Annex to:

EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Schrenk D, Bignami M, Bodin L, Chipman JK, del Mazo J, Grasl-Kraupp B, Hogstrand C, Hoogenboom LR, Leblanc J-C, Nebbia CS, Nielsen E, Ntzani E, Petersen A, Sand S, Schwerdtle T, Wallace H, Benford D, Fürst P, Rose M, Ioannidou D, Nikolič M, Ramos Bordajandi L and Vleminckx C, 2021. Scientific Opinion – Update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food. EFSA Journal 2021;19(3):6421, https://doi.org/10.2903/j.efsa.2021.6421

ANNEX E - Outcome of the public consultation on the draft update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food

E.1. Rationale for the public consultation and brief summary of its outcome

In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, the draft Opinion on the update of the risk assessment of HBCDDs in Food together with its Annexes was released for public consultation from 14 October 2020 to 25 November 2020 by means of an electronic comment submission tool together with explanatory text on the EFSA website (See **Appendix 1**).

Comments were received from three interested parties from three countries. **Table E.1** provides an overview on the interested parties that have submitted comments.

Table E.1. Overview on stakeholder comments received

Stakeholder	Category [(a)]	Country
German Federal Institute for Risk Assessment (BfR)	National Authority	DE
Food Standards Agency (UK FSA)	National Authority	UK
National Institute for Public Health and the Environment (RIVM)	University/Public Research Institute	NL

(a): As specified by the commenter.

E.2. Assessment of comments and use for finalisation of the Opinion

The comments received were duly evaluated by the WG on BFRs in food and the CONTAM Panel and wherever appropriate taken into account for finalisation of the draft Opinion. **Table E.2** provides a detailed list with all comments as received from interested parties together with EFSA responses and explanations how the comments were considered for finalisation of the draft Opinion[1].

EFSA wishes to thank all stakeholders providing comments during the public consultation of this draft update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food.

[1] The outcome of the public consultation was endorsed by the CONTAM Panel in the form of a Technical Report at its 112th Plenary meeting held 26 January 2021. Due to the implementation of the new OpenEFSA portal there has been a change and the outcome of the public consultation is now reported as an Annex to the Opinion, and the Question number initially assigned to the Technical Report is no longer of use.

Table E.2. Stakeholder comments and EFSA responses

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
German Federal Institute for Risk Assessment (BfR)	1	3.1.1.3.1. Laying hens, broiler and ducks	P 36-37, lines 1302-1323: Instead of only reporting the experimental concentrations of HBCDDs in laying hens and eggs of Fournier et al. (2012), it may be more useful to calculate and report a mass balance (percentages accumulated, excreted in eggs, biotransformed and putatively excreted otherwise). We suggest calculating and reporting the transfer rate into eggs (total amount in eggs/total amount ingested) including the effect of stereoisomer biotranformation.	Additional text has now been added in Section 3.1.1.3.1 indicating that "*over the 21-day exposure period, 0.17% of ingested γ-HBCDD was excreted in egg yolk (as α-HBCDD) and 0.17% and 0.025% were measured in abdominal fat and in liver, respectively*". The transfer rate into eggs was already mentioned in the description of this study as: "*The authors estimated a transfer rate of 1.2% from ingested γ-HBCDD to egg yolk (at steady state)*".
			P 37, line 1328: "*The calculated* ***accumulation ratio***" should normally be called a transfer factor (concentration in food/concentration in feed). It would be good to additionally report transfer rates.	For consistency with Previous CONTAM Panel Opinions, the term now used is 'bioaccumulation factor'. The authors of the study did not provide sufficient data to calculate transfer rates.
	2	3.1.1.5. Physiologically Based Kinetic (PBK) modelling	P 46, line 1628: This model, with all its problems, could be touted as a point of departure for the development of better models	The CONTAM Panel acknowledges this comment and a recommendation was already made for improved information on toxicokinetics to develop a toxicokinetic model for HBCDDs.
	3	3.1.2.7. Carcinogenicity	P 61, line 1962 ff: EFSA`s conclusion on carcinogenicity is not comprehensible. Apparently, the carcinogenicity study was not available (also stated in the 2011 opinion) for the CONTAM Panel as it was only cited from a secondary source. We consider it not possible to conclude on carcinogenicity on this basis. There is insufficient data on carcinogenicity. Hence, the conclusion that carcinogenicity is not a critical point for HBCDDs cannot be drawn.	The CONTAM Panel acknowledges that the only available 18-month study was described in the comprehensive risk assessment report by ECB (2008), and that no new studies have become available since then. Based on the available information to the CONTAM Panel, i.e. the lack of carcinogenicity in the mouse study, the lack of direct genotoxicity and the information available on mode of action, there is no indication that HBCDDs are carcinogenic. This has now been made clearer in the Opinion in Sections 3.1.2.7, 3.1.5.1, Conclusions, Abstract and Summary.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	4	3.1.4.1. Hepatotoxicity and metabolic effects	P 72, lines 2264-2266: It is written: "*HBCDDs stimulated proliferation and migration of liver cell lines at picomolar to nanomolar concentrations and there is evidence that these effects are related to activation of the oestrogen receptor (ER) and the PI3K/AKT/mTOR signalling pathway*". We wonder, whether the chosen reference point and the selected sufficient MoE of 24 is protective of the described endocrine effects in vitro (also in human cells). Please describe thoroughly in the 3.1.5.3 section why the CONTAM Panel considers 1) The MoE of 24 is sufficient to protect from potential endocrine effects.	Although these effects occurred at low concentrations *in vitro*, there is insufficient data to support that they could also occur *in vivo* and/or have consequences on neurodevelopment. It is not possible here to extrapolate effective concentrations *in vitro* to the situation *in vivo*. The point of departure for neurodevelopment would be protective for any effects on reproductive endpoints as well as the effects in thyroid hormone levels, given that these effects occurred at higher doses (above 10 mg/kg bw per day).
			Page xx, Lines 2586-2887: Please provide evidence for the assumption: "*The slight induction of DNA strand breaks observed in some in vitro tests is most likely due to oxidative stress*."	HBCDDs are not mutagenic in bacteria, do not induce clastogenicity or aneugenicity in mammalian cells *in vitro* and are negative in an *in vivo* (i.p.) micronucleus test in mice (EFSA CONTAM Panel, 2011a). It is well documented that ROS can cause DNA strand breaks in the comet assay. See Section 3.2.1.6 of the Opinion on Genotoxicity: "*Oxidative stress was shown at the same concentration as the increase in strand breaks (Li et al., 2017b)*". "*Increase in DNA strand breaks were observed in parallel with increased ROS levels (An et al., 2013)*". See also Section 3.1.4.4 of the Opinion on MOA Oxidative stress: "*DNA breaks levels correlated positively with ROS (Li et al., 2017b)*". "*Excessive production of ROS has been reported in a variety of studies on HBCDD toxicology*". For completeness, the Panel described now in Section 3.1.2.6 on Genotoxicity the study by Wang et al. (2020) on results of the Comet assay available on line 18 September 2020, as well as under Section 3.1.4 the bioinformatics study by Dai et al. (2020) that identified effects of HBCDDs on hepatotoxicity and generation of

