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European Food Safety Authority

To:

Executive Director Dr. Bernhard Url

Scientific Committee Chair Dr. Simon More

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

Dear Dr. Url,

Dear Prof. More,

The Food Packaging Forum (FPF) is a charitable, science-based organization dedicated to raising awareness for hazardous chemicals in all types of food contact materials and articles. We welcome the opportunity to provide input from our scientific perspective on the EFSA Scientific Committee Opinion on non-monotonic dose responses (NMDRs). We have utilitzed the normal EFSA online interface for submitting our comments (s. Annex). However, **there are several shortcomings of such severity in this Scientific Opinion that we think it is important to bring these to your attention**.

1. Importance of NMDR for chemical risk assessment and insufficient funding

The issue of NMDR is critically important because it may require that the basic assumptions of chemical risk assessments are revised. The EFSA Scientific Opinion inadequately addresses this important topic, allegedly due to insufficient funding ("The available resources did not allow performance of a new systematic review" (line 249); "Considering the time and resource limitations" (line 202)). For such an important topic that is questioning the current chemical risk assessment approach fundamentally, **it is surprising that apparently no adequate resources were provided by EFSA for carrying out the task properly**. We urge you to provide adequate funding for finalization of this important Scientific Opinion.

2. Biological Plausibility as central to the Scientific Opinion

The Terms of Reference for this Scientific Opinion are described as follows: "The Scientific Committee was requested to prepare a scientific opinion on the biological relevance, if any, of the apparent non-

monotonic dose responses identified [...]" (line 177). This is concerning for two reasons.

Firstly, the commentary ("if any") may imply that the authors of the Scientific Opinion tackled the task with a bias against the plausibility of the biological relevance of NMDR, which would defy the purpose of providing a science-based, objective opinion on the matter—however, nothing else should be acceptable for a government agency. Indeed, the prevalence of commentary throughout the Scientific Opinion, as well as citations of work by biased authors (Mushak and Elliott 2015), indicates that this kind of bias may indeed be present. Therefore, **it is questionable whether this Scientific Opinion adequately does justice to the current scientific understanding of NMDR, or if it suffers from bias of the involved Scientific Committee members and EFSA staff who were responsible for its writing**. Further, it is unclear whether scientists with expertise in NMDR and endocrine disruption were consulted or involved in preparing the Scientific Opinion, as authorship is not indicated in the document, for unclear reasons.

Secondly, the term "biological relevance" in the title of this Scientific Opinion implies that for any NMDR observed in a scientific experiment the underlying mode of action, or even mechanism of action, must be known in order to validate an observation that is statistically significant. Such a requirement stands in stark contrast to chemical hazard characterization practice: when findings of monotonic dose responses are assessed, it is not common to determine underlying mechanisms of action. We refer to a statement made by Austin Bradford Hill (1965) about biological plausibility: "*It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand.* ***What is biologically plausible depends upon the biological knowledge of the day***."

Although 55 years old, this statement still has validity as it would be preposterous to assume that everything is known today about biology. Therefore, it is a logical fallacy to make the assessment of biological observations dependent on already available biological knowledge, when further scientific experiments are still needed to advance said knowledge. Or in other words, **if everything in biology were known, no additional experiments would be required**.

3. Non-monotonic dose responses are common in biology

Indeed, it is well known that dose-response relationships are not always monotonic, but still could be relevant for chemical risk assessment, as described by Bradford Hill (1965): "*if the association is one which can reveal a biological gradient, or dose-response curve, then we should look most carefully for such evidence. For instance, the fact that the death rate from cancer of the lung rises linearly with the number of cigarettes smoked daily, adds a very great deal to the simpler evidence that cigarette smokers have a higher death rate than non-smokers. That comparison would be weakened, though not necessarily destroyed, if it depended upon, say, a much heavier death rate in light smokers and a lower*

rate in heavier smokers. We should then need to envisage some much more complex relationship to satisfy the cause-and-effect hypothesis. The clear dose-response curve admits of a simple explanation and obviously puts the case in a clearer light."

In other words, **a non-monotonic dose response relationship may not allow for a simple explanation (of causality or mechanism of action), but cannot simply be dismissed because an underlaying explanation is missing.** This would not be in line with a scientific approach to assessing the relationships between chemicals and their impacts on biological targets.

