**Chemical Mixtures**

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# Introduction

This summary documents aims to outline the current regulatory activities regarding chemical mixtures in the EU. This includes both intentional and unintentional mixtures.

## Definitions

Intentional mixture – manufactured products e.g. pesticide/biocide formulations, cosmetic products, laundry detergents.

Unintentional mixtures – coincidentally formed and variable mixtures originating from one or several sources, such as surface water contaminations or pesticide residues in food.

Combined exposure – exposure to multiple chemicals via one or several sources and routes, also called exposure to chemical mixtures.

Aggregate exposure – sum of exposures to one chemical via several sources and routes.(JRC, 2018)

Simple mixture – consists of a relatively small number of chemicals (≤10) with a qualitatively or quantitatively known composition.

Complex mixture – comprises ≥10 chemicals, with a composition which is not fully qualitatively or quantitatively known.(Kienzler *et al.*, 2014)

## Challenges Identified

Humans and animals are exposed to an incalculable number of mixtures, both intentional and unintentional, as a result of exposure via food, consumer products, the workplace and the environment. Combined exposures to mixtures may lead to unacceptable effects, even when individual substances in mixtures are below their individual safety thresholds (specific concentration limits and generic concentration limits under the CLP Regulation). At present, the assessment and management of mixtures is only partly covered by the chemicals legislative framework, which tends to focus on individual substances and, in some cases, intentional mixtures e.g. pesticides and biocides. Unintentional mixtures are difficult to regulate as their composition is often unknown and is subject to change. At present, the assessment and management of unintentional mixtures is limited to pesticide residues in food.(JRC, 2018)

In 2009 a study by the Danish Authorities was published which considered the exposure of toddlers to chemical mixtures in the form of multiple endocrine disruptors (EDs) from multiple sources. The exposure sources considered were food, indoor air and dust, clothes and shoes, contact with toys, application of healthcare or hygiene products and contact with articles (changing mats and bath mats). On the basis of the predicted concentration of various substances it was concluded that there was a need to reduce exposure to anti-androgen and oestrogen substances via the above-mentioned exposure sources.(European Commission, 2012)

It was acknowledged by the Commission in their communication to the Council (2012), that current EU legislation does not provide for a comprehensive and integrated assessment of cumulative effects of different chemicals, taking into account different routes of exposure. Where mixtures contain a substance regulated under different pieces of EU legislation, no mechanism exists for promoting an integrated and coordinated assessment across the different pieces of legislation. The Commission identified that where chemicals have a similar mode of action there is the potential for cumulative effects. The majority of chemical legislation is built on the assessment of individual substances. There is a need to understand where, how often and to what extent humans and the environment are exposed to certain chemical mixtures and temporal changes in exposure to these chemical mixtures. In order to do this, it has been proposed that monitoring and modelling are utilised. At present one the largest areas of concern in mixture assessments, is the lack of data regarding mode of action, including a defined set of criteria for how to characterise or predict a mode of action for data-poor chemicals.(European Commission, 2012)

Challenges in mixture assessment can be separated into three areas: combined exposure, combined effects, and combined risks.

### Combined exposure

As previously mentioned, identifying the composition of unintentional mixtures can be difficult and if certain constituents are not accounted for during assessment, then there can be an underestimation of the risks posed. Sequential exposures to substances and mixtures at different points in time can be difficult to assess, but biomonitoring of chemical concentrations in humans and animals has potential to identify realistic co-exposure.

Chemical monitoring data is increasing as a result of the European Commission platform IPCHEM, but it is still lacking in places and in general, exposure modelling tools require further development. (JRC, 2018)

### Combined effects

At present it is not feasible to test all possible mixtures given the large number of potential combinations. The prediction of mixture effects is based on individual chemicals and this is limited by the lack of information on toxicological effects and modes of action. New modelling tools are required in order to rely less on *in vivo* testing.

### Combined risks

It is not only the hazards presented by chemicals mixtures which pose a problem. Managing the risks from exposure to mixtures also presents a policy challenge. On an individual level, substances or intentional mixtures may be present at a safe level of exposure (≤ specific/generic concentration limit), but the combination of substances or mixtures may pose a risk. Certain mixtures may be regulated under certain sectors, but the lack of regulation under other sectors does not suggest a lack of exposure. Therefore, risk management decisions may need to be taken regarding which chemicals or sources of chemicals should be subject to regulation. In order to do this, priority mixtures of concern need to be identified, as well as their individual constituents which drive their risk.(JRC, 2018)

## Assessment of Chemical Mixtures

There are currently two approaches to assessment of chemical mixtures: testing of the mixture as a whole; or estimating the combined risk based on the concentration and toxicological information of the individual substances within the mixture. International frameworks exist for the assessment of mixtures, outlined by WHO and IPCS.

