TOX/2014/24

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

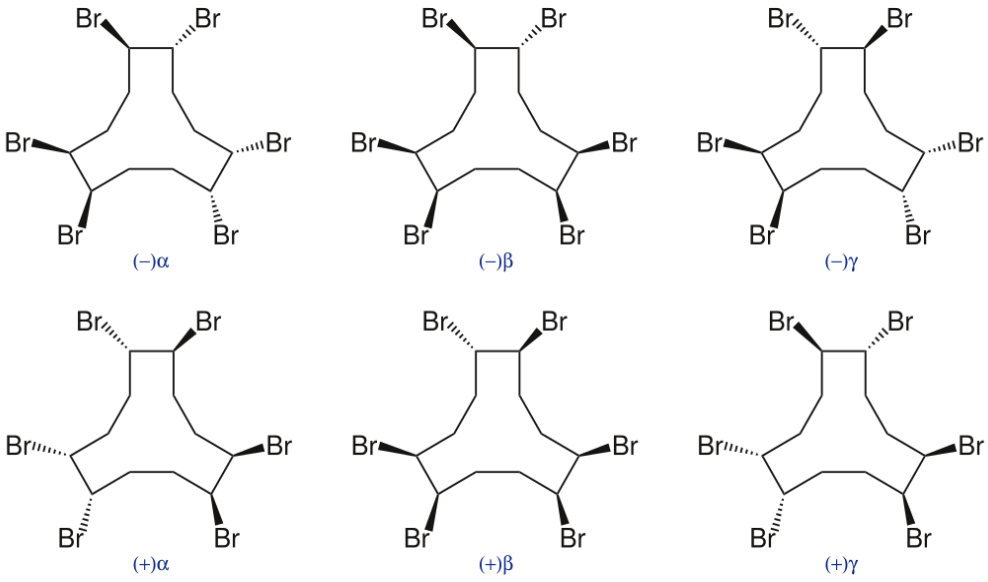
Scoping paper on the potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet

Introduction

1. The Committee on Toxicity (COT) has been asked to consider aspects related to the toxicity of chemicals in food, in support of a review by the Scientific Advisory Committee on Nutrition (SACN) of Government recommendations on complementary and young child feeding. Members concluded that brominated flame retardants (BFRs) should be considered as part of that body of work.

2. 1,2,5,6,9,10-Hexabromocyclododecane (HBCDD, sometimes also abbreviated as HBCD) is a member of the large chemical class of bromochemicals referred to as brominated cycloalkanes. HBCDD is a man-made chemical that is widely used as an additive flame retardant in fabrics and polystyrene products.

3. Technical HBCDD consists of diastereomeric pairs of enantiomers, the main constituents being designated α, β and γ, as shown below.



4. Evaluations of HBCDDs in fish have been conducted by the COT[1,2] (see Annex A), and the European Food Safety Authority (EFSA) (EFSA, 2011) (see Annex B). This scoping paper draws on information from those reviews and in addition provides an estimate of the exposure of infants to HBCDD from breast milk, food and non-dietary sources. It also summarises toxicokinetic, toxicology and

[1] http://cot.food.gov.uk/pdfs/bfrstatement.pdf
[2] http://multimedia.food.gov.uk/multimedia/pdfs/cotstatementfishsurveys.pdf

epidemiology studies that have been published since the most recent evaluation by EFSA.

Previous evaluations of COT and EFSA

COT

5. COT, in its statement on BFRs in fish from the Skerne-Tees rivers system (2004)[1] observed that the uncertainties and deficiencies in the toxicological databases for HBCDDs prevented establishment of tolerable daily intakes (TDIs) and so adopted a Margin of Exposure (MOE) approach to its risk assessment. Although neurodevelopmental effects were recognised as the most sensitive end point for HBCDD toxicity, the 2004 statement concentrated on exposure of fish and the available data did not allow extrapolation to infants of a comparable developmental stage. In the absence of a NOAEL, the LOAEL of 100 mg/kg for liver toxicity was used as the point of departure to determine MOEs. In 2006 COT produced another statement on chlorinated and brominated flame retardants in fish and shellfish[2].

