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

Addendum to the 2015 COT Statement on potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet.

Background

1. The Scientific Advisory Committee on Nutrition (SACN) is undertaking a review of scientific evidence that will inform the Government's dietary recommendations for infants and young children. SACN is examining the nutritional basis of the advice. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked to review the risks of toxicity from chemicals in the diet of infants and young children. The reviews will identify new evidence that has emerged since the Government's recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised.

2. In 2015 the COT issued a statement on the potential risks from the flame retardants hexabromocyclododecanes (HBCDDs) in the infant diet[1]. This addendum to the 2015 statement updates the exposures for infants aged 0-12 months as new data have become available and provides estimated HBCDD exposures for children in the UK aged one to five years. There are currently no Government dietary recommendations for infants and young children which relate to HBCDDs.

3. In its 2015 statement, the COT concluded that a Margin of Exposure approach should be taken for the risk assessment, in which estimated exposures to HBCDDs were compared to a reference point of 3 μg/kg bodyweight (bw)/day. This was derived from a study in which neonatal mice were given a technical mixture of HBCDDs by a single gavage administration and behavioural changes were observed in adulthood (Eriksson *et al*., 2006). A body burden approach, taking into account the slower rate of elimination of HBCDDs in humans compared to rodents, was used in line with the approach taken by EFSA (2011).

4. EFSA (2011) had considered that the potential for toxicokinetic differences between species had been taken into account using this approach. Furthermore, since the reference point was derived from

[1] http://cot.food.gov.uk/sites/default/files/HBCDDsstatementfinal.pdf

neurobehavioural effects in mice induced during the most critical period for brain development, and the body burden applied to the entire life span in humans, EFSA (2011) took the view that individual differences in susceptibility had been covered. EFSA thus concluded that a factor of 2.5 was needed to cover inter-species differences in toxicodynamics and a factor of 3.2 to cover uncertainties in the toxicokinetics in humans. This implied that an MOE greater than 8 (2.5 x 3.2) would indicate that there was no concern for health. In their 2015 Statement, the COT agreed that *"inter-species differences in toxicokinetics were accounted for by the body burden approach, and that the use of data relating to a critical period of development reduced uncertainties in the risk assessment.".* However, they considered that *"MOEs should be rather higher than 8 to provide reasonable assurance of safety.*"

New toxicological data

5. Members considered new toxicological data that had become available since the 2015 COT statement. In particular, a paper of Maurice *et al.* (2016), indicated a possible lower toxicological reference point. The COT expressed a number of reservations about the study, possibly compromising the validity of the statistical analysis, and concluded that the new data required confirmation and were not a sufficient basis upon which to modify the reference point.

HBCDD exposures in infants aged 0-12 months and young children aged 1 to 5 years

New data on sources of HBCDD exposure

Breast milk

6. There were no new UK data for HBCDD levels in breast milk. Occurrence data used previously for estimating exposure from breast milk were used to estimate exposure from this route in this paper.

Infant formula and commercial infant foods.

7. Data on the concentrations of HBCDDs in infant formula were not available previously. The concentrations of α-, β- and γ-HBCDDs in different varieties of infant formula and commercial infant foods were investigated recently in an FSA survey (Rose *et al.,* 2015). HBCDDs were not detected in 30 infant formula samples. The limit of detection (LOD) of 0.01 µg/kg for each congener was used in an upper-bound (UB) approach[2] for estimating exposure.

8. α-HBCDD was reported in only two out of 120 individual commercial infant food samples (at a level of 0.03 µg/kg). The UB mean concentration

[2] Using the value of the LOD concentration for data that were < LOD

was 0.01 µg/kg, which was equivalent to the LOD, and this value was used in the exposure assessment. The LOD value was similarly used for the other congeners in an UB approach to estimating exposure.

Other food

9. The most recent measurements of HBCDDs in other foods sampled in the UK were for the composite food groups of the 2012 Total Diet Study (TDS) (Fernandes *et al.,* 2012), as used previously (COT 2015)

Air

10. There were no new UK data on HBCDD levels in indoor air. Occurrence data used previously (COT 2015) for estimating exposure from air were used to estimate exposure from this route in this paper.

