Committee Procedures

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Draft EFSA Scientific Committee Opinion on scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals

1.84 In May 2021, EFSA released draft guidance, prepared by its Scientific Committee, on the grouping of chemicals for risk assessments of combined exposure to multiple chemicals. The Committee were asked to comment on the draft opinion as part of EFSA's public consultation process.

1.85 Overall, the Committee agreed that the proposed guidance provides a pragmatic and scientifically sound approach for grouping chemicals for a combined risk assessment.

1.86 The main comments of the Committee were as follows:

· Sorting different chemicals into assessment groups on the basis of common key events is appropriate but for data-poor chemicals, this may result in the formation of very large chemical assessment groups (CAGs), particularly if grouping is done on the basis of adverse effects, such as potential liver effects.

- Although the scientific criteria for dose addition were provided in the draft EFSA guidance, the underlying assumption of dose addition is not clearly stated.
- With regards to the prioritisation methods for grouping chemicals into assessment groups, the default threshold values appeared to be rather arbitrary, and not entirely supported by scientific data; thus, the threshold values should be tested, and re-evaluated after some time.
- Appendix C ('statistical methods to study the probability of combined risk or combined exposure') was not directly referred to in the draft guidance document. It would be useful to have some examples where these statistical methods were used, such as use of correlation matrices for multivariate

pattern analysis. Furthermore, it may be possible to obtain a high probability of co-exposure (‘r’ value) from assessment of a low number of chemicals.

Draft EFSA Scientific Committee Opinion on biological plausibility of non-monotonic dose responses and their impact on the risk assessment

1.87 In 2016, the European Food Safety Authority (EFSA) published the results of a contracted-out report on a systematic review of the existing literature where signs of non-monotonic dose responses (NMDRs) had been observed (Beausoleil et al., 2016). In the report, the scientific evidence for such NMDRs was assessed with a systematic review being performed in line with the EFSA guidance. The report extracted dose-response datasets from studies having at least 5 dose groups, which were then analysed by the PROAST software package. The strength of the evidence was characterised using visual/statistics-based checkpoints.

1.88 The EFSA Scientific Committee (SC) was asked to prepare a scientific opinion on the biological relevance, if any, of the apparent non-monotonic dose responses identified in the commissioned report and to address the possible consequences for the human health risk assessments conducted by EFSA. The COT was asked to comment on the opinion as part of the public consultation process. The opinion is a review of the previous methods used for assessing the presence of non-monotonic dose responses, not of the responses.

1.89 The COT made a number of specific comments which are presented below:

- A critical review of the key studies claiming NMDR is needed to compare against, for example, OECD guidelines, and to more fully address randomisation.
- Some of the evidence supporting the study showing a biphasic effect on heart rate was not included, suggesting that the conclusion regarding NMDR, or otherwise, could be seen as biased.
- Consideration was not given as to whether NMDR might affect the upper and lower confidence limits of the Benchmark dose (BMD), even if the curve was fitted only to those data points before the sign of the dose-response changed.

- The implications of NDMR of key events at low doses in the context of homeostatic control needs greater consideration.
- The opinion concludes that if an effect for which NMDR is observed is an apical effect and NMDR is supported by further experimental work, no further investigations are needed. The corollary of this is that when such an observation was not supported by further experimental investigations, more work was needed. This meant that the opinion only provides for two possibilities 1) a conclusion of NMDR or 2) that more work was needed.
- Ethical justification is needed for the increased animal use that would be necessary in order to have sufficient data points to fully explore non-monotonicity. Moreover, possible confounders should be taken into account, and study design reviewed carefully before committing further resources to investigating possible nonmonotonicity.
- It was unclear whether the Scientific Committee's view is that there are additional data on apical effects suggesting that relevant NDMR do occur; and, if this is the case, then it is unclear why these were not considered in the earlier reports. Conversely, if the data suggested these effects do not occur, then it appears to be unclear why there is emphasis later on the need to consider the possible implications of NMDR at low doses, which should be investigated on a case by case basis (e.g. "in cases where biological considerations or previous results suggest that NMDR may be present"). Hence, the overall message of this opinion could be clearer.