EFSA

6. EFSA (2011) identified neurodevelopmental effects as the critical end-point and derived a benchmark dose lower confidence limit for a benchmark response of 10 % ($BMDL_{10}$) from the study of Eriksson et al. (2006). Eriksson et al. administered a single oral gavage dose of HBCDD (α-, β- and γ-HBCDD with a relative content of 3 %, 8 % and 89 %, respectively) at either 0.9 or 13.5 mg/kg bw to NMRI mouse pups at the age of 10 days, the peak time of brain growth activity in mice. At 3 months of age the mice were tested for changes in locomotion and memory. The mice treated with HBCDD at the higher dose initially scored lower than controls and low dose animals in the locomotion tests but maintained their level of activity so that after 40 minutes they were significantly more active than the other two groups ($p < 0.01$). The higher dose group also took significantly longer than the other groups to complete a swim maze test ($p < 0.05$), suggesting that spatial learning was impaired. EFSA modelled the dose-response data from this study to derive a $BMDL_{10}$ of 0.93 mg/kg bw.

7. The much slower rate of elimination in humans compared to rodents led EFSA to take body burden into account by estimating human intake associated with the body burden at the $BMDL_{10}$ (assuming 85% uptake of the single oral dose). The body burdens were then converted into a human intake of 3 µg/kg bw/day estimated to result, following attainment of steady state, in the body burden at the $BMDL_{10}$. EFSA concluded that, due to the limitations and uncertainties in the available data on HBCDDs, a MOE approach for the risk characterisation of HBCDDs should be taken using the estimated human intake at the $BMDL_{10}$, of 3 µg/kg bw/day, as the reference point.

8. EFSA also concluded that by applying this body burden to the entire life span in humans, individual difference in susceptibility had been covered. Therefore, the calculated MOE should be sufficient to cover interspecies differences in dynamics for the effects observed (factor 2.5). Considering the uncertainty in the elimination half-

life in humans EFSA concluded that the MOE should also cover individual differences in kinetics (factor 3.2) and that an MOE larger than 8 (2.5 × 3.2) might indicate that there is no health concern.

Differences in the approaches of COT and EFSA

9. Both the COT and EFSA concluded that, due to the inadequacies of the data generated by published toxicology assessments on the HBCDDs, a TDI could not be established and a MOE approach to risk assessment was more appropriate. COT derived their MOE from a LOAEL value of 100 mg/kg in the absence of a NOAEL value.

10. EFSA modelled the dose-response data in order to calculate a $BMDL_{10}$, followed by toxicokinetic modelling to estimate the daily intake that would result in the body burden at the $BMDL_{10}$.

New Data

11. A literature search was conducted for toxicokinetic, toxicology and epidemiology studies published since the EFSA Opinion (2011). The search strategy is included in Annex C and the data are summarised below.

Absorption, distribution, metabolism and excretion

Absorption

12. In an *in vitro* colon extended physiologically based extraction test (CEPBET) incorporating human gastrointestinal tract (GIT) parameters (including pH and chemistry, solid-to-fluid ratio, mixing and emptying rates), following ingestion of indoor dust, the uptake of γ-HBCDD (72%) was less than that for α- and β-isomers (92% and 80% respectively). This may be attributed to the lower aqueous solubility of the γ-isomer (2 µg/l) compared to the α- and β-isomers (45 and 15 µg/l respectively) but does not completely exclude the possibility of *in vivo* enantioselective absorption of HBCDDs. (Abdallah et al., 2012).

13. A single oral dose of 3 mg/kg of [^{14}C]-labelled β-HBCDD was absorbed rapidly (≥ 85% total dose) in the female C57BL/6 mouse. The C_{max} for β-HBCDD-derived radioactivity in tissues, except adipose, was 3h following gavage dosing. Approximately 90% of the administered dose was excreted in urine and faeces within 24h, primarily as β-HBCDD-derived metabolites, but about 9% was excreted in faeces as γ-HBCDD. Oral administration of 30 or 100 mg/kg of β-HBCDD resulted initially in slower rates of [^{14}C] elimination but cumulative excretion was similar across the dosing range 4 days post dosing. Residual concentrations of [^{14}C] in tissues were highest in adipose and liver. β-HBCDD-derived radioactivity accumulated in most tissues following four consecutive daily oral doses of 3 mg/kg. The extent of metabolism and excretion of β-HBCDD in female C57BL/6 mice was similar to that for γ-HBCDD. The potential for accumulation of β-HBCDD-derived material in most tissues appeared to be less than for α-HBCDD (Sanders et al., 2013).

