing.

- The present status indicate that significant progress on the MRA issue is not achievable without the driving force of corresponding legal provisions.

4. There should be uniform principles for performing MRAs across regulatory silos

Where rules and guidance documents for performing mixture risk assessments have already been established under different pieces of European legislation and for different protection goals, both the approaches and the terminology are not always consistent. This is confusing and can result in differing protection levels. The need for harmonisation and integration is well recognised, but progress is too slow.

- MRAs should be handled in a more systematic and transparent manner. Better coordination is needed especially on waste and chemicals management, land use, water quality, food and outdoor and indoor air.

5. There is a need for defining regulatory acceptable levels for mixture risks

Rules for deriving regulatory acceptable exposure and risk levels are largely missing for MRAs.

Without such rules, inconsistent assessments may result, in particular due to differing ways of accounting for inherent uncertainties in MRAs. The rules which have been established for using assessment factors or margins of safety in single substance assessment are not readily transformable into corresponding rules for MRAs. In environmental MRAs, whole mixture assessments building on effect-based monitoring should be evaluated for routine application complementing compound-based approaches that might miss important drivers of risk.

- Based on initial efforts¹¹ the development of effect-based regulatory values for mixtures with similar effects need to be developed.

6. Action is needed now, but taking benefit from stepwise translation of the science

We must not wait to have a perfect model to address mixtures in risk assessment and regulation, as some tools, data and approaches already exist. MRAs can be developed based on more data rich chemicals, and transferred to data poor chemicals. For instance, the use of QSAR and other in silico tools can be applied for data poor chemicals (while accepting some uncertainties). Nevertheless, more sophisticated MRA models should be adopted over time. Key issues for supporting risk management include¹²:

- Approaches for grouping chemicals such as pesticides into cumulative assessment groups¹³ need to be further developed considering also other approaches for grouping such as adverse outcome pathways (AOPs) networks. Currently, complex AOPs networks, including information on mode of actions, are seen as a better scientific approach for grouping pesticides into cumulative assessment groups (CAGs). Once the AOPs network is known, tests can be identified to measure the effect of single chemicals and mixtures of chemicals at relevant key-events representing similar and dissimilar mode of action. Also other chemicals than pesticides should be included in the testing.
- Different types or levels of exposure will need different regulatory management, concerning intentional exposure (e.g. drugs, pharmaceuticals, alcohol, tobacco), occupational exposures or unintentional environmental exposures. Also population groups and/or sub-populations need to be taken into account in order to protect the most vulnerable groups, such as children and women.
- Assessment is needed within a regulatory sector and overarching across regulatory sectors including all relevant types of mixtures. However, in case of overarching approach, a question remains on how to divide the acceptable risk per regulatory sector.
- There is also a need for a multi-causal framework that integrates data from multiple exposures and hazards and enables the development of proper prevention strategies and tools.

7. Proactive and proper level of communication and action is important for maintaining public trust and credibility to regulatory systems

The perceived severity and susceptibility affects risk prevention strategies and actions both at regulatory level and the level of individual behaviour. It is essential that citizens are informed

¹¹ Escher et al. (2018). Effect-based trigger values for in vitro and in vivo bioassays performed on surface water extracts supporting environmental quality standards (EQS) of the European Water Framework Directive. *Sci. Tot. Environ.* 628-629: 748. doi:10.1016/j.scitotenv.2018.01.340

¹² Bopp S., et al. (2018). Current EU research activities on combined exposure to multiple chemicals. *Manuscript in preparation.*

¹³ EFSA (2013). European Food Safety Authority Panel on Plant Protection Products and their Residues. Scientific Opinion on relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticides residues in food. *EFSA Journal* 2013;11(12):3472. 40 pp. doi:10.2903/j.efsa.2013.3472.

early on of potential risks and risk prevention strategies. This requires reliable data, understanding of the risk and trust in governmental institutes.

- Public openness and access to data and risk models are needed to strengthen the transparency of the regulatory systems and also the trust in it. Therefore, access to industry studies would be of high benefit. Once a risk is identified, the burden of action cannot be placed on the shoulders' of individuals, but regulators and policymakers must address the concerns and prevent risks in a timely and systematic manner. This should include proper resources allocated to the implementation and enforcement.

8. Declarations of chemicals in materials and goods is lagging far behind

There is a need to move away from reactive management of chemicals towards more proactive and effective risk management. In order to be able to prioritize and use resources more effectively, insight is needed which chemicals are being used and where.

- There has been a long lasting demand on declarations of chemical content in materials and goods, through which the understanding of exposure to chemical mixtures could be significantly improved. This should be manifested promptly to allow science to work in collaboration with the society for prioritisation of the most important chemicals and mixtures of chemicals and to identify chemicals of concern both as single chemicals but in particular in mixtures.

9. Safety assessments should be seen as a competitive advantage

Novel chemicals being put into the market are assessed for their safety by EFSA for food and by ECHA for non-food. The dietary exposure to mixtures can be assessed, but the non-dietary exposure is quite often difficult to assess. New applications under REACH must undergo safety assessments to avoid harmful environmental and health effects.

- Proactivity is required to avoid expensive and complicated reactive measures later, but also to be able to apply the circular economy cycle to materials and goods. Including safety and sustainability criteria is a competitive advantage and should be seen as an integral part of the innovation processes of developing new commercial materials, chemical products and goods.

10. Interdisciplinary and multidisciplinary education and training are integral to secure expert competences in the future and to promote sustainable innovation

Currently, there is a growing lack of sufficiently skilled experts in the area of environment, health and safety sciences. Fragmentation, disciplinary boundaries and lack of integrating societal and economic aspects hamper a holistic view and urgently needed competence provision.