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				oxidative stress. These additions do not change the final conclusions.
	5	3.1.5.2. Dose-response analysis	Page 80 f, lines 2616 ff: The point of departure (PoD) for the risk assessment was based on the results in a single dose study in mice investigating neurotoxic effects (Eriksson et al., 2006). The LOAEL of 0.9 mg/kg bw was corrected for limited oral bioavailabilty leading to a systemic dose of 0.747 mg/kg bw. From this, a chronic human dietary intake of 2.35 µg/kg bw per day was calculated. We wonder why the same study and LOAEL were not also selected as PoD for acute scenarios. Considering that the study showed adverse effects after administration of a single dose, an acute risk assessment is triggered. As accumulation/slow elimination is less relevant for an acute setting, 0.747 mg/kg bw could serve as PoD to assess acute exposures.	In Section 3.4 of the Opinion the CONTAM Panel had noted that: "*Although the LOAEL was identified from a study involving a single administration on PND10, it is not viewed as an acute effect because HBCDDs are persistent in the body*". The Panel has now added "*and an acute high level exposure is not likely to occur during the critical period of development of the human brain*" for additional clarification.
	6	3.1.5.3. Derivation of a health-based guidance value or margin of exposure approach	P 81 f, lines 2671 ff: It is proposed to also select a PoD for acute exposure scenarios. Similar to the argumentation for the chronic setting, a MOE approach could be used. A MOE higher than 300 (10 x 10 x 3) could be selected to indicate a low health concern, taking into account inter and intra species extrapolation (10 x 10) and the extrapolation from LOAEL to NOAEL (3). In case the panel agrees with this proposal, further changes in the opinion would be needed to align the text (e.g., sections 2.4, 2.6, 3.3, 3.4). Deriving a PoD for acute exposures would facilitate the risk assessment of samples taken for food surveillance purposes, when they exceed maximum levels (which will be set).	See response to Comment 5.
			P 81 f, lines 2702-2703: "*Thus, the Panel concluded that an MOE higher than 24 (2.5 × 3.2 × 3) would indicate a low health concern.*" We consider a MOE of 24 is too low to cover for the uncertainties and an additional uncertainty factor should be applied covering the insufficient information on carcinogenic, genotoxic and endocrine effects.	The CONTAM Panel considered whether an additional factor should be applied to allow for limitations in the database, and this was explained in Section 3.1.5.3 of the Opinion: the Panel noted that reproductive toxicity studies, that include a battery of tests for evaluating potential neurotoxicity, showed only sporadic effects, and that there is no indication that HBCDDs are carcinogenic. Taking all this information into account, the Panel concluded that no additional uncertainty factor for limitations in the toxicological database was needed. See also the reply to Comment 4 (first

