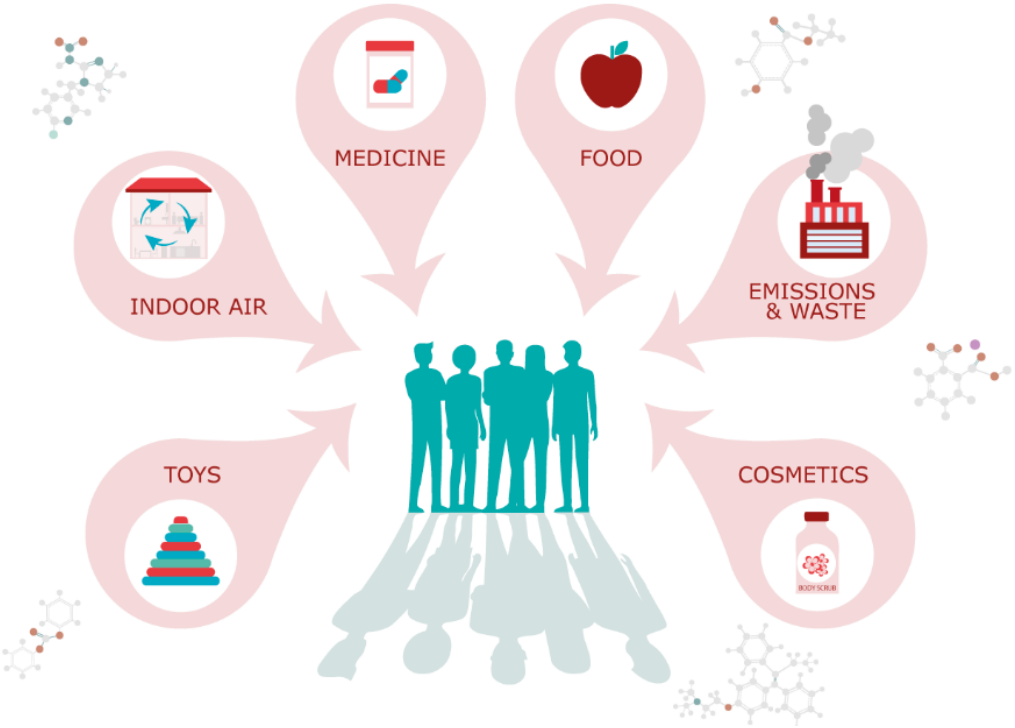
Assessment and Management of Chemical Mixtures

What is the issue with chemical mixtures?

Humans and wildlife are exposed to different combinations of multiple chemicals, via food, consumer products and the environment (Figure below). Combined exposure to multiple chemicals can lead to adverse effects, even if single substances in the mixtures are below their individual thresholds of toxicological concern.



Exposure to Multiple Chemicals (©EU, 2018)

The assessment and management of chemical mixtures is only partly covered by current legislation globally, which focuses on single substances in isolated sectors. Manufactured products, such as pesticide formulations or cosmetic products, are assessed as an intentional mixture for which the composition is known.

However, while formulated products are covered in many cases, unintentional mixtures are not consistently addressed. Their composition is often unknown and changes over time, making them difficult to regulate. The assessment of unintentional mixtures is therefore usually limited to specific legislative sectors, such as pesticide residues in food. The European Commission has recently outlined actions they will take on tackling chemical mixtures in a report: Chemical Strategy for Sustainability (Commission Communication (2020) 667 and a related Progress report on Chemical Mixtures (SWD (2020) 250). The issue of chemical mixtures is addressed in other regions, like in US, Canada, Japan and an overview of different approaches recently compiled.

What are chemical mixtures?