For intentional mixtures, the composition is known, and assessments can be based on the known constituents and data can be supplemented by tests on the mixture as a whole. This approach is taken for mixtures under CLP, cosmetics, medicinal products for human use and veterinary medicines.

When mixtures originate from a single source, e.g. discharges to the environment from production facilities, if the composition is known or can be identified by analytical methods, then assessments can be made based on knowledge of the constituents. If the composition is unknown, then assessment has to be made based on the whole mixture. Very few pieces of EU legislation require the testing of whole mixtures. However, the Water Framework Directive requirements for water bodies focused not only on individual concentrations of substances, but also their effect in combination.

There are very few examples of assessment of mixtures which originate from multiple sources or exposure occurs through multiple pathways. REACH guidance ahs been developed for multiple sources of exposure to single substances and specific cases for assessment of several closely related and similarly acting substance, e.g. different salts of the same metal. In the workplace, employers are required to assess the risks presented by all hazardous chemical agents in combination and EFSA have developed approaches for taking account of cumulative and synergistic effects when maximum residue limits (MRLs) for pesticides with similar mode of action. EFSA are also developing a methodology for occupational exposure to pesticides with different modes of action.

Work from the Scientific Committees of the Commission has indicated that, under certain conditions, chemicals present in a mixture will act jointly in a way that affects the overall toxicity, particularly those with a common mode of action. Those with a common mode of action can act together to produce combination effects that are greater than the effects of each of the constituents of the mixture individually. In 2012 the Scientific Committees highlighted that the lack of robust evidence available to indicate that exposure to a mixture of chemicals with different modes of action where the individual constituents are present at or below their zero-effect level presents a health concern. Their conclusion in related to human health was “if the intended level of protection is achieved for individual substance, the level of concern for mixtures of dissimilarly acting substances should be assumed to be negligible”.

The Scientific Committees have recommended that for mixture constituents which have a similar mode of action, a dose/concentration addition approach is appropriate. For chemical mixtures where the constituents have different or unknown modes of action, a dose/concentration addition approach may overestimate toxicity of the mixture. This being said, an independent action approach may underestimate toxicity. As such, in order to provide an adequate level of protection, it is proposed that dose/concentration addition approaches should be used for both known and unknown modes of action. (European Commission, 2012) For pesticides, EFSA has proposed a tiered approach for cumulative risk assessment of human exposure to pesticides. There is a possibility that this approach could be applied to other groups of mixtures.(Kienzler *et al.*, 2014)

EDC-MixRisk believe that current EU regulations concerning man-made chemicals underestimate the health risks associated with combined exposure to (potential) EDCs. So far, interdisciplinary collaborations and the integration of multiple methods have proven successful for developing novel approaches for testing and risk assessment of EDC mixtures. These approaches can be used to define acceptable levels of exposure based in epidemiological data or integration of human and experimental data. Currently, whole mixture approaches can only be used retrospectively for chemicals for which epidemiological data are available. For “new” chemicals, a prospective risk assessment is required. EDC-MixRisk have concluded that EDCs and mixtures require complementary models for testing, which cover several molecular, cellular and organismal effects. It is the hope of EDC-MixRisk that identifying and testing a small number of chemical mixtures that are broadly relevant for the exposed population could pave the way for similar efforts at an EU and global level. It is also hoped that new approaches may provide empirical support for estimating the size of a potential additional mixture assessment factor that could take mixtures into account in chemical risk assessment. (Berman *et al.*, 2019)

## Activities to Address Chemical Mixtures in the EU

### The Joint Research Council (JRC)

The JRC provides scientific input to and facilitates discussions with EU regulatory bodies from Commission DGs and Agencies, whilst also being actively involved in international initiatives under the auspices of the OECD and WHO. The JRC is currently researching the use of alternative (non-animal) methods and new strategies for assessing the combination effects of chemicals. They are also exploring the links between mixtures and disease, the interaction effects of chemicals, and the use of biomonitoring data in exposure assessment. The JRC currently collaborates with five EU funded research consortia focusing on chemicals mixtures:

* In the environment – SOLUTIONS;
* For human health – EuroMix, HBM4EU;
* Endocrine disruption – EDC-MixRisk; and
* Alternatives for animal testing – EUToxRisk.(JRC, 2018)

### European Commission

The European Commission was invited by the European Council to “assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to consider appropriate modifications, guidelines and assessment methods and report back to the Council by early 2012 at the latest”.