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				part of the reply). It should also be noted that another commentator agreed with the CONTAM Panel approach (see Comment 14).
	7	3.3.3. Non-dietary sources of exposure	P 99 ff, lines 3220 ff: The draft EFSA opinion addresses the potential exposure to hexabromocyclododecanes (HBCDDs) by mouthing and by ingestion of plastic toy material, thereby citing findings of Fatunsin et al. (2020). In addition, the presence of HBCDDs in toys was reported at the Dioxin2017 conference (Strakova et al. 2017): 104 products (including 88 magic cubes) purchased in 24 countries were analysed for HBCDDs. In 45 samples a content of 1 - 1 586 ppm was found. The highest content of HBCDDs in a product sold within the EU was 375 ppm in a toy gun from the Czech Republic, while higher levels were found in products from non-EU countries. Additional results were presented at the Dioxin2018 conference (Strakova et al. 2018): Seven other toy samples collected in the Czech Republic were analysed for HBCDDs. The substances were found in five toys with a content of 0.3-91 ppm HBCDDs. Strakova J, Bell L, DiGangi J, Gramblicka T, Pulkrabova J: Hexabromocyclododecane (HBCD) found ewaste is widely present in children's toys. Organohalogen Compounds (2017) 79, 571-574. http://dioxin20xx.org/wp-content/uploads/pdfs/2017/9997.pdf, last access at 22.11.2020. Strakova J, Petrlik J, Pulkrabova J, Gramblicka T: Toxic recycling, or How unsorted waste may contaminate consumer products in the Czech Republic. Organohalogen Compounds (2018) 80, 365-368. http://dioxin20xx.org/wp-content/uploads/pdfs/2018/414.pdf, last access at 22.11.2020	The CONTAM acknowledges this information and notes that the sub-section on 'Non-dietary sources of exposure' does not claim to be complete, but aims at providing some examples of non-dietary oral exposures, including unintentional ingestion of parts of plastic toys. However, the Panel considers of interest the information provided in these non-peer-reviewed (extended) abstracts published in the proceedings of the Dioxin symposia, and reference to these studies has now been made in Section 3.3.3 of the Opinion.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	8	3.5.3. Hazard identification and characterisation	P 107-108, lines 3589 ff: EFSA stated "*In the Eriksson et al. (2006) study a single dose of HBCDDs was administered to mice on PND10, which marks the start of a critical period in the development of the rodent brain. It is unclear whether PND10 is the most critical day and if exposure at another time point would produce a response at a lower dose. There is also uncertainty as to whether an effect would have been observed at a lower dose following repeated dosing. However, the current assessment was done based on body burden, and repeated dosing even at lower levels might have resulted in a higher body burden.*" This is an assumption but the contrary is also possible. Lower dosing (single or repeated) may have resulted in lower body burden. This is an uncertainty that should at least be covered by an UF considering a sufficient value of the MoE.	The approach used in the current Opinion is conservative, as the estimated body burden suggests that repeated dosing would provide a higher body burden than that calculated with single exposure at the same initial dose, and therefore a higher reference point. This has now been made clearer in Section 3.5.3 of the Opinion. Thus, the Panel did not consider it was necessary to apply an additional uncertainty factor
	9	5. Recommendations	P 113, lines 3799-3802: Given the fact that the most sensitive group are high-milk consumption breastfed infants, we fully agree that there is a pressing need for development of a high-quality human HBCDDs toxicokinetic model including excretion into milk. It may be better to express it as a need for a general human HBCDDs toxicokinetic model and one including lactation explicitly. Placental transfer of HBCDDs may also need to be included in those models.	The CONTAM Panel agrees and the recommendation has been modified to include excretion into breast milk and placental transfer.
Food Standards Agency (UK FSA)	10	Summary	The Opinion on the Update of the risk assessment of Hexabromocyclododecanes (HBCDDs) in food has been referred to the UK's independent Committee on Toxicity (COT) by the Food Standards Agency (FSA). The COT was asked to comment on the approach used for the risk assessment. As a general comment the Committee noted that EFSAs decision-making process was unclear on certain aspects. Lines 155-172: Given the effect of HBCDDs on the constitutive androstane receptor (CAR) and pregnane-X-receptor (PXR) in the liver of rodents, the Committee questions the conclusions drawn by EFSA on the mode of action for changes in liver weight and noted that more clarification in this regard would be helpful.	 See reply to Comment 11.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	11	3.1.2.2. Repeated dose toxicity studies	Studies considered in the previous assessment. Lines 1686-1690: Given the effect of HBCDDs on the constitutive androstane receptor (CAR) and pregnane-X-receptor (PXR) in the liver of rodents, the Committee questions the conclusions drawn by EFSA on the mode of action for changes in liver weight and noted that more clarification in this regard would be helpful.	The Panel agrees that the effects of HBCDDs on CAR and PXR are likely to contribute to the increase in liver weight. Newer data point also towards possible involvement of PPARα and PPARγ in HBCDD-induced hepatic triglyceride accumulation and proliferation of liver cells. It diverts from the previous Opinion in that it does not consider this the likely Mode of Action behind the effects on neurodevelopment. New text has now been inserted in the concluding lines of Section 3.1.4.1 of the Opinion: "*These effects might contribute along with activation of CAR, PXR and PPRAs to the observed increase in liver weight in rodent studies with HBCDDs*".
	12	3.1.2.5. Neurotoxicity studies	Studies published since the previous EFSA assessment lines 1864-1921: The Committee noted that EFSA confirmed the critical endpoint from 2011, however it was not substantiated by any new or additional findings. A recent study in rats supported the findings by Eriksson et al. (2006) (the study on which the previous and the current assessment was based), albeit at higher doses, however this study was disregarded by EFSA and the Committee were unclear regarding the justification/reasoning for this.	Assuming that this refers to Zhang et al. (2017), the CONTAM Panel noted in Section 3.1.5.1 of the Opinion that: "*This study is supportive of the Eriksson et al. (2006) study in that HBCDDs induced neurobehavioral effects, but it was not considered further for the derivation of a Reference Point due to limitations in the study*". The considerations and limitations noted by the Panel for this and the other available studies were discussed in Section 3.1.2.5 of the Opinion.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	13	3.1.5.2. Dose-response analysis	The Committee acknowledged the general problem of comparing different modelling approaches such as BMDS and PROST, without the underlying algorithms and therefore would have found it useful if not only the model version but additional information on parameters underlying the specific version would have been provided. Given the limited information provided by EFSA the Committee found it difficult to follow EFSAs decisions making process and approach to modelling and to identify the underlying quality control measures of the current model version.	The BMD analysis performed is described in Appendix C of the Opinion, which contains all information available related to the functions and parameters used. To perform the BMD modelling, EFSA utilises the web-app 'EFSA-Proast platform' (https://efsa.openanalytics.eu/) that is based on the PROAST software package developed by RIVM. Further information about PROAST can be found at: https://www.rivm.nl/en/proast. This has now been made clear in Section 2.2 of the Opinion.
	14	3.1.5.3. Derivation of a health-based guidance value or margin of exposure approach	General: The Commitee was unable to follow and understand EFSAs decision making process to apply the NOAEL/LOAEL approach; this was considered especially pertinent given EFSA's previous efforts to apply BMD modelling and the that the difference in the calculated/estimated chronic human intake was minimal between the previous (BMD) and current (NOAEL/LOAEL) approach.	See reply to Comment 20. Re-analysis of the Eriksson et al. (2006) data with the new EFSA guidance for BMD modelling (EFSA Scientific Committee, 2017, see Appendix C), led to wider intervals around the BMD. This is mainly due to differences in methods recommended by the two guidance documents. In the current guidance, for continuous data only four models are used, and only two models per nested family (Hill and exponential). Moreover, the new BMD guidance (EFSA Scientific Committee, 2017) does not recommend constraining the steepness/shape parameter in the models. Therefore, if the shape of the dose-response curve is not sufficiently constrained by the data itself in the region of the BMR (e.g. due to the low number of dose groups, and/or the dose spacing, and/or limited sample size) a large BMD confidence interval can result as a consequence. The CONTAM Panel noted that the BMDLs for horizontal locomotion and rearing are far below the lowest dose administered. A correction has now been made in the paragraph below Table 12 of the Opinion: it was

