**TOX/2018/34**

# COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

## EFSA public consultation on the MIXTOX guidance

### Introduction:

1. The European Food Safety Authority (EFSA) have launched a public consultation on a draft Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. This document describes harmonised risk assessment methodologies for combined exposure to multiple chemicals for all relevant areas within EFSA's remit.

2. The deadline for the submission of comments is Saturday, 15th of September 2018.

3. Members were invited to submit their comments on the draft guidance to the Secretariat. These have been compiled and presented in Annex 1 of this document for discussion. Once the comments have been agreed, they will be submitted to EFSA by the Secretariat.

### Questions to the Committee:

I. The members are invited to comment on this document.
II. Do the Members have any other comments?

**Secretariat**

**September 2018**

# EFSA public consultation on the MIXTOX guidance

## Background:

1. The European Food Safety Authority (EFSA) have launched a public consultation on a draft Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. This document describes harmonised risk assessment methodologies for combined exposure to multiple chemicals for all relevant areas within EFSA's remit. These are: human health, animal health and ecological areas.

2. The Members' comments on the draft Guidance are presented below for discussion and are addressed in two sections: The general comments on the document and specific comments where particular parts of the document are being discussed.

3. The aim of this document is for the Members to discuss and agree on the comments that will be submitted to the EFSA for consideration.

## General comments:

4. It was noted that this is a useful guide to the assessment of the risks from combined exposure to multiple chemicals, covering a range of scenarios, from human health to ecological impact. Both whole mixtures and component-based exposures are covered. The focus is on dietary exposure, which is the intention, and whilst the general principles would be applicable to other exposure routes, additional considerations would be necessary in such an assessment.

5. Despite the guidance being relatively comprehensive, a couple of areas which are not addressed in any detail, which can be important in such assessment were identified. The first of these is the chemical space to be covered. This is clearly part of problem formulation. Some clarifying text on this difficult issue would be helpful. There is little specific guidance on the use of MOA/AOP in deciding which chemicals should be included in assessment groups. Whilst this may well vary with the problem being addressed, some guidance on the scientific issues involved and how such information could or should be used would be helpful. Finally, whilst a helpful glossary is provided, there are a number of additional concepts and terms that would benefit from inclusion, with clear definitions.

6. The lack of emphasis on the importance of human biomonitoring and epidemiological evidence when assessing mixture effects on health was also highlighted.

**Specific comments:**

7. It might be helpful to define what is meant by harmonisation in this guidance. For example, it is stated on line 378 that differences in protection goals are not subject to harmonisation. But this would not prevent the same approach being used for mixture risk assessment in the different scenarios; only the inputs would differ.

8. 1.3. Legislation is possibly easier to interpret if the concept of intentional and unintentional/incidental mixtures is used. Other than pesticide residues (and dioxin-like compounds), most of the legislation relates to intentional mixtures (constituents present in a substance or product). It might also be helpful to include definitions of some of these terms (chemical, constituent, substance, ingredient, product, etc).

9. Table 1. Under Reference Point, mention is made of Critical Effect. This should be defined, as should Common Effect.

10. Line 418: The timeline for this is potentially misleading. Pharmacologists have been well aware of the phenomenon of dose/concentration addition, and other possible consequences of combined exposure, from the first half of the 20$^{th}$ century. Albeit toxicologists were either unaware of this or ignored it for a number of years. But the text should not imply that knowledge of combined effects is recent.

11. Line 425: This section states that 'the overall evidence on combination effects indicates that combined effects can arise when each mixture component is present at doses around or above its no effect level…'. Since uncertainty factors spanning orders of magnitude are typically applied during the risk assessment process for human health effects, it seems likely that exposure to each mixture component will usually be significantly lower than the corresponding no effect level. Under these circumstances, a specific mixture risk assessment would be unnecessary. The text should address this point.

12. Line 429: This will enable the hazard of the mixture to be assessed. But risk assessment also requires an estimate of exposure, which for a whole mixture may be a complex exercise (as discussed later in the document).

13. Another comment on this line was that the text gives the impression that the only reason for not assessing each and every mixture in toxicity tests is one of practicality and logistics. In order to avoid unnecessary animal testing, this text should also make clear that there is no scientific justification for assessing each and every mixture in toxicity tests in order to address human health effects.

14. Line 438: The text here is around interactions that can occur between chemical molecules and target molecules. However, much of the issue in assessing risk from mixtures is about not just primary interaction at a toxicophore, but about interaction at different key events in an AOP/MOA. This is then a question of

additivity at the next level of biological complexity. A critical issue is the exposure level for which the assessment is being performed.

15. Line 444: “when the toxicity of the components is known”. This seems very straight forward but for such predictions to work, that knowledge must encompass all potential, relevant endpoints, for which there might be additivity, including well-defined reference points for all common effects (at least for higher tier assessments).