Distribution

14. HBCDD levels in visceral fat and subcutaneous abdominal fat in 52 obese patients undergoing bariatric surgery in Belgium as 4.0 and 3.7 ng/g lipid respectively. (Malarvannan et al., 2013).

15. HBCDDs were found in the placentas of Canadian women following elective pregnancy terminations over a range of concentrations from <LOD (<1 ng/g) to 5,600 ng/g lipid and in fetal liver up to 4,500 $ng.g^{-1}$ lipid. Measurable concentrations were present in placenta and fetal liver from as early as 6.5 weeks gestation (Rawn et al., 2014).

Metabolism

16. In adult C57BL/6 female mice orally administered α- or γ-[^{14}C]HBCDD (3 mg/kg bw), four hydroxylated metabolites were detected in faecal extracts from mice exposed to α-HBCDD, and one of these metabolite isomers was consistently characterised in liver, brain and adipose tissue extracts. In contrast, faecal extracts from mice exposed to γ-HBCDD contained multiple isomers of monohydroxy-pentaBCDD, dihydroxy-pentaBCDD, and dihydroxy-pentaBCDD, while in liver and adipose tissues extracts only a single monohydroxy-pentaBCDD metabolite was observed. Both α- and γ-HBCDD were transformed to metabolites that formed covalent bonds to proteins and/or lipids in the gut (Hakk et al., 2012).

Toxicological Data

Repeat dose toxicity

17. Dietary administration of HBCDD to mice at 199 mg/kg bw/day for 28 days resulted in an increase in liver weight and fat content and changes in thymus and thyroid tissues. Serum testosterone and testosterone/ oestradiol ratio were also increased (Maranghi et al., 2013).

18. Five-week-old male C57BL/6JJcl mice fed a high-fat diet (HFD) and dosed concurrently with HBCDD by oral gavage increased in body weight when compared with controls fed the HFD alone. Weight increase was significant when HBCDD was given once a week for 15 weeks at 35 μg/kg/week ($p<0.05$) or 700 μg/kg/week ($p<0.01$) but not at 1.75 μg/kg/week. Liver weights also increased significantly at the same doses ($p<0.01$ for 35 and 700 μg/kg/week) over the same period These increases were paralleled by increases in blood glucose and insulin levels and enhancement of micro-vesicular steatosis and macrophage accumulation in adipose tissue. HBCDD-treated high-fat-fed mice also had increased mRNA levels of PPARγ (peroxisome proliferator-activated receptor-γ) in the liver and decreased mRNA levels of Glut4 (glucose transporter 4) in adipose tissue compared with vehicle-treated high-fat-fed mice. (Yanagisawa et al., 2014).

Neurotoxicity

19. Rasinger et al. (2014) fed juvenile BALB/c mice a diet containing 1.3 g/kg HBCDD, resulting in a dose of 200 mg HBCDD/kg bw per day, for 28 days. HBCDD penetrated the blood brain barrier and reached a concentration in the cerebral cortex of 4.75 ± 0.7 μg/g dry weight. HBCDD induced 90 genes in the brain including sets relating to olefactory receptor activity and dephosphorylation, in particular protein tyrosine phosphatase activity. A highly significant cohort of 33 HBCDD regulated genes were involved in G-protein coupled receptor signalling. HBCDD also uniquely induced significant changes in the protein abundance of adenosine kinase (ADK), heatshock 105 kDa/110 kDa protein 1(HSPH1) and septin 6 (SEPT6).