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				the BMDLs for horizontal locomotion and rearing (not total activity) that were far below the lowest dose administered.
			Lines 2684-2687: The Committee noted that the reasoning (and/or wording) regarding interspecies effects and derivation of the uncertainty factor for interspecies differences were not clear.	The CONTAM Panel used the body burden as a starting point for the MOE approach. The body burden provides a more appropriate dose metric for a direct comparison of effects in animals and humans, and for this reason the CONTAM Panel considered that the uncertainty factor to cover for interspecies differences between animals and humans (factor 4) was not needed. The Panel did consider it necessary to cover the uncertainty related to interspecies differences in dynamics for the effects observed, and thus applied the corresponding factor of 2.5. The text in the Opinion has now been modified to express this more clearly.
			Lines 2694-2703: Based on the NOAEL/LOAEL approach, the COT agreed with EFSAs additional uncertainty factor of 3 for the extrapolation from a LOAEL to a NOAEL and that an MOE of 24 would not be of concern.	The CONTAM Panel acknowledges the comment.
	15	4.3. Conclusions – Risk characterisation	Overall, the Committee agreed with EFSA that exposures from the diet were of no concern to human health, however, were unable to conclude on the effect of breastmilk. According to EFSAs calculations and conclusions breastfed infants are the subgroup with a potential risk to health, however the Committee were unable to ascertain whether EFSA's assessment/conclusions were conservative, as the derivation of the breastmilk exposures by EFSA was unclear.	The exposure assessment for breastfed infants was described in detail in Section 3.3.1 of the Opinion. The estimation is based on an age of the infant of three months, equivalent to a weight of about 6.1 kg, with an estimated average daily consumption of about 800 mL and a high consumption of 1,200 mL of human milk, each with a mean fat content of 3.5% (EFSA CONTAM Panel, 2011a). The occurrence data are taken from the reported UB range for the sum of HBCDDs (predominantly α-HBCDD) in pooled human milk samples collected in European countries between 2014 and 2016 as part of the WHO/UNEP field studies (see Table 8 of the Opinion).