16. Line 450: “and response addition provide reasonable approximations”. There were extremely few examples of this and those that are known are in the field of ecotoxicology.

17. Line 453: In the context of human and animal dietary risk assessment, it is questioned whether a specific assessment step is required to evaluate potential factors leading to synergistic interactions. Toxicological end-points used in dietary risk assessment (ADI, ARfD) are calculated by applying uncertainty factors to the NOAEL; thus the permissible dietary exposure is significantly lower than the dose at which a synergistic interaction could be observed

18. Line 459: “is available in the vast majority of cases for binary mixtures”. This needs to be reworded. It is not correct that the vast majority of binary mixtures show synergy, which is the current meaning of the sentence.

19. Line 469-70 (and line 638): “and the indirect consequences on the structure and functioning of the European Union”. This would be an extremely dramatic outcome.

20. Line 527: “In the pesticide arena, the MoA concept is used in a similar way as in the human and animal health area.” It is not clear what is meant here.

21. Line 534: “but [AOP] has so far found little practical application in mixture risk assessment”. Given the relative stage of mixture risk assessment and of the AOP approach, this statement is probably unnecessary and provides little useful information.

22. Line 546: “must exhibit decreased conservatism”. It is not that higher tiers are necessarily less conservative, but rather they should be less uncertain, i.e. there should be greater certainty, the higher the tier.

23. Line 549: “one progresses to risk management”. Risk assessment always progresses to risk management. Presumably what is meant here is risk mitigation or control?

24. Line 564-565: But this should be taken into account in the uncertainty assessment.

25. Line 575: “with all chemicals being grouped together”. This rather begs the question of what is meant by **all** chemicals. In practice, there is always some grouping, either explicit or implicit, based either on exposure and/or effect, even at tier 0.

26. Line 623: The conclusion from a lower tier assessment is either that there is no concern, or that the possibility there is a concern cannot be excluded. It is not correct to say “or that there are concerns”, even is the assessment is stopped at this point. It is important that the strength of any conclusion is correctly communicated.

27. Line 739-740: In the case where exposure to all components is below the respective reference value, presumably an estimate of response could be obtained using a simple algorithm.

28. Line 872: A difficulty in any risk assessment of combined exposures, not well addressed in guidance to date, is the scope of the chemical space that is to be considered in the assessment. Defining this is necessary before any subsequent consideration. Often it is implicit, but it part of problem formulation, and there should be transparency of what is within scope for the assessment. In the case of the PPR Panel, this is relatively clear, it is all pesticides that might occur on food consumed within the EU (i.e. those that are approved for use in the EU and those that might occur as residues in imported food). But for almost all other chemical areas, there is no clear, or obvious, definition.

29. Line 916: Again, if lower tier, it is not “suggests insufficient protection” but provides insufficient assurance of protection. The Guidance should avoid promulgating the view that not passing a lower tier is in itself an indication that there is necessarily a problem. There may be, but this cannot be known without refinement of the assessment (albeit the risk manager may decide to take precautionary action without waiting for further refinement).

30. Line 1056: A marker substance should presumably also account for an appreciable fraction of the toxicity of the mixture.

31. Line 1074-1080: The issue of taking account of information on toxicokinetics and toxicodynamics to determine likelihood of co-occurrence is not well described in existing guidance. In the case of toxicokinetics it is relatively straightforward, although the information may not always be available. What should be done in such circumstances? In the case of toxicodynamics, the situation is more complicated and it might be helpful to provide some further guidance on this.

32. Line 1200: Will the use of RPFs not depend on the tier?

33. Line 1229: Does this not depend on the mechanism of genotoxicity. For example, would there be no consideration of assessing the combined risk from exposure to a group of topoisomerase inhibitors?

34. Line 1329-1330: Is the BMDL not the preferred reference point, even if, for example only adequate in vivo data are available? Consider rewording text here?

35. Line 1343-1344: There is no definitive scientific guidance available on how to group chemicals for a combined risk assessment. The basis is often determined by the risk manager, which will include a number of considerations, not all strictly scientific (as discussed in the document), and will be specified in problem

formulation. But there are occasions when it is decided on an ad hoc, scientific basis. Here, some specific guidance might be of value, to make transparent what is already being done for example by CONTAM. Why group dioxin-like compounds, but exclude PAHs, all of which act on the AHR. Why group phthalates and PFAS separately, when both act on PPARalpha? There are good reasons for this, but greater clarity would be helpful.

36. Line 1366: Whilst accepting that MOA/AOP data are often not available (though methods are being developed to help impute this), rather than target organ, common adverse outcome/pathological effect is preferred (see PPR Panel CAGs, and as indicated later in the document).