Developmental Toxicity

20. Following on from the work of Saegusa et al (2009), who found that maternal exposure of rats to 10,000 ppm HBCDDs in the diet may affect glial cell development in fetuses, Saegusa et al. (2012) showed that feeding the same dietary concentration of HBCDD to rats from gestational day 10 to weaning at postnatal day 20 caused aberrant neuronal migration in the hippocampal dentate gyrus of their pups. Fujimoto et al.(2013), using the same dosing period also found that HBCDDs at > 1,000 ppm in the maternal diet may affect glial cell development in fetuses.

Immunotoxicity

21. Transient changes in the titre of T, B and NK cells were observed in the immune system of rat pups following administration of HBCDD at 100 – 10,000 mg/kg in the diet to the dams from gestational day 10 to post-natal week 3 (PNW3). Titres of activated T cells decreased, inactivated B cells increased and spleen NK cells were decreased in PNW3 but these changes disappeared by PNW11. Production of anti- Keyhole limpet haemocyanin (KLH) IgG following KLH immunisation was reduced by treatment with 10,000 mg/kg HBCDD in the diet. (Hachisuka, 2010). (abstract only available in English, paper in Japanese)

In vitro studies

22. HBCDD increased the proliferation of MCF-7 human breast cancer cells and up-regulated the expression of the oestrogen receptor-related Trefoil factor 1 gene in a concentration-dependent manner. The anti-oestrogen ICI 182,780 inhibited this up-regulation, indicating that HBCDD displays oestrogen-like effects on MCF-7 cells (Dorosh et al., 2011).

23. HBCDD (1- 10 μM) inhibited human chorionic gonadotropin- and forskolin-supported cAMP accumulation and steroidogenesis in peripubertal rat Leydig cells. It also inhibited basal cAMP production, but elevated basal steroidogenesis. HBCDD also inhibited the expression of several cAMP-dependent genes, including steroidogenic acute regulatory protein, cholesterol side chain cleavage enzyme, and 3β-hydroxysteroid dehydrogenase. This was not accompanied by a decrease in steroidogenic acute regulatory protein expression, as documented by western blot analysis. The activity of steroidogenic enzymes was unchanged, and steroidogenesis was unaffected in the presence of permeable 22(R)-hydroxycholesterol. However, HBCDD caused a significant decrease in

mitochondrial membrane potential in both untreated and human chorionic gonadotropin-treated cells. (Fa et al., 2013).

24. HBCDD significantly reduced the chemosensitivity of human hepatocellular carcinoma cells to cisplatin, increasing the cell viability and decreasing DNA damage. HBCDD also induced the transcriptional activity of NF-κB and suppressed the p53 expression in HepG2 and MHCC97H cells. In MHCC97L cells, however, opposite changes for NF-κB protein expression, NF-κB transcriptional activity, and p53/Mdm4 expression were observed after HBCDD exposure. HBCDD exposure significantly increased the expression level of p-Akt and mammalian target of rapamycin (mTOR) in HepG2 and MHCC97H cells, but reduced that in MHCC97L cells. PI3K inhibitor LY294002 relieved the influence of HBCDD on chemoresistance in HepG2 and MHCC97H cells (An, Wang et al., 2014).

25. HBCDD at 40 and 60 μM significantly decreased the viability of HepG2 human hepatocellular carcinoma cells and elevated cell apoptosis ratio, intracellular Ca^{2+} level, cytoplasmic cytochrome c level, and reactive oxygen species production. This effect was accompanied by a loss of mitochondrial membrane potential. Mobilization of nuclear factor erythroid 2-related factor 2 (Nrf2) increased, indicating an activation of stress-responsive genes (An, Chen et al., 2014).

26. HBCDD has been found to kill SH-SY5Y human neuroblastoma cells with a LC_{50} of 3 μM. There was a high correlation (0.94) in potency between lethality and inhibition of the sarcoplasmic-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) (IC_{50} = 2.7 μM), indicating a high probability that SERCA inhibition is the mechanism behind the toxicity. (Al-Mousa & Michaelangeli, 2014).