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
				In addition, in Section 3.4 on risk characterisation and in relation to the health risk for breastfeed infants, it has been added that the MOEs could only be increased by reducing the concentration of HBCDDs in breast milk by addressing exposure of the mother before and during lactation.
	16	Annex C - Benchmark dose (BMD) analysis	The Committee acknowledged the general problem of comparing different modelling approaches such as BMDS and PROST without the underlying algorithms and therefore would have found it useful if EFSA could provide not only the software version but additional information on parameters underlying the specific model used. Given the limited information provided by EFSA the Committee found it difficult to follow EFSAs decisions making process and approach to modelling and to identify the underlying quality control measures of the current model version.	See reply to Comment 13.
National Institute for Public Health and the Environment (RIVM) [One attachment was submitted by this commenter during the public consultation. See **Appendix 2**]	17	Abstract	We would like to thank EFSA for the draft opinion and possibility to comment on it. We hope to provide a useful contribution by sending in our comments and remain at your disposal for any questions or additional explanations.	The CONTAM Panel acknowledges the comment.
	18	3.1.2.5. Neurotoxicity studies	Paragraph 3.1.2.5 p57. line 1864-1873: RIVM acknowledges the study of Eriksson et al. (2006) and Zhang et al. (2017) being complementary to each other. However, from the study of Zhang et al (2017) a LOAEL of 0.3 mg/kg bw can be derived, which is a factor of 3 lower than the LOAEL of the Eriksson study. RIVM notes that using the Zhang study instead of the Eriksson study would lead to factor 3 decline in the calculated MOEs (line 3414, Table 17). Though using the Zhang study instead of the Eriksson study will not affect the risk characterization for most of the population, it will aggravate the risk attributed to breastfed infants (paragraph 3.4, line 3431-3432). Therefore, based on the precautionary principle RIVM would prefer the Zhang study over the Eriksson study in the risk characterization of HBCDD. EFSA is requested to consider this and comment on this.	EFSA takes a conservative approach in its risk assessments, taking into account the scientific merits of the data. In this instance, the CONTAM Panel, having consulted with hearing experts in neurobehavioural studies, noted the limitations regarding spatial learning and memory of both Zhang et al. (2017) and Eriksson et al. (2006). Due to these limitations, these effects were not considered further for the derivation of a Reference Point. This was described in Sections 3.1.2.5 and 3.1.5.1 of the Opinion.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	19	3.1.3. Observations in humans	Paragraph 3.1.3, lines 2064 – 2077: Though RIVM acknowledges the mentioned limitations of the available human data it questions whether the limitations present in the animal data (paragraph 3.1.5.1, lines 2577-2584) warrant the conclusion that the available human data are indicative for a substantial higher human sensitivity for HBCDD induced neurodevelopmental toxicity compared to animals. On the basis of extrapolation from mice to humans a chronic human dietary intake of 2.35 µg/kg bw/day was calculated as a "safe" human exposure corresponding to a body burden of 0.747 mg/kg bw (described /calculated in paragraph 3.1.5.2. Dose-response analysis line 2662-2670, p81). Assuming the body weight of a pregnant woman is 75 kg and a bodyfat percentage of 30% results in a total of 22500 g of body fat. The safe body burden of 0,747 mg/kg bw in this case corresponds to a concentration of body fat of 0.747*75*106 ng HBCDD/22500 g fat ≈2490 ng HBCDD/g body fat. This value is several orders of magnitude higher than the reported effective serum lipid concentrations in pregnant woman in the Groningen Infant COMPARE birth cohort, i.e. 0.8 – 7,5 ng/g lipid, (see paragraph 3.1.3, line 2016-2020). Could EFSA comment on this discrepancy between observed neurotoxic effects observed in the Groningen Infant COMPARE birth cohort (paragraph 3.1.3. Observations in humans: P63, line 2030-2044) and the assumed "safe" chronic human exposure of 2.35 µg/kg bw/day?	The CONTAM Panel notes that the comment does not include kinetics considerations in the calculation of a "safe" body burden in human from body burden in mice. The calculation is therefore not correct. The CONTAM Panel made a comparison of body burden in adults in addition to the MOE calculated for exposure via the diet and this can be found in Section 3.4. None of the epidemiological studies available (described in Section 3.1.3 of the Opinion) were considered appropriate for the derivation of a reference point for the risk characterisation. Of note, the Groningen Infant COMPARE (GIC) birth cohort studies show inconsistent results for neurodevelopment. Therefore, it is not possible to conclude if humans are more of less sensitive based on the data available. Thus, a discussion of the discrepancy indicated by the commentator is not warranted.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	20	3.1.5.2. Dose-response analysis	Paragraph 3.1.5.2 lines 2635 – 2639: The use of constraint on steepness/shape parameter is based on a false argument that the dose–response curve could have infinite slope at dose zero. This rationale is explained in the current guidance for BMD modelling (https://doi.org/10.2903/j.efsa.2017.4658). Not constraining shape parameter could lead to a wider BMD confidence interval in the situation when the data itself is not informative enough in the region of the BMR of a dose-response curve. This situation sometimes can be improved by using e.g. historical information on the shape parameter or the covariate approach, or by selecting a higher BMR as illustrated in the current guidance for BMD modelling. Below we give an example of using higher BMRs in the doseresponse analysis based on the so-called Effect Size Theory for continuous data. In the current guidance for BMD modelling, a BMR of 5% is recommended for the continuous data. However this single value of BMR does not reflect an equivalent severity for all toxicological endpoints. For instance, a 5% change in liver enzyme in serum can hardly be considered as equivalent to a 5% change in brain weight. Therefore it seems more sensible to use endpoint-specific BMRs in carrying out BMD modeling, rather than applying a fixed default BMR for all endpoints. The Effect Size Theory explains how endpoint-specific BMR should be scaled based on relevant quantitative properties of the endpoint, in particular the maximum fold change M and the within-group variation (or equivalently, the standard deviation, SD). For more details on how to derive a BMD(L) based on an endpoint-specific BMR see https://doi.org/10.1080/10408444.2016.1241756. It is possible that the endpoint-specific BMR is sometimes higher than the default 5% for continuous data, which could improve the precision of the BMD. We provide, along the comments, the results of a BMD modeling using endpoint-specific BMRs for the three datasets from Eriksson et al. (2006), using PROAST 70.2. For details please see Table 1, Figures 1, 2, and 3 in the attached document 'Supplementary BMD'. RIVM requests EFSA to consider using the lowest BMDL of these three endpoints of 0.24 mg/kg bw per day as the PoD for the MOE approach for HBCDD. According to the Effect Size Theory this PoD relates to a small effect size (e.g. scaled to 1 SD on log-scale in PROAST 70.2).	To date, there is no agreement on official implementation of the Effect Size Theory in the EFSA Guidance for BMD modelling. See reply to Comment 24 for the BMR selection.