37. Line 1401-1402: Some of the considerations listed would be used in a weight of evidence assessment for a single chemical. For example, an effect seen at only one dose level (not the highest dose), with no dose-response relationship would likely be considered not substance-related. Why use a different approach for a combined exposure assessment? Or alternatively, why not use the same approach for individual chemical assessment, albeit it would add appreciably to the work load. Has a sensitivity analysis been conducted to determine the added value of including compounds with a low probability of CAG membership, given that each compound added incurs a penalty in terms of resource and time required to complete the assessment.

38. Line 1419-1421: Note that such data may be particularly useful in **excluding** a common AOP/MOA.

39. Lines 1473 & 1477 (also line 1737): These lines are potentially contradictory, in that the compound for which the toxicological data are most robust will not necessarily be the one that it is most toxic.

40. Line 1478: TEFs could be better explained here. Perhaps clarify the difference between a TEF and an RPF?

41. Line 1494-1495: How is it envisaged that knowledge of AOP/MOA will be used to refine the grouping? Will compounds with clearly different AOPs/MOAs not be considered members of the same group? What if they produce the same adverse outcome. Will the initial group be split into sub-groups, each considered separately?

42. Line 1592: This does not seem entirely scientific. The evidence for synergy at human relevant exposures, i.e. below respective reference values is all but non-existent. The occurrence of synergy at effect levels should not in itself be a basis for an extra uncertainty factor, without a more robust scientific case. Or is this an example of the application of the precautionary principle? If so, this should be clearly stated.

43. Interactions at effect levels are more likely for compounds that do not share an AOP/MOA. Hence, paradoxically, it is those combinations that would otherwise not be considered to show an increased risk in combination (e.g. PBO plus any one of many pesticides), that would be affected. In such cases, to what would the

additional factor be applied, if the compounds are not otherwise expected to show dose addition?

44. Line 1604: Again, the magnitude of any interaction is likely to be dose-dependent. For example, if a high dose of A completely inhibits the detoxication of B, the interaction could well exceed 10, whilst at lower, though still unrealistic, dose levels, where inhibition is less than complete, the interaction might be only 2. This section would benefit from some further clarification.

45. Line 1902: Presumably this is covered in more detail in the separate guidance on mixtures of genotoxic compounds? The situation is complex, and there are nuances not apparent in the brief description given here.

46. Line 1917: It should be possible to model the necessary factor based on the variance of the toxicity data, rather than just choosing a number. Will any guidance be provided on this? Human exposure is usually below one hundredth of the NOEL/BMDL10. Even if one accepts that humans are more sensitive than the tox species, the HBGV applies to a potentially sensitive sub-population and so this needs to be taken into account in estimating population level combined risk from multiple chemicals, where there is response addition.

47. Line 1963: In table 6, mention is made of “Assessment Group”. This probably needs to be expanded, to include more than just the components to be considered. For example, the chemical space under consideration should be indicated; the principles for grouping chemicals should be clearly stated.

48. Line 2297: file:///C:/Users/Chris/Downloads/Risk-Assessment-Procedures_Levy_9.pdf This is not an accessible URL (it was the location on the author’s computer).

49. The comments below address the Glossary.

50. The reference for ADI and Adverse Effect is EFSA, 2013, but there are two references to EFSA in that year. The definitions are different from those given on the EFSA website at https://www.efsa.europa.eu/en/glossary-taxonomy-terms

51. AOP: What is meant by “AOPs may be related to other mechanisms and pathways as well as to detoxification routes”?

52. Aggregate exposure: Does this not also include different routes (e.g. dermal, oral).

53. Antagonism/synergism: For pharmacological antagonism/synergism, the use of the term “toxicity” is not necessarily appropriate. Certainly not in human medicine.

54. Combined Margin of Exposure: The definition is not quite correct.

55. Complex mixture: Why include recommendation in a definition? There are no such recommendations for “component-based”.

56. Hazard Index: The reference value may not be based on the common effect.

57. Identity of mixture: This goes from a very general to a very prescriptive definition. Is it possible to meet all of these requirements in all of the assessment performed by EFSA?

58. Index chemical: The definition provided is that widely agreed. But note that contrary to the main text, no mention is made of this being the most toxic, or likely the most toxic compound.

59. LOD and LOQ: Definitions should be more general than for a pesticide.

60. Marker substance: Does the substance not also have to be representative of the effects of the mixture in some way?

61. Stability: No definition is provided. Is a glossary the lpace to provide instructions/guidance? (“The stability of the mixture should be evaluated”).

62. Regarding Line 2628 in Appendix A: Consideration might be given to the use of sensitivity analysis here, when this might be appropriate, with some guidance on the parameters that should be explored.

**Secretariat**
**September 2018**