27. HBCDD affected the FSH-driven signal transduction and ovulatory competence of rat granulosa cells by over-activating the FSH-stimulated extracellular-regulated kinase 1/2 (ERK1/2) and protein kinase B (PKB or AKT). HBCDD also potentiated FSH-stimulated epidermal growth factor receptor phosphorylation in granulosa cells and decreased the FSH-induced luteinizing hormone receptor (Lhr) expression (Fa et al., 2014).

28. Koike et al., (2013) found that splenocyte viability was reduced by more than 40% by incubation with 10 μg/ml HBCDD for 24 hours whereas the viability of bone marrow cells was enhanced by 30% over 6 days of differentiation into dendritic cells. Markers for T-cell activation were increased in splenocytes and bone-marrow derived dendritic cells, indicating that immune/allergic responses may be increased by exposure to HBCDD.

29. A low-dose (10^{-10} M) HBCDD suppressed Thyroid Hormone (TH) receptor-mediated transcription and significantly suppressed TH-induced dendrite arborization of Purkinje cells in primary cerebellar culture derived from newborn rat. Ibhazehiebo et al. (2011a).The same dose of HBCDD also significantly suppressed TH-induced neurite extension of cerebellar granule cells This effect that was rescued by brain-derived neurotrophic factor (BDNF) in the presence of T3, suggesting that HBCDD may disrupt the T3 stimulated increase in BDNF that promotes granule cell development. Ibhazehiebo et al 2011b)

Epidemiological studies

30. Kim & Oh (2014) found a statistically significant ($p < 0.05$) negative correlation between exposure to β-HBCDD and the level of triiodothyronine (T3) in the mothers of children with congenital hypothyroidism. There was also a correlation between β-HBCDD and thyroid stimulating immunoglobulin (TSI) in their infants but this was not significant ($p < 0.1$). These authors concluded that although the findings were suggestive of effects on human thyroid function, the small number of subjects tested (26 mother-infant pairs) meant that a larger study would be needed to verify these results.

31. The HBCDD concentration in house dust has been correlated ($p = 0.004$, Spearman's $r = 0.46$) with decreased sex hormone binding globulin and increased free androgen index in men from couples seeking fertility treatment (Johnson et al., 2013).

32. Meijer et al. (2012) found a Spearman rank correlation of -0.31 between maternal blood concentration of HBCDD in 34 women at the 35th week of pregnancy and free testosterone level in their male infants at 3 months after birth but the effect was not significant ($p< 0.1$). There was no reported effect on infant testes volume nor penile length, the other measured parameters of the study. The authors suggested that more and longer term studies were required to clarify any potential effects on early male sexual development.

Sources of exposure to HBCDDs

33. Since HBCDD is not bound to the material it is intended to flame-proof, it can migrate into its surroundings and has become widely distributed in the environment. Temporal measurement trends seem to be variable (Law et al., 2014; Dietz et al., 2013). Considering the ubiquitous use of HBCDD it may potentially be found in food, breast milk, drinking water, indoor dust and soil particles.

Breast milk

34. A study conducted in Birmingham, UK, found HBCDDs in 34 samples of human milk, collection period unspecified, (average ΣHBCDDs = 208.3 ng/kg whole weight) where α-HBCDD comprised 62-95% of ΣHBCDDs while β- and γ-HBCDD constituted 2-18% and 3-33% respectively (see Table 1). Enantioselective enrichment of (-)-α-HBCDD (average enantiomer fraction = 0.29) was observed indicating potential enantioselectivity associated with HBCDD absorption, metabolism and/or excretion (Abdallah & Harrad, 2011). These values were in broad agreement with a comprehensive study from Ireland that covered HBCDDs and other halogenated flame retardants in breast milk and found the mean sum of HBCDD enantiomers to be 123.2 ng/kg whole weight, with α-HBCDD representing over 70% of the total (Pratt et al., 2013).

Table 1. HBCDD in breast milk sampled in the UK.

Reference	Isomer	HBCDD concentration in breast milk (ng/ kg whole weight) [a]			
		Mean	Minimum	Median	Maximum
Abdallah & Harrad 2011	α	171.9	26.3	110.0	689.9
	β	11.2	2.8	10.5	26.3
	γ	25.6	4.6	19.6	80.2
	Σ	208.3	36.4	134.0	783.9

[a] Data converted to whole milk basis from fat weight basis assuming breast milk contains 3.5% fat.