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			Paragraph 3.1.5.2 lines 2641-2643: For several reasons, which will not be listed here, the BMD approach is scientifically better to derive a point of departure (PoD) compared to the NOAEL/LOAEL approach. This is acknowledged by EFSA (https://doi.org/10.2903/j.efsa.2017.4658). Deriving a NOAEL (or LOAEL) in case a low BMDL is obtained seems to contradict this and is, according to RIVM, ill-advised for the following reasons: In the NOAEL approach, the decision to accept a data set for deriving a NOAEL as a potential PoD is important since poor or limited data (e.g. due to high variability within the dose groups, high limit of quantification of analytical methods, small sample sizes) will tend to result in high NOAELs. Acceptability of the data will therefore depend upon expert judgement. In contrast, the BMD approach itself provides a formal quantitative evaluation of data quality, by taking into account all aspects of the specific data. When the data are relatively poor or uninformative, the resulting BMD confidence interval for that data set will tend to be wide, and the BMDL might be much lower than the true BMD. But the meaning of the BMDL value remains as it was defined: it reflects a dose level where the associated effect size is unlikely to be larger than the BMR used. Nonetheless, it might happen that the data are so poor that using the associated BMDL (or BMD confidence interval) as a potential PoD appears unwarranted. In this case the data are also insufficiently informative to derive a NOAEL (or LOAEL). A NOAEL derived from such poor data is not justified because it hides the lack of dose-response information and ignores the uncertainties associated with the data. RIVM asks EFSA to provide an explanation for their choice of a NOAEL-LOAEL approach instead of BMD modelling with regard to the above mentioned aspects.	See also reply to Comment 14. As described in Section 3.1.5.2 of the Opinion, the CONTAM Panel performed BMD analysis for the data on horizontal locomotion, rearing and total activity in mice as reported by Eriksson et al. (2006) using the latest EFSA Guidance for BMD modelling (EFSA Scientific Committee, 2017) and noted wider intervals around the BMD, and that the BMDLs for horizontal locomotion and rearing were far below the lowest dose administered. Therefore, the no-observed-adverse effect-level (NOAEL) approach was considered more appropriate. The CONTAM Panel took the uncertainty in the reference point (see Section 3.5.3 of the Opinion) into account and thus did not find appropriate to establish a HBGV values based on this reference point, but used the MOE approach. A correction has now been made in the paragraph below Table 12 of the Opinion: it was the BMDLs for horizontal locomotion and rearing (not total activity) that were far below the lowest dose administered.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	21	3.2.1. Occurrence data	Paragraph 3.2.1, lines 2784-2814: In four bullets EFSA explains how concentrations were assigned to FoodEx levels 2 and 3 foods. RIVM was not able to reconstruct EFSA's procedure for assigning concentrations. Together with information in Annex A table B2, which shows the used level 2 and 3 foods, this would have maybe been possible, but the table does not present the percentage of left-censored data per food which makes a reconstruction not possible. Therefore, RIVM requests EFSA to provide a clarification for the used procedure. Additionally, RIVM asks EFSA to add a data column containing the percentage of left-censored data to Table B2 in Annex A. In addition, regarding the in- and exclusion of data, in line 2784 the words 'more than six samples' is used and in line 2805 the words 'less than six samples' is used, e.g. we read n>6 and 6<n respectively. EFSA did not specify whether a food category was in- or excluded when exactly 6 samples were available. EFSA is requested to address this.	Annex B has now been amended to include in Table B.2 additional columns with the percentage of left-censored data for all three stereoisomers. A column explaining how the food category was considered has now been included. The text in Section 3.2.1 of the Opinion has now been amended to better clarify the exclusion criteria.
	22	3.3.3. Non-dietary sources of exposure	Paragraph 3.3.3, lines 3334- 3338 and lines 3398-3400: Line 3334-3338 and 3398-3400 present the conclusion for non-dietary oral exposure and dermal exposure, respectively. The addressed exposures are typically part of consumer exposure which are covered by the regulatory frameworks REACH and Biocides (both ECHA), e.g. these exposures are assessed by prescribed harmonised REACH/Biocide models and their defaults. The advised model to use is ConsExpo. ConsExpo provides low and high tier models and defaults and is supported by a range of factsheets. See https://www.rivm.nl/en/consexpo EFSA assessed the exposures with different models and US EPA defaults instead of European models and defaults. The European models and defaults are based on European data and therefore describe the European situation. Therefore, RIVM is of the opinion that these are the preferable models to be used for the exposure assessment, also with the goal of harmonization within the EU. We therefore ask EFSA to provide and explanation supporting its choice to deviate from this.	The exposure assessment for dust performed in the Opinion is a rough estimate, to put the dietary exposure estimates into context and is not meant as a robust exposure assessment. The CONTAM Panel considers appropriate to use the values proposed by the US-EPA (2017) for dust ingestion for adults and children for the purpose of the CONTAM Panel estimation, noting that values proposed for biocides, refer to products that are purposely applied (e.g. by spraying). The CONTAM Panel did not attempt any dermal exposure assessment but described the evidence available.