The EU chemicals legislative framework aims to ensure that, although the general population is exposed to small concentrations of multiple chemicals, none of those chemicals should be present above their individual safe limits. It is suggested by the Commission that REACH could be used as a regulatory instrument to reduce some of the uncertainties around exposure to mixtures.

 Due to almost infinite number of possible combinations of chemicals, the Scientific Committees have identified a set of criteria for setting priorities:

* “Human and/or environmental exposure at significant levels.
* Chemicals that are produced and/or marketed as multi-constituent substances or commercial mixtures with several components and/or active ingredients and/or substances of concern.
* Potential serious adverse effects of one or more chemicals at the likely exposure levels.
* Likelihood of frequent or large-scale exposure of the human population or the environment.
* Persistence of chemicals in the body and/or in the environment.
* Known information of potential interaction at levels of human and environmental exposure.
* Predictive information that chemicals act similarly.
* Particular attention should be paid to mixtures for which one or more components are assumed to have no threshold for its effects.” (European Commission, 2012)

A number of actions were developed in the 2012 Commission communication to the Council on the combination effects of chemicals. In order to strengthen coordination across different pieces of legislation and to promote the integrated assessment of priority mixtures the Commission aimed to establish an ad hoc working group of relevant services and associated Agencies and Authorities (EFSA, ECHA, EMEA, EEA). This working group would bring together the data and oversee the integrated assessment of priority mixtures. It was suggested that where follow up action is required; it would be carried out under the frame of the relevant legislation.

The Commission set themselves a deadline of June 2014 for the creation of technical guidelines to promote a consistent approach to the assessment of priority mixtures across the EU chemicals legislative framework. These guidelines were not intended to replace existing rules or impose additional obligations or burdens on economic operators.

In order to improve understanding of chemical mixtures, the Commission aimed to review monitoring data which is currently collected under EU legislation or generated by EU funded projects, and promote a more coherent approach to the generation, collection, storage and use of chemical monitoring data through the creation of a platform.

The Commission also aimed to examine the opportunities for addressing the knowledge gaps related to: modes of action; grouping of chemicals; predicting chemical interactions; and identifying chemical substances that are the main drivers of mixture toxicity.(European Commission, 2012)

Tables 1-1 and 1-2 identify the status of EU chemicals legislation with regard to the assessment of mixtures.

| **Table 1‑1**: **Summary table – chemical and mixture assessment requirements in European legislation. Intentional mixtures** |
| --- |
| **Legislative area** | **Act**  | **Chemical monitoring and analysis** | **Encouraging alternative methods to animal testing** | **Chemical risk assessment** | **Mixture assessment** | **Prospective RA** | **Retrospective RA** |
| **Human health** | **Environmental health** | **Human health** | **Environmental health** |
| Plant protection products | Reg 1007/2009 | No (Environment)/ Yes (Residues) | Yes | Yes | Yes | Yes – WM approach (for formulation) | Yes | No |
| PPP – AI Requirement  | Reg 283/2013 |
| PPP – Formulation Requirement | Reg 284/2013 |
| Biocides | Re 528/2012 | No (Environment)/ Yes (Residues) | Yes | Yes | Yes | Yes – WM approach, plus risk assessment, if the biocidal product is intended to be used in combination with other biocidal product | Yes | No |
| Human medicines | Dir 2001/83/EC | No  | Not specified  | Yes | Yes | Yes | No | Yes | No |
| Veterinary medicines | Dir 2001/82/EC | No (Environment) / Yes (residues in foodstuff) | Not specified  | Yes | Yes | Yes | No | Yes | No |
| Cosmetics  | Reg 1223/2009 | No | Yes | Yes | Through REACH | Yes | No | Yes | No |
| CLP | Reg 1272/2008 | No | Yes | Yes | Yes | Yes | Yes | Yes | No |
| REACH | Reg 1907/2006 | No | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Food additive | Reg 1333/2008 | Yes (intake)  | No | Yes | No | No | No | Yes | No |
| Feed additive and feed additive assessment  | Reg 1331/2008; Reg 429/2008 | Yes (residue) | No | Yes | Yes | Additive with multiple components: consideration is given for the cumulative effects or WM assessment. No consideration for mixture assessment from different sources.  | Yes | No |
| Source: (Kienzler *et al.*, 2014) |