Infant Formula and Drinking Water

35. No data were available

Air and dust

36. Searches for HBCDDs in the air found a number of papers where there was some ambiguity as to whether the phase analysed was atmospheric gas or particles suspended in it and therefore the distinction between "air" and "dust" was unclear. Abdallah et al. (2008b) found a median concentration of 180 pg Σ HBCDD/m^2 in the indoor air from 33 homes in Birmingham UK and the authors suggested that inhalation constituted only a minor route of exposure. Both air and dust showed isomeric proportions had shifted from those in technical HBCDD (α:β:γ 3:8:89) with air being 22% α: 11% β: 65% γ and dust being 33% α: 11% β: 56% γ. Table 2 shows measurements of HBCDD in dust from houses and cars.

Table 2. HBCDD in domestic dust

Sampling date where given	Environment	Σ[HBCDD] (ng/g)	Reference
March – December 2007	House Car	228 – 140774 (range,n = 21) 194 – 55822 (range, n=12)	Abdallah et al., 2009
	House	1 300 (median, n = 45)	Abdallah et al., 2008a
	House	730 (median n = 31	Abdallah et al., 2008b
2009	Car	9200 (median n = 14)	Harrad and Abdallahl, 2011

37. A study investigating spatial and temporal enantiomeric shifts in ΣHBCDD (the sum of the total amounts of each isomer) in household dust revealed a rapid photolytically-mediated shift from γ-HBCDD to α-HBCDD that was complete after one week of exposure, and a slower degradative loss of HBCDDs via elimination of HBr. When exposed to light the decay of ΣHBCDD was faster than in light-shielded samples ($t_{1/2}$ =12 weeks and 24 weeks respectively) Spatial variation within sampled rooms was substantial and in one room correlated negatively with distance from a television that was identified as the source of HBCDDs. Significant negative correlation was observed in one room between concentrations of ΣHBCDD and dust loading (g dust/m^2 floor), implying that "dilution" occurs at higher dust loadings. (Harrad et al., 2009).

Soil

38. Atmospheric dust in the internal and external environment may contain a variable amount of soil contaminated from industrial sources that may be ingested as wind-blown particles. Most papers found in a search for levels in soil relate to polluted industrial sites in China and other Far East countries. These are unlikely to have any relevance to the exposure of UK infants to HBCDDs in soils

Food

39. The most recent measurements of HBCDD in food sampled in the UK are in the composite food groups of the 2012 Total Diet Study (TDS) (Fernandes et al., 2012). The three major diastereomers were measured individually. The levels were mostly below the limits of detection, as shown in Table 3.

Table 3. Concentrations of individual HBCDD isomers in food expressed on a whole weight basis

Food group	Concentration of HBCDD isomer in food item (µg/kg)		
	α-HBCDD	β-HBCDD	γ-HBCDD
Bread	0.03	<0.02	0.03
Cereals	0.03	<0.02	<0.02
Carcase meat	0.25	<0.01	<0.01
Offal	0.03	<0.01	<0.01
Meat products	0.1	0.02	<0.02
Poultry	<0.01	<0.01	<0.01
Fish	0.08	<0.01	<0.01
Fats & oils	0.16	<0.03	<0.05
Eggs	<0.01	<0.01	<0.01
Sugar and Preserves	<0.02	<0.01	<0.02
Green vegetables	0.01	<0.01	<0.01
Potatoes	<0.01	<0.01	<0.01
Other vegetables	<0.01	<0.01	<0.01
Canned Vegetables	<0.01	<0.01	<0.01
Fresh Fruit	<0.01	<0.01	<0.01
Fruit Products	0.04	<0.02	<0.03
Milk	<0.01	<0.01	<0.01
Dairy Products	0.03	<0.02	<0.02
Nuts	<0.06	<0.10	0.06

Exposure to HBCDDs

40. The exposure assessments for air, soils and dust and the diet presented here are based on external exposure. Bodyweight data are from the UK Dietary and Nutrition Survey of Infants and Young Children (DNSIYC, DH, 2013), with average bodyweights of 7.8, 8.7 and 9.6 kg for infants aged >4 – 6.0, >6.0 – 9.0 and >9.0 – 12.0 months old respectively. Since DNSIYC did not include infants younger than 4 months, in this statement a value of 5.9 kg for infants ages 0 – 3 months from an earlier survey (DH, 1994) is assumed for infants aged 0 – 4 months.