Stakeholder	Comment number	Chapter	Comment[(a)]	EFSA response
	23	3.5.2. Exposure scenario/exposure model	Paragraph 3.5.2, lines 3476-3502: The full occurrence dataset did not contain samples for vegetable oils, ready-to-eat meal for infants and young children or dietary supplements due to high LOQ values and a high proportion of left-censored data. EFSA did not present these excluded occurrence data in the document nor in Annex B. Therefore, RIVM was not able to see what EFSA means with high LOQ values. RIVM asks EFSA to provide the occurrence data that was excluded based on the above mentioned criteria. In addition, EFSA is requested to explain whether the occurrence data excluded because of too high LOQs, contained quantified concentrations.	In Annex B a new table has now been included (Table B.5) reporting the summary statistics including percentage of left-censored data on data reported for Total HBCDDs (analysed by GC-MS), not considered for the exposure assessment due to high LOQs and high proportion of left-censored data. With the publication of the Opinion the raw data on occurrence of HBCDDs in food used will be publicly available (in Zenodo).
	24	Annex C - Benchmark dose (BMD) analysis	Annex C. EFSA states in ANNEX C lines 14-17 that "*the CONTAM Panel considered the default BMRs of 5% and 10% for continuous and quantal data, respectively, as indicated in the EFSA guidance on BMD in risk assessment (EFSA SC, 2017). Deviations from the default BMR were selected on a case by case basis and are justified in the specific modelling reports in this Appendix*." Could EFSA please explain why a BMR of 10% is used for continuous data as described in Table 2 or give justifications thereof?	The CONTAM Panel performed BMD modelling using the default BMR of 5% for continuous data. The BMDLs obtained for horizontal locomotion, rearing and total activity were far below the lowest dose administered and resulted in large BMD confidence intervals. Thus, the CONTAM Panel decided to use a BMR of 10%. In that case, the BMDLs obtained were also far below the lowest dose administered for horizontal locomotion and rearing, and/or resulted in large BMD confidence intervals (horizontal locomotion and total activity). Therefore, the Panel decided to use the traditional NOAEL/LOAEL approach for risk characterisation and presented only BMD modelling with a BMR of 10% for illustration in Annex C. The selection of the BMR has not been made clearer in Annex C.