Dust and soil

11. A concentration range of 95-27477 µg/kg was reported for the sum of α-, β- and γ-HBCDDs in household dust collected from the living rooms of 29 UK homes in the West Midlands area during 2015, by Kuang *et al.* (2016). These levels are lower than those reported previously by Abdallah *et al.* (2008) for 45 different homes from the same region of the UK (range: 228 – 140774 µg/kg). The catchment area and methodology used by Kuang *et al.* (2016) were the same as those used by Abdallah *et al.* (2008), and in the absence of an explanation for the difference in levels, the two data sets have been combined in this paper[3]. The median, 97.5th percentile and maximum concentrations for the sum of α-, β- and γ-HBCDDs in the combined dataset were 725, 48667 and 140774 µg/kg, respectively . The median HBCDD level in 24 samples of UK soil from various urban and rural locations was reported to be 0.77 µg/kg (range 0.07 – 424 µg/kg) (Harrad *et al,* 2010).

Exposure

12. Consumption data (on a bodyweight basis) from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), and from years 1-4 of the National Diet and Nutrition Survey Rolling Programme (NDNS) (Bates *et al*., 2014) have been used for the estimation of dietary exposures for ages 4-18 months, and 18-60 months respectively. Bodyweight data used in the estimation of exposures by other routes are shown in Table 1 below.

Table 1: Body weights used in exposure assessments

Age bands (months)	Weighted bodyweight
0 - <4	5.9 kg[a]

[3] The COT is grateful to Professor Stuart Harrad, University of Birmingham UK, for provision of the individual data for this analysis.

4 - <6	7.8 kg[b]
6 - <9	8.7 kg[b]
9 - <12	9.6 kg[b]
12 - <15	10.6 kg[b]
15 - <18	11.2 kg[b]
18 - <24	12.0 kg[c]
24 - <60	16.1 kg[c]

[a] *DH, 1994.*
[b] *DH, 2013.*
[c] *Bates et al., 2014.*

Dietary exposure to HBCDDs

Breast milk

13. The estimated exposures of exclusively breast-fed infants, aged 0 to 6 months for HBCDDs (Table 2) are those in the 2015 COT statement. Data on breast milk consumption were used in estimating exposure from breast milk in the 6 - <18 months age groups (Table 2). There were too few records of breast milk consumption for children older than 18 months in NDNS to allow a reliable exposure assessment, and breast milk is expected to contribute minimally in this age group. Mean and high level estimates of exposure to α-, β- and γ-HBCDDs were 0.0020-0.11 ng/kg bw/day and 0.0041-0.16 ng/kg bw/day, respectively. High-level exposure to the sum of α-, β- and γ-HBCDDs from human milk was up to 0.16 ng/kg bw/day; α-HBCDD was the main contributor to total exposure.

Table 2: Estimated exposure to HBCDDs from breast milk

Isomer (maximum concentrations in ng/kg whole weight)		**HBCDD exposure from breast milk (ng/kg bw/day) by age group (months)**					
		0 - <4[a]	**4 - <6[a]**	**6 -<9[b]**	**9 - <12[b]**	**12 - <15[b]**	**15 - <18[b]**
α (0.69)	Mean	0.094	0.071	0.046	0.026	0.020	0.017
	High level	0.14	0.11	0.11	0.080	0.052	0.036
β (0.26)	Mean	0.035	0.027	0.017	0.0099	0.0076	0.0066
	High level	0.053	0.040	0.041	0.030	0.020	0.013
γ (0.080)	Mean	0.011	0.0082	0.0053	0.0030	0.0023	0.0020
	High level	0.016	0.012	0.013	0.0093	0.0060	0.0041
Sum (0.78)[c]	Mean	0.11	0.080	0.052	0.030	0.023	0.020
	High level	0.16	0.12	0.12	0.090	0.059	0.040

[a] *Mean and high level HBCDD exposures were based on exclusive breastfeeding and consumption of 800 and 1200mL of milk for mean and high level, respectively (COT, 2015).*
[b] *Consumption data from DNSYIC: high level is 97.5th percentile.*
[c] *Sum of $\alpha + \beta + \gamma$*
All values are rounded to 2 significant figures

Infant Formula

14. Possible UB HBCDD exposures from exclusive feeding on infant formulae were calculated for infants up to 6 months of age using the LOD for ready-to-feed 'first milk' infant formula (0.01 µg/kg) (Table 3). Exposures were up to 6 ng/kg bw/day.

