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Public consultation on draft guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals

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Public consultation on draft Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals

*Select the chapters you want to comment

- [ ] General comments
- [ ] Abstract
- [ ] Summary
- [x] 1. Introduction
- [x] 2. Mixture risk assessment
- [ ] 3. Problem formulation
- [x] 4. Exposure assessment
- [x] 5. Hazard identification and characterisation
- [x] 6. Risk characterisation
- [ ] 7. Reporting a mixture risk assessment
- [x] 8. Way forward and recommendations
- [ ] References - not for comment
- [ ] Glossary
- [ ] Abbreviations - not for comment
- [ ] Appendix A – Uncertainty analysis
- [x] Appendix B – Case study 1: Human health risk assessment of combined exposure to hepatotoxic contaminants in food
- [ ] Appendix C – Case study 2: Animal health risk assessment of botanical mixtures in an essential oil used as a feed additive for fattening in chicken
- [ ] Appendix D – Case study 3: Quantifying the impact of binary mixture interactions on hazard characterisation in bees

1. Introduction

- [ ] 1.1. Background and Terms of Reference as provided by EFSA - not for comment
- [ ] 1.1.1. Background - not for comment
- [ ] 1.1.2. Terms of Reference as provided by EFSA - not for comment
- [ ] 1.2. Interpretation of the Terms of Reference
- [x] 1.3. Existing EFSA regulatory mandates for mixture risk assessment
- [ ] 1.4. Rationale for harmonising methods for mixture risk assessment across human health, animal health and ecological areas
- [ ] 1.5. Audience and degree of obligation

1.3. Existing EFSA regulatory mandates for mixture risk assessment

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General comment:
CHEM Trust welcomes EFSA`s activities on the assessment of combined exposures to chemical mixtures because there is a clear need to move forward to address risks from cumulative exposures (simultaneous

and/or subsequent exposures to multiple chemicals). So far EU chemicals policy has failed to develop a response to the potentially very harmful combination effect from chemicals. Wildlife and humans are now exposed to many different substances from multiple sources, many of them with problematic characteristics such as endocrine disrupting properties. A Danish report from 2017 highlighted the concern about current exposure levels of antiandrogenic substances and the resulting risks for children and unborn children from the combined effects (Exposure of children and unborn children to selected substances, Danish Environmental protection Agency, 2017 ISBN: 978-87-93529-84-7).
CHEM Trust takes the view that additional uncertainty factors are needed to address risks from cumulative exposures. Moreover, at a policy level, generic risk considerations and substitution should be applied more frequently to reduce exposures to harmful chemicals across the board.
Recommendation for the introduction (Chapter 1):
- It should be clearly stated that whilst suitable scientific tools are available in principle and described in this guidance document, the current risk assessment methods in use under EU regulation usually do not take proper account of these joint actions. This may lead to a systematic under-evaluation of risks. It can no longer be assumed that setting acceptable daily intakes will lead to lifetime protection in the case of chemical exposures.
- It would be useful to add some further explanation about the scope of the guidance and in which cases and scenarios in will be applied and for what purpose. For example, will mixture effects taken into account in the pesticide authorisations which are currently based on a single substance risk assessment? It would be very important to develop more prospective approaches at the market approval stage and pre-empt expected situations of co-exposures.
- In relation to human health, even if there is the ability within the Pesticides Regulation to look at the joint toxicity of certain pesticides in some instances – the risk assessment for humans would currently not take into account the concurrent exposure that may occur to industrial chemicals in consumer products. Neither does it take into account the existing body burdens of many pollutants. In short, ‘mixtures’ assessment does not straddle the legislative ‘silos’ that currently exist, and does not look at exposure from even all chemicals with similar modes of action to which humans are exposed via the diet, via inhalation, or via the dermal route. Many of these chemicals will have additive action at specific endpoints. Single substance risk assessment is not adequately protective to account for possible mixture effects, see e.g. Martin et al. Environmental Health 2013, 12:53 http://www.ehjournal.net/content/12/1/53.
These limitations should be highlighted more clearly.

