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Annex E

Public consultation on the draft Scientific Opinion on the update of the risk assessment on tetrabromobisphenol A (TBBPA) and its derivatives in food

European Food Safety Authority (EFSA)

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1 Introduction

1.1. Rationale for the public consultation and summary of its outcome

In line with the European Food Safety Authority's (EFSA) policy on openness and transparency, and to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key topics. Accordingly, the draft Opinion on the update of the risk assessment of Tetrabromobisphenol A (TBBPA) and its derivatives in food together with its Annexes was released electronically for public consultation from 26 March 2024 until 7 May 2024 by means of an e-submission tool. The comments were made publicly available immediately after the closure of the public consultation in Open EFSA1.

Comments were received in the electronic tool from one interested party from one country. **Table 1** provides an overview on the interested parties that have submitted comments through the electronic submission.

Table 1. Overview of the stakeholder comments received

Stakeholder	Category[(a)]	Country
RIVM	Academia/research institute	NL

NL: Netherlands; RIVM: National Institute for Public Health and the Environment.

(a): As specified by the commenter.

1.2. Assessment of comments and use for finalisation of the Opinion

The comments received were duly evaluated by the EFSA Working Group on Brominated Flame Retardants in food and the Panel on Contaminants in the Food Chain (CONTAM Panel) and wherever appropriate taken into account for the finalisation of the draft Opinion. **Table 2** provides a detailed list with all comments received from interested parties together with EFSA responses and explanations of how the comments were considered in the final Opinion. Some comments, especially those suggesting editorial changes, have been directly addressed in the text of the Opinion, if they were considered appropriate.

EFSA wishes to thank all stakeholders who provided comments during the public consultation of this draft update of the risk assessment of TBBPA and its derivatives in food.

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2 Comments received

Table 2. Stakeholder comments and EFSA responses

Stakeholder	Comment number	Section	Comment	EFSA response
National institute for public health and the environment (RIVM)	1	3.1.5 Consideration of critical effects and dose-response modelling	Lines 3325 – 3326 As EFSA knows, RIVM has a number of reservations about the 2022 EFSA Guidance on the use of the BMD approach in risk assessment. Details of these reservations can be found at https://www.efsa.europa.eu/en/supporting/pub/en-7585. Line 3336, Table 14 RIVM would prefer to only report the BMDL and BMDU in Table 14, as it would make it easier for the readers to assess the ratio between the BMDL and BMDU, which reflects the precision of the estimated BMD.	The CONTAM Panel applied the EFSA BMD guidance (EFSA Scientific Committee, 2022) as there was no compelling reason to deviate. EFSA is aware of the reservations of RIVM towards the 2022 EFSA BMD Guidance (EFSA Scientific Committee, 2022), and the replies can be found here: https://www.efsa.europa.eu/en/supporting/pub/en-7585 The Panel considers it important to retain the BMD values in Table 14 of the Opinion: these values, representing the median of the posterior distribution, and offer a probabilistic interpretation where there is 50% chance of the BMD value to be above or below the value reported. The Panel considered it informative to present the most likely value of the BMD besides the 90% credible interval. BMD values obtained with the Bayesian approach provide valuable information for the interpretation of the modelling outcome. They also provide insight into the acceptability of the BMDL as a Reference Point, as defined by the EFSA Scientific Committee (2022). For this reason, BMD values are reported in the tables.

	2	3.1.6 Approach for risk characterisation	Lines 3355-3358 RIVM questions if the quality of the study of Kim et al., 2015 is sufficient for deriving a PoD. In this study only one dose level was included and uncertainty in the results was not shown in the article (e.g. error bars in the graph). When looking at the three different compounds tested, the difference between social behaviour with the familiar and stranger mouse showed a different pattern. In the case of BPS social behaviour increased with the stranger mouse, where it decreased for TBBPA and was similar for BDE-47. This could indicate that there was a lot of variation in the measurements and uncertainty in the results. In addition, the decreased social behaviour seen in TBBPA exposed mice is only borderline statistically significant (P=0.05). Furthermore, in the opinion several $BMDL_{10}$'s were derived for neurotoxicity studies, which were all at least a factor 10 higher, than the LOAEL from Kim et al., 2015. Lastly a LOAEL is very uncertain in general, however there are no criteria to judge this uncertainty because the uncertainty is not visualised. Taken everything into account, RIVM would prefer to use a $BMDL_{10}$ from another study as PoD.	The CONTAM Panel acknowledges the limitations of the critical study Kim B et al. (2015), including the fact that it was a one dose level study, and that only a LOAEL could be identified. These limitations were considered in the uncertainty analysis (see Appendix I, Table I.2). Several studies demonstrate the ability of TBBPA to induce long-term behavioural disturbances after an early exposure. Two studies including 3 dose groups and a control examined the neurobehavioural effects of TBBPA (Kim AH et al., 2017; Rock et al., 2019). However, the effects reported appears at much higher doses (LOAEL of 25 mg/kg bw per day for Rock et al., 2019, 2nd experiment and 100 mg/kg bw per day for Kim AH et al., 2017) than in the one dose level neurobehavioural studies (LOAEL of 0.2 mg/kg bw per day for Kim B et al. (2015) and LOAEL of 0.1 mg/kg bw per day for Rock et al. (2019). The $BMDL_{10}$ calculated for light box entries in mice (only acceptable $BMDL_{10}$ for a specific effect) was also higher (77.6 mg/kg bw per day Rock et al. (2019), 2nd experiment). The CONTAM Panel considered that different compounds with different structure, even if they contain bromine and are used as brominated flame retardants, can have different toxicological properties. In addition, it is noted that the p-values reported in Figure 3b of the study are false discovery rate (FDR) adjusted T-test, which takes account of multiple comparisons, therefore indicating the difference observed is robust.