Table 3: Estimated UB exposures to HBCDDs of infants aged 0 to 6 months from exclusively feeding on infant formula.

HBCDD isomer	UB HBCDD exposure (ng/kg bw/day) from exclusive infant formula (first milk) by age group (months)			
	0 - <4		4 - <6	
	800 mL[a]	1200 mL[a]	800 mL[a]	1200 mL[a]
α	1.4	2.0	1.0	1.5
β	1.4	2.0	1.0	1.5
γ	1.4	2.0	1.0	1.5
Sum[b]	4.2	6.0	3.0	4.5

[a] *Mean and high level exposures were based on exclusive feeding on infant formula and consumption of 800 and 1,200mL, respectively (COT, 2015).*
[b] *Sum of α, β and γ*
All values are rounded to 2 significant figures.

15. Possible UB exposures of infants and children aged 4.0 to <18 months from infant formula were also estimated using DNSIYC consumption data (DH 2013) (Table 4). UB exposures to the sum of α-, β- and γ-HBCDDs, based on consumption of all varieties of infant formulae, were up 4.7 ng/kg bw/day.

Table 4: Estimated UB exposure to HBCDDs from infant formula as part of the diet at age 4 to <18 months.

HBCDD isomer	UB exposure to HBCDDs (ng/kg bw/day) by age group (months)									
	4 - <6		6 - <9		9 - <12		12 - <15		15 - <18	
	Mean	High[a]	Mean	High[a]	Mean	High[a]	Mean	High[a]	Mean	High[a]
α	0.73	1.9	0.80	1.9	0.66	1.8	0.22	1.2	0.12	0.74
β	0.65	1.4	0.52	1.1	0.38	0.91	0.15	0.69	0.083	0.50
γ	0.65	1.4	0.52	1.1	0.38	0.91	0.15	0.69	0.083	0.50
Sum[b]	2.0	4.7	1.8	4.1	1.4	3.6	0.52	2.6	0.29	1.7

[a] *High level is 97.5th percentile*

[b] *Sum of α, β and γ*
All values are rounded to 2 significant figures.

Commercial infant foods

16. Table 5 summarises the exposures to HBCDDs from commercial infant foods estimated for infants and young children up to 18 months using DNSIYC consumption data (DH 2013). UB exposures to the sum of α-, β- and γ-HBCDDs, based on consumption of all varieties of commercial infant foods, were up to 1.6 ng/kg bw/day.

Table 5: Estimated UB exposures to HBCDDs from commercial infant foods at age 4 to <18 months.

HBCDD isomer	UB dietary exposure to HBCDDs (ng/kg bw/day) by age group (months)									
	4 - <6		6 - <9		9 - <12		12 - <15		15 - <18	
	Mean	High[a]	Mean	High[a]	Mean	High[a]	Mean	High[a]	Mean	High[a]
α	0.099	0.46	0.14	0.53	0.12	0.51	0.067	0.36	0.04	0.22
β	0.099	0.46	0.14	0.53	0.12	0.51	0.067	0.36	0.04	0.22
γ	0.099	0.46	0.14	0.53	0.12	0.51	0.067	0.36	0.04	0.22
Sum[b]	0.30	1.4	0.42	1.6	0.36	1.5	0.20	1.1	0.12	0.66

[a] *High level is 97.5th percentile*
[b] *Sum of α, β and γ*
All values are rounded to 2 significant figures.

Other foods

17. UB mean and high-level estimates of infant dietary exposure to HBCDDs were previously calculated using measurements for the 19 composite food groups analysed in the 2012 TDS in combination with data on the consumption of those foods from DNSIYC. Table 6 summarises UB dietary exposures to α-, β- and γ-HBCDDs for 12 to 60 month old children. These were also estimated using concentrations reported previously for the 2012 TDS (Fernandes *et al.,* 2012) together with consumption data from the DNSIYC (DH 2013) and NDNS (Bates *et al.,* 2014).