2. Mixture risk assessment

- [ ] 2.1. Key terminology
- [x] 2.2. Scientific basis of mixture assessment
- [ ] 2.3. Approaches to risk assessment of chemical mixtures
- [ ] 2.4. Tiering in mixture risk assessment
- [x] 2.5. Existing guidance for mixture risk assessment
- [ ] 2.5.1. Human and animal health risk assessment of mixtures
- [ ] 2.5.2. Ecological risk assessment
- [ ] 2.6. Harmonised overarching framework
- [ ] 2.6.1. Assessment sequence
- [x] 2.6.2. Dose addition as the default model
- [x] 2.6.3. Bridging data gaps

2.2. Scientific basis of mixture assessment

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Line 419
The text says that combined effects can be larger or smaller. How often have studies reported smaller effects in mixtures? We suggest to reformulate the sentence to reflect the fact that the majority of mixture experiments reported higher effects, and even in cases when all substances are present below their individual effect concentrations.

2.5. Existing guidance for mixture risk assessment

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Line 614
We are very sceptical concerning the application of the TTC approach as its scientific validity is dependent on the reliability of the underlying data which are often insufficient, in particular for chronic toxicity and endocrine disruption. Moreover, this concept which determines the TTC threshold values that will be applied, and the use of this approach, which is based on a presumption of safety below threshold values, is likely to result in inaccurate assessments for many chemicals.

2.6.2. Dose addition as the default model

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Line 726
CHEM Trust strongly supports the application of dose addition as the default model as extensive dose-response data are usually not available.

2.6.3. Bridging data gaps

5000 character(s) maximum

Line 745
The issue of data gaps cannot be overemphasized and solutions for ways forward should be addressed more prominently. For example, recent attempts to conduct a mixture risk assessment for pesticides failed due to lack of suitable single-chemical data (see Kortenkamp and Faust, Science 361 (6399), 224-226, 2018, DOI: 10.1126/science.aat9219). Thus the likelihood of getting stuck due to data gaps on exposure or toxicity is quite high and more work is needed to close data gaps.

4. Exposure assessment

- [x] 4.1. General considerations
- [ ] 4.2. Whole mixture approach
- [ ] 4.3. Component-based approach
- [ ] 4.4. Stepwise approaches
- [ ] 4.4.1. Whole mixture approach
- [ ] 4.4.2. Component-based approach

4.1. General considerations

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It would be helpful to develop some scenarios for priority exposure situations of concern. For example, to assess the overall daily exposure of a child to neurodevelopmental toxicants it needs to be expanded to include chemicals from all sources, including indoor air pollution, dust and food contact materials (see CHEM Trust report `No brainer. The impact of chemicals on children`s brain development: a cause for concern and a need for action, http://www.chemtrust.org/brain/) .
We support the view that the uncertainty factors currently applied are not sufficiently protective to cover mixture effects. There is a need to introduce an extra uncertainty factor to take account of multiple chemicals from multiple routes, including co-exposures from those arising from sources not controlled by the legislation in hand.

5. Hazard identification and characterisation

- [ ] 5.1. General considerations
- [ ] 5.2. Characterisation of mixtures and their similarities
- [ ] 5.3. Whole mixture approach
- [ ] 5.3.1. Data availability and tiering
- [ ] 5.4. Component-based approach
- [x] 5.4.1. Grouping chemicals into assessment groups
- [x] 5.4.2. Refinement of Grouping
- [x] 5.4.3. Data availability and tiering
- [ ] 5.4.4. Response addition
- [x] 5.4.5. Dealing with interactions
- [ ] 5.5. Stepwise approaches
- [ ] 5.5.1. Whole mixture approach
- [ ] 5.5.2. Component-based approach

5.4.1. Grouping chemicals into assessment groups

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Line 1339
Assessment groups should not be made too narrow and the analysis should not be overcomplicated. It will always depends on question that needs to be answered, so the illustration of some specific examples /scenarios would be useful to make that clearer.

5.4.2. Refinement of Grouping

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Line 1376
This suggested approach seems overly complicated and burdensome and requires lots of data which may even have to be generated first. The question is why it would be justified to make these additional analyses and what the added value would be.

5.4.3. Data availability and tiering

5000 character(s) maximum

Line 1439
We are sceptical about the feasibility of the approaches described in this chapter as the data will not be available in the majority of cases.