The correct terminology is to refer to **combined exposure** for the exposure **to multiple chemicals** via one or several sources and routes. This is often also called exposure to **chemical mixtures** or

cumulative exposure. In contrast, **aggregate exposure** is used for the sum of exposures to one chemical via several different sources and routes.
For combined exposures to multiple chemicals it is important for risk management to distinguish between **intentional mixtures**, i.e. manufactured products such as pesticide/biocide formulations, cosmetic products, laundry detergents, and **unintentional mixtures**, which are coincidentally formed and may comprise substances originating from one or several sources, such as surface water contaminations, atmospheric pollution or pesticide residues in food.

How are mixtures assessed?

Mixture risks are assessed either by testing the whole mixture (e.g. effect-based monitoring of surface water) or by predicting the combined risk based on concentration and effect information of the individual components within the mixture (component-based approaches). In a regulatory context, mixtures are most often addressed using component-based approaches which stem from the concept of concentration or dose addition. This assumes that chemicals contribute to the combined risk of the mixture based on their potency and on their concentration in the mixture.
In regulatory risk assessment, it is often assumed in a first default approach that all chemicals in a mixture contribute to a combined risk related to a specific endpoint. This assumption can be refined for the exposure and hazard assessment when moving to a higher tier, e.g. considering the specific mode of action of the chemicals or their environmental monitoring levels. Several international frameworks and guidance documents are available for the assessment of chemical mixtures, e.g. from WHO/IPCS, OECD or EFSA. However, major data and knowledge gaps still hamper their general application, e.g. in terms of understanding the exposure to chemical mixtures, the toxic effects, modes of action and potential interactions of chemicals, as well as the identification of specific, high priority mixtures.

Specific challenges

1. Combined exposure: *Unravelling the composition of unintentional mixtures* remains difficult. Neglecting relevant mixture constituents can lead to an under-estimation of risks. However, chemical monitoring data are scarce, although they are becoming more consistently available, e.g. via the EC platform IPCHEM. Moreover, chemical analyses only measure chemicals which are expected to be present. Another challenge is to consider sequential exposures at different moments in time. Biomonitoring chemical concentrations in wildlife or humans is a means to identify realistic co-exposure. Modelling tools for exposure assessment require further development.

2. Combined effects: It is not feasible to test all possible mixtures experimentally, considering the *large number of potential chemical combinations*. On the other hand, prediction of mixture effects based on the individual chemicals is often limited by lack of knowledge of their toxicity and toxic modes of action. Therefore, smart strategies and more efficient tools are needed, relying less on *in vivo* testing but instead on alternative experimental models (such as *in vitro* testing and mechanistic assays) and computational tools.

3. Combined risks: *Managing the risks from exposure to chemical mixtures* presents a policy challenge. Each individual chemical might be at a safe level of exposure, but the combination of chemicals may pose a risk. Even if chemicals within a legislative sector are addressed as mixtures, combined effects from chemicals regulated under different sectors might occur. Thus, risk management decisions may need to be taken on which chemicals or sources should be subject to restrictions. To cope with the large number of possible mixtures, priority mixtures of particular concern should be identified, as well as the individual chemicals driving their risk. Societal risk-benefit decisions may also need to be addressed.

Ways forward to tackle mixtures in the European Union legislative framework for chemicals have been recently published in the Chemical Strategy for Sustainability . Currently, it is considered neither realistic nor economically feasible to specifically assess and regulate an almost infinite number of possible combinations of chemicals. Therefore, effects of chemical mixtures need to be taken into account and integrated more generally into chemical risk assessments. Hence, a recently proposed first step: to introduce a mixture assessment factor in single substance risk assessment under EU legislation and to reinforce provisions to take combination effects into account in other legislation also. Another important step is to improve the sharing and reuse of information on chemicals, to facilitate more specific risk assessment of mixtures in different legislative areas, by overcoming the data and knowledge gaps.

Science has helped to progress the assessment of chemical mixtures in a regulatory context and thus, to increase the protection of human and environmental health. However, knowledge and data gaps still remain and new scientific methodology should be implemented in regulatory approaches, to improve the management of risks from combined exposures to multiple chemicals.