18. Mean and high level UB exposures in other foods were higher than those estimated from infant formula or commercial infant foods. The highest UB high-level exposure to the sum of α-, β- and γ-HBCDDs was 7.5 ng/kg bw/day in 12 to <60 month old children. This exposure is slightly lower than the corresponding value (10 ng/kg bw/day) estimated for the 4 to 12 month old infants in the 2015 COT statement. As with infant formula and commercial foods, HBCDDs were not detected in most of the food groups in TDS and thus, it is possible that actual exposures are substantially lower than the UB estimates .

Table 6: Estimated exposure to HBCDDs from food at age 12 to 60 months.

HBCDD Isomer	UB dietary exposure to HBCDDs (ng/kg bw/day) by age group (months)							
	12 - <15		15 - <18		18 - <24		24 - <60	
	Mean	High[a]	Mean	High[a]	Mean	High[a]	Mean	High[a]
α	1.5	3.2	1.7	3.1	1.9	3.9	1.5	2.7
β	0.90	1.8	0.93	1.6	1.0	1.7	0.81	1.3
γ	0.95	1.9	0.99	1.7	1.1	1.9	0.90	1.6
Sum[b]	3.4	6.9	3.6	6.4	4.0	7.5	3.2	5.6

[a] *High level is 97.5th percentile*
[b] *Sum of α, β and γ*
All values are rounded to 2 significant figures.

19. Although dietary supplements like cod liver oil are not recommended for children under 3 years of age, there were five recorded cases in the DNSIYC in which infants aged 12 to 18 months were given daily doses of 9 to 45 mg fish oil /kg bw, either by spoon or from capsules. Assuming the highest UB concentration of HBCDDs (2.99 ng/g) reported by EFSA for bottled fish oil, 45 mg fish oil /kg bw/day would lead to an exposure of 0.13 ng HBCDDs /kg bw/day. The NDNS recorded no cases of children aged 18 to 24 months being given fish oil dietary supplements like cod liver oil. There were six recorded cases in the NDNS in which children aged 24 to 60 months were given daily doses of 11 to 117 mg fish oil /kg bw, either by spoon or as capsules. Assuming the highest UB concentration of HBCDDs reported by EFSA, 117 mg fish oil /kg bw/day would lead to an exposure of 0.35 ng HBCDDs /kg bw/day. The small number of consumers in DNSIYC and NDNS and the incompleteness of the recorded data on consumption mean that there are large uncertainties in performing a risk assessment for HBCDDs in fish oil, and it is not clear how relevant the data reported by EFSA are to fish oil on the UK market.

Environmental exposures to HBCDD

Air

20. The estimated exposures to the sum of HBCDDs from air that were reported for infants previously (COT, 2015) are updated in Table 7, together with estimated exposure for 12 to 60 month old children, on the basis of ventilation rates for infants and young children (US EPA, 2011) using the total mean reported occurrence value of 250 pg/m^3 (range 67 – 1300 pg/m^3) in indoor air from 45 homes in Birmingham UK. The exposure to the sum of α-, β- and γ-HBCDDs via air ranged from 0.13 to 0.19 ng/k bw/day.

Table 7: Estimated exposure to the sum of α–, β– and γ–HBCDDs from air

Sum HBCDD mean concentration	Exposure to HBCDDs in air (ng/kg bw/day) by age group (months)							
	0 - <4 (3.6)[a]	**4 - <6** (4.1)[a]	**6 to <9** (5.4)[a]	**9 to <12** (5.4)[a]	**12 - <15** (8.0)[a]	**15 - <18** (8.0)[a]	**18 - <24** (8.0)[a]	**24 - <60** (10.1)[a]
250pg/m^3	0.15	0. 13	0. 16	0.14	0.19	0.18	0.17	0.16

[a] *Ventilation rate in m^3/day.*
All values are rounded to 2 significant figures

Dust and soil

21. Exposure to HBCDDs through ingestion of dust and soil were estimated assuming ingestion of 60 mg/day at age 6 to 12 months and 100 mg/day at age 12-60 months (US EPA, 2011), based on the median, 97.5th percentile and maximum concentrations of dust reported in paragraph 11 (Table 8). Since there were no recent data for soil, the exposure calculations below were based on concentrations in dust, with the assumption that the value is the same as for soil. However, as earlier data from the UK (Harrad *et al*, 2010) indicated that HBCDD levels in soil were much lower than those for house dust, (median 0.77 µg/kg vs. 725 µg/kg), these estimates of total exposure are likely to be conservative. Estimated exposures were up to 6.8, 460 and 1300 ng/kg bw/day for the sum of α-, β- and γ-HBCDDs when using the median, 97.5th percentile and maximum concentration, respectively (725, 48667 and 140774 µg/kg).