(a): Comments are shown as received from the commenters.

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Abbreviations

BFRs	Brominated Flame Retardants
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit
BMDU	Benchmark dose upper confidence limit
BMR	Benchmark response
bw	body weight
CAR	Constitutive androstane receptor
CONTAM	Panel on Contaminants in the Food Chain
COT	Committee on Toxicity
EC	European Commission
ECB	European Chemicals Bureau
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
ER	Oestrogen receptor
GC-MS	Gas chromatography - mass spectrometry
GIC	Groningen Infant COMPARE
HBCDDs	Hexabromocyclododecanes
HBGV	Health-based guidance value
LC	Liquid chromatography
LOAEL	Lowest-observed-adverse-effect level
LOQ	Limit of quantification
MOE	Margin of exposure
NOAEL	No-observed-adverse-effect level
OECD	Organisation for Economic Cooperation and Development
PBDEs	Polybrominated diphenyl ethers
PBK	Physiologically Based Kinetic modelling
PND10	Postnatal day 10
POD	Point of departure
PXR	Pregnane-X-receptor
RIVM	Dutch National Institute for Public Health and the Environment
ROS	Reactive oxygen species
SD	Standard deviation
TBBPA	Tetrabromobisphenol A
UK FSA	United Kingdom Food Standards Agency
UNEP	United Nation Environment Programme
WG	Working Group
WHO	World Health Organization

Appendix 1 - Explanatory note to the Public Consultation

EFSA's Panel on Contaminants in the Food Chain (CONTAM) has launched an open consultation on the draft scientific Opinion on the update of the risk assessment of hexabromocyclododecanes (HBCDDs) in food. This document presents an estimation of the human dietary exposure to HBCDDs, and an assessment of the human health risks related to this dietary exposure.

Interested parties are invited to submit written comments by **25 November 2020**.

Please use the electronic template provided: https://ec.europa.eu/eusurvey/runner/Public_Consultation_HBCDDs to submit comments and refer to the line and page numbers. While the template is the only platform to be used for submitting comments, additional information to support your comments can be submitted using the upload function available in the tool (for files with a maximum size of 1 Mb). In case of technical issues in the upload of the supporting files you can contact specific unit's functional mailbox: biocontam@efsa.europa.eu.

All comments related to the EFSA draft scientific output shall be inserted in the electronic submission. Comments will not be considered when these are made outside the platform, for instances as part of any attachments.

Please note that comments will not be considered if they:

- are submitted after the closing date of the consultation
- are presented in any form other than what is provided for in the instructions and template
- are not related to the contents of the document
- contain complaints against institutions, personal accusations, irrelevant or offensive statements or material
- are related to policy or risk management aspects, which are out of the scope of EFSA's activity.

EFSA will assess all comments which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant. Due to time constraints, EFSA cannot use additional data on chemical contaminants submitted during the public consultation for the dietary exposure assessment in this risk assessment. These have to be submitted in SSD format to the EFSA Data Collection Framework (DCF) via the call for collection of chemical contaminants occurrence data in food and feed. Please contact data.collection@efsa.europa.eu to obtain further information and the credentials to access the DFC web interface. Occurrence data submitted following this process during the public consultation will be stored and considered for future risk assessments.

Copyright-cleared contributions

Persons or organizations participating in a Public Consultation of EFSA are responsible for ensuring that they hold all the rights necessary for their submissions and consequent publication by EFSA. Comments should inter alia be copyright cleared by taking into account EFSA's transparency policy and practice to publish all submissions. In case the submission reproduces third-party content in the form of charts, graphs or images, the required prior permissions of the right holder(s) should have been obtained by the PC respondent

Publication of contributions

Contributions will be published (as part of an EFSA report published together with the final opinion) and may be re-used by EFSA in a different context. It should be noted that contributions submitted by individuals in a personal capacity will be published as such, indicating the author's first and family name, unless a substantial justification for protection is provided by the respondent. Contributions submitted on behalf of an organization are also made publicly available and attributed to the organization in question.

Please note that additional information provided to support comments will be published as well. Besides ensuring that the submission is copyright-cleared, PC respondents shall therefore make sure that the material can be published by EFSA as such without any need for further editing or redaction, including the masking or suppression of any personally identifiable information (e.g.: names, contact details of individuals, signatures).

Submit comments (deadline: **25 November 2020**)

Published: 14 October 2020

Appendix 2 – Contribution submitted by RIVM

The following file was submitted by RIVM together with their contribution to the public consultation:

- **Supplementary _ BMD**

This file is available on the EFSA Knowledge Junction community on Zenodo at: http://doi.org/10.5281/zenodo.4476149