The lack of detailed, mechanistic knowledge has also been highlighted by experts in endocrinology (Zoeller et al. 2014): "*Likewise for EDCs, biological plausibility will likely strengthen our confidence in the causal nature of relationships of interest. Moreover, our knowledge of hormone actions will likely drive us to evaluate specific relationships. However, there is a great deal we have to learn about the endocrine system, and requiring complete knowledge of the endocrine mechanism mediating a relationship of interest is unrealistic.*"

Other **governmental bodies have addressed the issue of NMDR previously**, for example in a 2019 report for the Danish Environmental Protection Agency (Hass et al. 2019), stating that "*In many of the cases, the observed NMDR is likely to directly reflect the way the endocrine system works. In other cases, the NMDR may reflect that the substance has multiple ED [Endocrine Disruption] modes of action operating simultaneously, but with different dose-response curves. As detailed mechanistic knowledge is limited for most EDs it is often difficult to evaluate the MoA behind NMDR.*" There is no reference made to this work in the Scientific Opinion, nor to a report about endocrine disruptors commissioned by the European Parliament's PETI Committee (Demeneix and Slama 2019).

Again, we thank EFSA for the opportunity to provide input on this highly important issue which will affect decision-making in a large range of areas, including food contact materials. **We trust that the revision of this Scientific Opinion will be made a high priority by EFSA's leadership** and carried out in an appropriate manner which does justice to EFSA's commitments to scientific excellence and transparency. A better protection of public health can only be achieved if chemical risk assessment principles are based on current scientific understanding and evidence.

Sincerely,

Martin Scheringer, President

Jane Muncke, Managing Director

References

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Zoeller, R. T., et al. (2014). A path forward in the debate over health impacts of endocrine disrupting chemicals. Environmental Health 13(1): 118. https://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-13-118

Annex

Line-by-line comments submitted via EFSA's public consultation online interface

1. Introduction
Why is this section not for comment? How is this aligned with EFSA's commitment to openness? We have included our comments on the introduction in the section 2. Data and Methodologies.

2. Data and Methodologies
Line 32: definition of NMDR is not disputed. Refer to line 116: Curves were characterized as non-monotonic based on the definition that it is a "change of sign in slope somewhere in the dose range tested".
Line 97ff: there is redundancy here with line 133ff.
Line 153 (and others): requiring biological plausibility for justifying statistically significant observations of NMDR is illogical and not aligned with scientific principles. We refer to a statement made by Austin Bradford Hill (1965) about biological plausibility: „It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically

plausible depends upon the biological knowledge of the day.“ It would be preposterous to assume that everything is known today about biology. Therefore, it is a logical fallacy to make the assessment of biological observations dependent on already available biological knowledge, when carrying out scientific experiments serves to advance said knowledge. Or in other words, if everything in biology were known, no additional experiments would be required. In addition, it is not clear whether the Scientific Opinion's authorship indeed included experts on endocrinology and the phenomenon of NMDR who could contribute the knowledge that is already available on this issue.
Line 174: Reference the 2019 reports commissioned by the Danish Environmental Protection Agency http://www.cend.dk/files/ED_Risk_report-final-2019.pdf and the European Parliament https://www.europarl.europa.eu/RegData/etudes/STUD/2019/608866/IPOL_STU(2019)608866_EN.pdf
Line 202ff: why were time and resources limited? Why were academic studies not included in the information sources listed here, but then in the methodology a search strategy is shared?
Line 224: „statistical considerations cannot address biological plausibility“ – this statement must be substantiated with evidence. Please refer in your explanation to https://doi.org/10.1210/er.2011-1050
Line 236ff: the work of Calabrese and Baldwin has been a subject in agnotology, with implicating findings. It is therefore inappropriate to refer to this work here as this introduces bias https://muse.jhu.edu/article/606407
Line 249: why were time and resources limited? Why were academic studies not included in the information sources listed in line 202f, but then in the methodology a search strategy is shared? Why does EFSA not invest resources and the best available scientific expertise to prepare this Scientific Opinion? Why are the names of the authors for this Scientific Opinion not listed in the publication?