				Having considered the points raised in the comment, the CONTAM Panel still considers that this study provides a sufficient basis to establish the Reference Point for the risk assessment of TBBPA.
	3	3.2.1 Occurrence data on food submitted to EFSA	In lines 3377-3378, the following is described 'The occurrence data submitted to EFSA were not systematically checked for possible duplications with the data reported in the literature (see Section 3.2.2)'. Reference to section 3.2.2 is unclear. Lines 3458-3465 refer to the occurrence data used in the previous EFSA opinion on TBBPA and its derivatives. It is described that all reported analytical results were left-censored. It would be helpful if it could be explained why in the 'update of the Scientific Opinion' occurrence data are reported with a numerical value. E.g., is this due to a lower LOQ, or have TBBPA concentrations increased in food, or is there another reason?	The cross-reference to Section 3.2.2 of the Opinion was not correct. Now the correct cross-reference is given to the correct Section, i.e. Section 3.2.3, on previously reported occurrence data in the literature. It is likely that more sensitive analytical methods in recent data together with wider data availability played a role in the finding of quantified results. Due to the nature of the data, a time trend analysis was not possible.
	4	3.2 Occurrence data	Overall: Also conjugated TBBPA could be present in food (at least in human milk; see section 3.1.1.3.1). Therefore, further consideration could be given to the conjugated fraction of TBBPA. When conjugated TBBPA is hydrolysed during digestion, humans are exposed to a larger quantity of TBBPA than estimated now.	The CONTAM Panel agrees that conjugated TBBPA might be present, e.g. in food of animal origin. Information on whether an hydrolysis step was applied to cleave any conjugates present in the food samples was not reported, but is not common practice in food control. For breastfed infants, a study in human milk was identified in which an hydrolysis step was applied, and these data were included in the risk characterisation of this population group (see **Section 3.3.1.3** and **3.4**).

				A new recommendation has been added for studies to understand the contribution of TBBPA conjugates to the overall exposure.
	5	3.4 Risk characterisation	For the sake of completeness and readability, RIVM suggests to include here that no risk characterization was conducted for the 5 derivatives of TBBPA.	A sentence has been added in Section 3.4 to acknowledge that no risk characterisation could be performed for any of the five TBBPA derivatives included in the TORs, due to insufficient or lack of data both on the toxicity and occurrence.
	6	3.5 Uncertainty analysis	For the sake of completeness and readability, RIVM suggests to include here that no risk characterization and uncertainty analysis was conducted for the 5 derivatives of TBBPA.	It is now acknowledged in Section 3.4. of the Opinion that no risk characterisation (and hence no uncertainty analysis for any of the five TBBPA derivatives included in the TORs could be performed. It is not considered necessary to repeat this in Section 3.5. of the Opinion.
	7	4.2 Occurrence and exposure for the European population	For the sake of completeness and readability, RIVM suggests to include here that no exposure assessment could be conducted for the 5 derivatives of TBBPA.	A sentence has been added at the start of Section 4 on Conclusions to acknowledge that no risk characterisation could be performed for any of the five TBBPA derivatives included in the TORs, due to insufficient or lack of data both on the toxicity and occurrence.
	8	4.3 Risk characterisation	For the sake of completeness and readability, RIVM suggests to include here that no risk characterization could be conducted for the 5 derivatives of TBBPA.	See reply to Comment 7.

	9	Appendices	Appendix D Page 144 should be shown landscape, as information is missing now. Appendix I; Table I.1 For the uncertainties regarding 'consumption data', the impact is described as '1-low priority'. This seems not to be in line with the description for other uncertainties, and with the explanation in footnote (a).	The page shows in landscape format in the final publication of the Opinion. Thank you for noticing this, it has now been corrected to read 'impact' instead of 'priority'.

References

EFSA Scientific Committee, More SJ, Bampidis V, Benford D, Bragard C, Halldorsson TI, Hernández-Jerez AF, Bennekou SH, Koutsoumanis K, Lambré C, Machera K, Mennes W, Mullins E, Nielsen SS, Schrenk D, Turck D, Younes M, Aerts M, Edler L, Sand S, Wright M, Binaglia M, Bottex B, Cortiñas Abrahantes J and Schlatter J, 2022. Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal, 2022;20(10):e07584, 67 pp. doi: 10.2903/j.efsa.2022

Kim AH, Chun HJ, Lee S, Kim HS and Lee J, 2017. High dose tetrabromobisphenol A impairs hippocampal neurogenesis and memory retention. Food and Chemical Toxicology, 106, 223–231. doi: 10.1016/j.fct.2017.05.053

Kim B, Colon E, Chawla S, Vandenberg LN and Suvorov A, 2015. Endocrine disruptors alter social behaviors and indirectly influence social hierarchies via changes in body weight. Environmental Health, 14, 64. doi: 10.1186/s12940-015-0051-6

Rock KD, Gillera SEA, Devarasetty P, Horman B, Knudsen G, Birnbaum LS, Fenton SE and Patisaul HB, 2019. Sex-specific behavioral effects following developmental exposure to tetrabromobisphenol A (TBBPA) in Wistar rats. Neurotoxicology, 75, 136–147. doi: 10.1016/j.neuro.2019.09.003

Abbreviations

BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
$BMDL_{10}$	benchmark dose lower confidence limit for a benchmark response of 10%
BMDU	benchmark dose upper confidence limit
CONTAM Panel	Panel on Contaminants in the Food Chain
FDR	false discovery rate
LOAEL	lowest-observed adverse effect level
LOQ	limit of quantification
NL	The Netherlands
RIVM	National Institute for Public Health and the Environment
TBBPA	Tetrabromobisphenol A
TORs	Terms of Reference