5.4.5. Dealing with interactions

5000 character(s) maximum

Line 1544
The application of an uncertainty factor to address interactions seems a good way forward. In addition, more uncertainty factors are needed more to reflect co-exposures to other substances from other sources (see also comment in uncertainty analysis).

6. Risk characterisation

- [ ] 6.1. General considerations
- [ ] 6.2. Whole mixture approach
- [ ] 6.3. Component-based approach
- [ ] 6.3.1. Dose addition
- [ ] 6.3.2. Response Addition
- [ ] 6.3.3. Interactions
- [x] 6.4. Uncertainty Analysis
- [ ] 6.5. Interpretation of risk characterisation
- [ ] 6.5.1. Whole mixture approach
- [ ] 6.5.2. Component-based approach
- [ ] 6.6. Stepwise approach

6.4. Uncertainty Analysis

5000 character(s) maximum

Line 1840
It will be impossible to know the complete exposure profile to which humans and wildlife are exposed, and as there will be immense variation depending on location, lifestyle etc. Therefore it would be important to routinely include extra assessment factors to cover mixture effects, particularly where chemicals act on an endpoint which is common to many chemicals. The RIVM proposed a factor of 10 for environmental safety assessment under REACH (Broekhuizen et al RIVM Report 2016-0162). In CHEM Trust view this factors need to be larger when applied across the silos, i.e. including not only industrial chemicals but also pesticide, biocides and pharmaceuticals and other uses.

8. Way forward and recommendations

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Line 1972
We recommend including some principle recommendations and ways forward to ensure a high level or protection from cumulative effects of chemicals for human health and the environment in Europe:

- It should be clearly stated that current EU legislation does not provide for a comprehensive, integrated assessment of cumulative effects taking into account different routes of exposure and different product types. The policy, lagging many years behind the most up-to-date research, needs to be urgently addressed at the EU regulatory level. EU Ministers' concerns were already expressed at the December 2009 Environment Council meeting, outlining that the environment and the health of European citizens may not be properly protected from the combined effects of hazardous chemicals, particularly those that can disrupt hormones.
- Therefore, interim measures should be applied immediately to reduce exposures for all situations of known co-exposures to the general population, in particular to protect vulnerable groups and children.
- The priority should be more on developing ways forward for prospective mixture toxicity assessments rather than testing existing environmental mixtures. This would mean taking into account combination effects when setting environmental quality standards or in all legislation dealing with market approvals or authorization schemes.
- In its Communication on 'The Combination effects on chemicals', 2012, the Commission had promised a report reviewing the progress and experience associated with the actions on mixtures by the end of June 2015. However, the report has still not appeared.
- A risk assessment focusing on single substance should no longer be used to decide on safe use for

substances reported to contribute to the same adverse outcome either because they have the same mechanism of action or mechanisms of action that converge. Therefore, a regulatory approach for cumulative risk assessment needs to be developed that spans across the regulatory silos (Evans et al, Sci Total Env, Volume 543, Part A, 1 February 2016, Pages 757-764, https://doi.org/10.1016/j.scitotenv.2015.10.162)

• Data gaps on exposure and toxicity present an obstacle to doing mixture risk assessment and approached for closing theses data gaps often lead to many uncertainties. Therefore more work should be invested in routinely applying an extra assessment factor in risk assessment to cover mixture effects, particularly where chemicals act on an endpoint which is common to many chemicals.

Appendix B – Case study 1: Human health risk assessment of combined exposure to hepatotoxic contaminants in food

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One of the most inisightful and important mixture toxicity studies was the work from Martin et al, Environ Health Perspect. 2017 Aug; 125(8): 087016: A Human Mixture Risk Assessment for Neurodevelopmental Toxicity Associated with Polybrominated Diphenyl Ethers Used as Flame Retardants
We propose to add this as a case study to the guidance document.

Upload file(s) if necessary

*Do you need to upload file(s)?

- ○ YES
- ◉ NO

Background Documents

Draft MIXTOX Guidance.pdf

Privacy Statement on the Draft MIXTOX Guidance PC.pdf

Contact

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