Table 8: Possible HBCDD exposure from dust and soil in infants and young children aged 6 to 60 months

Sum α+β+γ HBCDD (µg/kg)	Exposure to HBCDDs in dust and soil (ng/kg bw/day) by age group (months)					
	6 - <9	**9 - <12**	**12 - <15**	**15 - <18**	**18 - <24**	**24 - <60**
Median (725)	5.0	4.5	6.8	6.5	6.0	4.5
97.5th percentile (48667)	340	300	460	430	410	300
Maximum (140774)	970	880	1300	1200	1200	870

All values are rounded to 2 significant figures.

Risk characterisation

22. MOEs were calculated as the ratio of the reference point of 3 μg/kg bw/day to the estimated exposures to the sum of HBCDDs from different sources (Table 9). All MOEs are 400 or greater and thus of no toxicological concern, with the exception of those based on the 97.5th percentile and the highest reported concentration of HBCDD in household dust, for which the MOEs were 7 – 10 and $\leq$ 3 respectively. The 97.5th percentile MOEs are close to the value of 8, considered by EFSA (2011) to be the limit for toxicological concern. Taking into account that the exposure estimate is conservative due to the assumption that soil could contain similar levels of HBCDDs to dust, this MOE does not indicate a toxicological concern The maximum reported concentration was very much higher than the median or 97.5th percentile, and while such exposure would potentially be of toxicological concern, it would, however, be expected to affect very few children. MOEs for fish oil were ≥9000.

Conclusions

23. Exposure to HBCDDs arises from its historical use as a flame retardant, and subsequent release to the environment. The major sources of exposure for infants and young children are food and household dust.

24. The risks associated with exposure of infants and young children to HBCDDs are assessed in this addendum in relation to a toxicological reference point of 3 μg/kg bw/day, used previously by the COT. The new toxicological data were not a sufficient basis on which to modify this reference point.

25. The margins of exposure to HBCDDs by dietary intake of breast milk, infant formula, commercial infant food, fish oil and food in general are at least 400 and not a cause for concern for any age group, as they are considerably greater than 8.

26. Data for household dust in the UK were available from two publications, with different ranges reported. Because there was no clear explanation for the differences, the COT decided to combine the datasets in order to calculate overall median and 97.5th percentile values for use in the risk assessment. The overall maximum level was also used since it is possible that this value is relevant for a small number of homes.

27. While the level of HBCDDs in the diet of infants and young children is not a cause for concern, the possibility of high levels in household dust continues to be so. Levels in dust should be monitored in houses to determine whether they decrease, now that production and usage of HBCDDs has largely ceased.

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Table 9. MOEs for exposure to the sum of HBCDDs from different sources

Source		MOEs by age group (months)							
		0 -<4	**4-<6**	**6-<9**	**9-<12**	**12-<15**	**15-<18**	**18-<24**	**24-<60**
Breast milk[a]	Mean	30000	40000	60000	100000	100000	200000	NR[b]	NR
	97.5th percentile	20000	30000	30000	30000	50000	80000	NR	NR
Infant formula[a]	Mean	700	1000	2000	2000	6000	10000	NR	NR
	97.5th percentile	500	700	700	800	1000	2000	NR	NR
Commercial infant food	Mean	NR	10000	7000	8000	20000	30000	NR	NR
	97.5th percentile	NR	2000	2000	2000	3000	5000	NR	NR
Other foods	Mean	NR	NR	NR	NR	900	800	800	900
	97.5th percentile	NR	NR	NR	NR	400	500	400	500
Air	Mean	20000	20000	20000	20000	20000	20000	20000	20000
Dust/soil	Median	NR	NR	600	700	400	500	500	700
	97.5th percentile	NR	NR	9	10	7	7	7	10
	Maximum	NR	NR	3	3	2	3	3	3

[a] *Based on exclusive feeding up to 6 months*
[b] *NR – not relevant*
All MOEs are rounded to 1 significant figure.

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