| **Table 1‑2**: **Summary table – chemical and mixture assessment requirements in European legislation. Generated or coincidental mixtures** |
| --- |
| **Legislative area** | **Act**  | **Chemical monitoring and analysis** | **Encouraging alternative methods to animal testing** | **Chemical risk assessment** | **Mixture assessment** | **Prospective RA** | **Retrospective RA** |
| **Human health** | **Environmental health** | **Human health** | **Environmental health** |
| Environmental Impact Assessment (EIA) | Dir 2011/92/EC | No | No testing | Yes | Yes | Should be addressed | Yes | No |
| Integrated pollution prevention and control (IPPC) | Dir 2010/75/EC | Yes | No testing | No | No | No | No | No | No |
| Waste and waste streams | Dir 2008/98/EC | No, but refers to other legislation, e.g. REACH, IPPC | No | Refers to CLP | Refers to CLP | No | No | No |
| Water Framework Directive (WFD) | Dir 98/83/EC | Yes | No testing | Yes | Yes | Mentioned in Guidance, but not addressed in detail  | No | Yes |
| Groundwater Directive | Dir 2006/118/EC | Yes, with reference to WFD | No | No RA, but contained additional threshold value for pesticides and nitrates | No | No  | No | No | No |
| EQS Directive  | Dir 2013/39/EU | Yes | Yes | No | No RA, but QS are derived from ERA studies | No  | Yes | No | No |
| Marine Strategy | Dir 2008/56/EC | Yes, with reference to WFD | No testing | No | Yes | No | No | No | No |
| Drinking Water | Dir 98/83/EU | Yes | No testing | No RA, but parametric values should be based on a RA method  | No | No | No  | No | No |
| Soil thematic strategy - Soil framework directive | COM(2006) 231 / COM(2006) 232 final, 2006/0086 (COD) | Yes | No | Yes | Yes | No  | No | No | Yes |
| Ambient Air quality and cleaner air for Europe | Dir 2008/50/EC | Yes | No testing | Yes  | Partly  | No | No | No | Yes |
| Food contact material | Reg 1935/2004 | Yes | Not specified | Yes | No | No | No | Yes | No |
| Food contaminant | Reg 315/93/EEC | Yes (food) | Not specified | Yes | No | No | No | Yes | No |
| Feed contaminant  | Dir 2002/32/EC | Yes (feed) | Not specified | Yes | Yes | No | No | Yes | No |
| Maximum residue levels (MRLs) | Reg 396/2005 | Yes | Not specified | Yes | No | Yes | No | Yes | No |
| Protection of the health of workers  | Dir 98/24/EC | Yes | Not specified | Yes | No | Yes | No | Yes | No |
| Toys  | Dir 2009/48/EC | Yes | No testing | No RA but threshold value and refers to CLP | No | Refers to CLP | No | No | No |
| Source: (Kienzler *et al.*, 2014) |

### EDC-MixRisk

EDC-MixRIsk started in 2015 and is a four-year project funded by the Commission’s Horizon 2020 programme. It focuses on the effects on children of mixtures of endocrine disruptive chemicals (EDC), by developing methods for risk assessment. The project has so far developed a novel approach based on identifying and testing real life EDC mixtures which are associated with adverse health impacts on humans. The epidemiological data, provided by the Swedish pregnancy cohort SELMA, is used to create reference mixtures which mimic real life internal exposures. Mixtures are tested in various experimental models and data gathered from these models is used to establish new methods and strategies for mixture risk assessment.

One approach which has been developed is the whole mixture approach. This approach enables more systematic integration of epidemiological and experimental data in mixture risk assessment strategies and complements current risk assessment methods which are based on the single compound approach or assumptions of addition. It is hoped that this new approach for mixture assessment could be incorporated in existing legislations currently dealing with chemical mixtures. This new approach may significantly contribute to more relevant risk assessment and management by providing more reliable empirical information and better reflecting real life scenarios.

EDC-MixRisk have suggested that current and future biomonitoring efforts should include:

* Analyses of complex mixtures;
* Assessment of adverse health outcomes in the same cohorts;
* Good quality toxicity data to identify hazardous chemicals;
* Long term resources to follow temporal trends and evaluate risk management measures.

EDC-MixRisk recommends that legislative measures should be taken to ensure full insight into which chemicals are used in products, materials and articles on the European market. It is suggested that this wold enable the allocation of research efforts to chemicals and mixtures of concern, increasing the diversity of chemicals under scrutiny and promote informed consumer purchasing decisions. Innovations at the cross section of science and policy making should be facilitated by creating platforms for collaboration between regulatory agencies, industry and academia. (Berman *et al.*, 2019)

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