2.2 Methodologies
It is unclear whether experts in endocrinology and NMDR were involved in preparing this Scientific Opinion. Given the complexity of the matter, and the relevance to public health in general, it is clearly desirable to include such experts for this task.
The language in the Scientific Opinion is often not appropriate for a scientific publication. For example:
o Use of terms such as „modest change“ (line 442) instead of using the clearly defined terms „statistically significant“ or „not statistically significant“ is imprecise and inappropriate.
o Commentary to describe scientific, peer-reviewed work, such as „Assessment of nonmonotonicity claims for phthalates“ (line 17); „systematic review of the literature claiming nonmonotonic responses“ (line 138); „there are a number of publications claiming NMDR for phthalates and DEHP“ (line 454) is common throughout the text and indicates bias.
o The text includes several passages that are redundant e.g. lines 133f and lines 54f and make the Scientific Opinion difficult to read and understand.
o a key reference (Beausoleil et al. 2016) is „referred to as „the Report““ (line 71) throughout the document, instead of citing it as is common in scientific publications (Beausoleil et al. 2016). This leads to confusion throughout the text, especially when the work by Beausoleil et al. (2016) is compared to other studies (e.g. line 278ff), and other reports are mentioned (line 159, 441). Sometimes there is also reference to an „external report“ and it is unclear if this refers to Beausoleil et al. (2016) or not (line 403, 882). Line 249: why were time and resources limited? Why were academic studies not included in the information sources listed in line 202f, but then in the methodology a search strategy is shared? Why does EFSA not invest resources and the best available scientific expertise to prepare this Scientific Opinion? Why are the names of the authors for this Scientific Opinion not listed in the publication?
Line 266: „NMDR claims“ this is not appropriate language for a scientific opinion. Replace with „observation“. Why is „the Report“ used here instead of referencing as is common in scientific publications? This is confusing and introduces ambiguity.
Line 294f: random text, irrelevant. Delete.

3. Assessment
Line 297f is redundant with line 306f. Delete one instance.
Table 3, page 17, column 5: what does *3. No“ refer to? There is no „3.“ In the first column. Please delete/rectify.

Line 377ff: who are the experts that concluded, based on what grounds? Please provide evidence and specifics for this statement.
Line 379f: „The biological plausibility was clear for all 380 datasets reported in Table 2, but remained doubtful for the majority of datasets reported in Table 3.“ This does not correspond to the contents of Table 3. Please rectify.
Line 403f: „possible NMDR had been examined or claimed“ – inappropriate personal commentary. Change to adequate terminology.
Line 418: „inverted U-shaped dose-response meaning, if anything, improved“ – inappropriate personal commentary. Delete „if anything“
Line 430f: „effect size observed in that study was modest“ inappropriate personal commentary and imprecise language. Please use correct and precise terminology to describe the observation.
Line 438: What own statistical evaluation was carried out? Please provide details here.
Line 443: „modest changes“ inappropriate personal commentary and imprecise language. Please use correct and precise terminology to describe the observation.
Line 450: „For body weight the probability for NMDR is 58.8%“ – How is this finding interpreted? Is this a relevant probability or not? Please elaborate and provide details.
Line 454: „there are a number of publications claiming NMDR“ – inappropriate personal commentary. Indicates a strong bias which seems to have strongly affected the conclusions and leads to question if the selection of working group members was appropriate.
Line 505: „Some early or intermediate effects may be even beneficial“ –delete, this is inappropriate commentary and propagates a theory which has been studied agnotologically, and its proponents have been found to be implicated in manufacture of doubt https://muse.jhu.edu/article/606407
Line 518: please provide a detailed explanation here why this approach „remains valid“, as it is not deducible from previous argumentation provided. It is not sufficient to state this without valid arguments.

4. Conclusions
Line 567: „expert judgement“ is not appropriately documented here: members of working group are not named, making it impossible for reviewers to judge if said expert judgement was available.
Line 571: an understanding of the underlying mechanisms is not necessary to judge if an observation of NMDR is statistically significant or not. A non-monotonic dose response relationship may not allow for a simple explanation (of causality or mechanism of action), but cannot simply be dismissed because an underlaying explanation is obscured. This would not be in line with a scientific approach to assessing the relationships between chemicals and their impacts on biological targets.
Line 591f: „No indications of NMDR have been detected for BPA“—this is not correct and also not in line with what is written in lines 426f and 441f. Delete.
Further, we point to a concise and accessible overview of NMDR in healthy organism development, and an explanation of the known underlying mechanisms in NMDR observed after chemical exposures (Soto 2019: https://youtu.be/MR90OOT50ns and https://www.foodpackagingforum.org/events/workshop2019). For example, androgens control cell proliferation during development, but in the adult, when levels are high, androgens induce inhibition of cell proliferation. This normal, biologically relevant NMDR phenomenon is what „really blocks men from being a prostate with legs“ (Soto 2019).