- Coordinated efforts at European scale should be initiated to guarantee a future where relevant competences can be obtained and serve the society in various sectors, including academia, regulatory fields and industry.
- Safe-by-design and mixture approaches are necessary to bring responsible and sustainable innovations to the market and to address the requirements for circular economy.
- The integration of environment, health and safety (EHS) aspects, including mixture aspects, should start early enough in the education system and be an integral part of R&D activities and innovation governance.

11. Translating research and knowledge to evidence-informed policies require knowledge exchange and dialogue as well as supporting structures or instruments

Strengthening the science-to-policy interface between research communities, regulators and other stakeholders takes time and resources. At the same time, the societal relevance of the research, proposed solutions and impact will likely increase.

- Research funding should facilitate developing interdisciplinary collaboration and evidence-based solutions together with other scientists but also with broader stakeholder communities and end-users (e.g. community of practice).
- Funding needs to be problem-oriented, helping to tackle the broad range of contributing factors, across disciplines and sectors. More targeted calls should be made possible as well, as scientific advances are required on specific questions and/or as stepping stones to further research. Also, pooling EU projects together can help gaining a helicopter perspective and create synergies between the funded projects.

12. Sustainability of funding, infrastructures and competence centres are key

Open, transparent and integrated governance and knowledge systems would facilitate the development and validation of new test methods, filling in data gaps, promotion of open data and addressing the challenges of data integration and data comparability. IPCHEM's further development should be considered, with prospective collaboration and data from Framework Programme funded mixture research projects. IPCHEM data should be linked to available models, as developed under national and EU funding, to perform combined exposure assessment to multiple chemicals via multiple exposure routes ¹⁴. Data and models should become transparently available to society.

- Networking of labs/centres in Members States is necessary at the European level to address the fragmentation and pooling of expertise. In the long-run, a joint European Research Infrastructure (labs and model facilities, either centralized or de-centralized) is worth considering as concerted and coordinated efforts are necessary to tackle the multiple aspects of the mixture exposure and hazard assessment and produce a harmonized European response.
- The Members States' involvement is crucial to safeguard sustainable solutions that help protecting both citizens and environment and addressing the mixture challenges.

High priority for further research and collective commitment

In addition to the pressing regulatory and governance aspects, there are many issues in science itself to be resolved so that more profound steps for sound mixture risk assessment can be taken. We consider that it is important to act rapidly with the available knowledge, but we also emphasize that more intensive research is needed in short-, medium and long-term to create a solid foundation and fine tune or even change our approaches as new data and knowledge become available.

Despite some clear progress and advances in the mixture risk assessment, several significant gaps exist. To mention a few, these include lack of mixture exposure data at European population level; the challenge of data availability in hazard assessment of mixtures; availability of validated and standardised test methods; and lack of toxicity information for the mixture components in component-based approaches ¹². Also the effects of chemical exposures on the health and resilience of humans and ecosystems are poorly known, particularly for vulnerable populations or during vulnerable times of exposures, such as foetal development. Furthermore, how these chemical

¹⁴ JRC (2018). IPCHEM supporting the assessment of Chemical Mixtures. *Workshop report under preparation*.

stressors work in combination with other stressors such as noise, diet and social behaviour, are other areas for which very limited knowledge is available.

The proposals for future research needs, addressing mixture issues, will be published within the next few months as a result of a mixture workshop and dialogue with broader scientific and policy community, taking place at the Joint Research Centre in Ispra, Italy, 29-30 May 2018.

Joint collaboration on chemical mixtures for greater impact

Several EC funded research projects [EDC-MixRisk](#), [EuroMix](#), [EU-ToxRisk](#), [HBM4EU](#), [SOLUTIONS](#), are working together to address different aspects of the impacts of mixtures on human health and the environment, including also research activities at the European Food Safety Authority and the Joint Research Centre. Through this collaboration, synergies, knowledge exchange and interoperability of methods and data will be promoted. A joint workshop ‘Advancing the Assessment of Chemical Mixtures and their Risks for Human Health and the Environment’ will be held 29-30 May 2018 at Joint Research Centre, Ispra. The aim is to discuss the current state of knowledge as well as further elaborate and prioritise areas for future policy and research needs. The active participation of experts from the European Food Safety Authority, the Joint Research Centre, the European Environment Agency and Directorate General Environment, as well as Directorate General for Research and Innovation ensures involvement of key actors as well as policy relevance of the discussions. The ultimate aim of this collaboration is to maximise the impact of the work on mixtures and to enhance chemical safety.

Authors and signatories of the position paper in alphabetical order:

Rolf Altenburger, Deputy Project Coordinator of SOLUTIONS
Helmholtz Centre for Environmental Research GmbH – UFZ, Germany

Robert Barouki, Work Package Leader of HBM4EU
French National Institute of Health & Medical Research – INSERM, France

Åke Bergman, Coordinator of EDC-MixRisk
Swetox; Karolinska Institutet and Örebro University, Sweden

Werner Brack, Coordinator of SOLUTIONS
Helmholtz Centre for Environmental Research GmbH – UFZ, Germany

Elina Drakvik, Project Manager of EDC-MixRisk
Swetox and Karolinska Institutet, Sweden

Jacob van Klaveren, Coordinator of EuroMix
National Institute of Public Health and the Environment – RIVM, the Netherlands

Marike Kolossa-Gehring, Coordinator of HBM4EU
German Environment Agency – UBA, Germany

Erik Lebret, Work Package Leader of HBM4EU
National Institute of Public Health and the Environment – RIVM, the Netherlands

Joëlle Rüegg, Vice-Coordinator of EDC-MixRisk
Swetox and Karolinska Institutet, Sweden

Bob van de Water, Coordinator of EU-ToxRisk
Leiden University, The Netherlands