EFSA draft opinion on "Identification and prioritisation for risk assessments of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food" and "draft protocol for the exposure assessment as part of the safety assessment of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food"

1.90 EFSA published a “draft opinion on identification and prioritisation for risk assessments of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food” and a “draft protocol for the exposure assessment as part of the safety assessment of phthalates, structurally similar substances potentially used as plasticisers in materials and articles intended to come into contact with food” for public consultation on the 5th of November 2021.

1.91 The new assessment follows on from EFSA’s previous update on the risk assessment of five phthalic acid esters (ortho-phthalates), namely di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2- ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP) for use in FCMs, in December 2019.

1.92 The Committee was asked to comment on the draft opinion as part of the public consultation process.

1.93 The main toxicological concern for phthalates are adverse effects on reproduction, with a mode of action involving fetal testosterone reduction. It is difficult to group phthalates for hazard assessment purposes, given that reproductive toxicity is not the main toxicological outcome for all substances (i.e., DIMP and DIPP). Oher compounds with different toxicities have yet to be assessed, including some higher molecular weight phthalates. The current EFSA prioritisation list is bases on the previous assessment date of phthalates. However, the COT some of these compounds were currently undergoing further assessment by ECHA, and hence additional data with a focus on genotoxicity and reproductive effects may be forthcoming.

1.94 Overall, the approaches proposed by EFSA to prioritise phthalates and the corresponding assessment of their exposure are logical and pragmatic. However, until a complete list and toxicological profile for these substances is available, further comment on the (hazard) assessment would prove difficult.

1.95 Clearer information on exposure assessment would be helpful. A deterministic approach can result in an overestimation of exposure while a probabilistic approach could be potentially more realistic, especially if human biomonitoring is used to validate the findings. It is a positive step that the EFSA approach appears to be integrating human biomonitoring data. However, Members further information should be provided on how PBPK modelling would be used to interpret the human biomonitoring data.

1.96 It may prove difficult to exclude and/or separate occupational exposure within biomonitoring data. Occupational data may contribute significantly to overall exposure, potentially more so than the diet. A questionnaire on occupational exposure may be beneficial to gather additional information on this.

1.97 The exposure protocol Is sensible and it is useful to include exposure in EFSA's prioritisation process. However, until data are available and estimation of combined exposures is possible, the current approach is mostly theoretical.

1.98 EFSA will not be considering the UK population as part of their exposure assessment, hence the FSA may need to consider how to follow up on EFSA's evaluation from a UK perspective.

Public Consultation on Code of Practice for Scientific Advisory Committees and Councils

1.128 The Code of Practice for Scientific Advisory Committees and Councils' (CoPSAC) applies to science advisory committees and councils affiliated to the UK government that provide independent expert advice to facilitate decision making. CoPSAC has been revised based on feedback received from Committee and Council stakeholders, and a wider consultation was now taking place. The consultation was aimed at academics and other experts who provide science advice to the UK government and sought views on the independence, transparency, diversity, and inclusion aspects of the CoPSAC in particular.

1.129 The Committee made a number of comments.

- In the recruitment section, there needed to be a mention of how to increase diversity through different channels of advertisement.
- Further clarification was needed to distinguish declarations of interest and conflicts of interest.
- More clarity is required on how SAC Members are appointed.
- More information was needed on lay membership. The document implies that the appointment of lay Members is not mandatory, and there is also a need to clarify the expectations of lay Members.
- Section 5.5 concerning liability might be perceived as unintentionally negative. The penalty section needs to be revised and details on conduct need to be made clearer.
- The Committee noted section 7.1 on the environmental impact, including attendees' travel. Whilst the environmental impacts are considered to have been lower for virtual meetings, the quality of discussions in virtual versus

in-person meetings may differ. Confidentiality may need to be reviewed, as this may be harder to control in a virtual meeting. However, virtual meetings may allow for greater diversity, as they may permit access for individuals who might otherwise be unable to attend in person. For future meetings, hybrid options could be useful.

- Guidance on the retention of both digital and physical documents by Members would be helpful.