Dietary exposure to HBCDDs

Breast milk

41. Table 4 shows estimated exposure of exclusively breast-fed infants based on the median and maximum values from the data of Abdallah and Harrad (2010) for average (800 mL) and high-level (1200 mL) daily consumption of breast milk.

Table 4. Estimated exposure of UK infants to HBCDD from exclusive breastfeeding.

Isomer	Exposure ng/kg bw							
	Average consumer 800 mL/day				High consumer 1200 mL/day			
	0 - 4 months		>4 – 6 months		0 - 4 months		>4 – 6 months	
	Median	Max	Median	Max	Median	Max	Median	Max
α	14.9	93.4	11.3	70.8	22.4	140.3	16.9	106.1
β	1.4	3.6	1.1	2.7	2.1	5.3	1.6	4.0
γ	2.7	10.9	2.0	8.2	4.0	16.3	3.0	12.3
Σ	18.2	106.3	13.7	80.4	27.3	159.4	20.6	120.6

Exposure values calculated from occurrence data from Abdallah and Harrad 2010.

Food

42. UK data on HBCDD in infant formula and commercially-produced infant food are not available. Table 5 summarises the upper bound mean and high level infant dietary exposure to HBCDD estimated using the 19 composite food groups of the 2012 TDS together with consumption data from DNSIYC. Since HBCDDs were not detected in most of the food groups, it is possible that the upper bound approach over-estimates actual exposure. The individual item data are in Annex D.

Table 5. Estimated total dietary exposure of infants to HBCDD in food

HBCDD isomer	**Upper bound dietary exposure to HBCDD isomers (ng/kg bw/day)**					
	4 – 6 months		6 – 9 months		9 – 12 months	
	Mean	P97.5	Mean	P97.5	mean	P97.5
α	1.39	4.41	1.62	4.50	1.74	3.70
β	0.92	2.94	1.00	2.85	1.02	2.25
γ	0.93	2.94	1.01	2.85	1.05	2.29

Environmental Exposure to HBCDDs

Air and Dust

43. Assuming the daily ingestion of 100 mg of dust per day (WHO, 2007), Table 6 shows the potential exposure of infants aged 9 – 12 months to HBCDD by this route, based on the range of available data. Children of this age are more likely to come into contact with floors and other surfaces than those in younger age groups. The exposure estimates have been generated based on levels of HBCDDs in houses, since this is likely to be a more relevant route than cars for prolonged exposure of

infants, and the data indicate that the levels in house dust are higher than those in cars (see table 2). The estimated values are shown in Table 6.

Table 6. Potential exposure of UK infants aged 9-12 months to HBCDD via ingestion of dust sampled in UK houses

Environment	ΣHBCDD exposure (ng/kg bw/day)
House	2.38 – 1466.40 [a]
House	13.54[b]
House	7.60 [c]

Values based on occurrence data from
[a] Abdallah et al 2009 (range)
[b] Abdallah et al 2008a (median)
[c] Abdallah et al 2008b (median)

Questions on which the views of the Committee are sought

44. Members are invited to comment on the information provided in this paper and to advise on the approach that should be taken in the COT evaluation of HBCDDs in the infant diet.

i) Is the $BMDL_{10}$ calculated by EFSA, based on neurodevelopmental effects in mice, appropriate for use in a margin of exposure approach to HBCDDs?

ii) Do Members agree with the approach of taking body burden into account by estimating human dietary daily intake associated with the body burden at the $BMDL_{10}$?

iii) Do Members agree that the human dietary daily intake value of 3 µg/kg bw/day should be used as the reference point for risk characterisation, and the approach of EFSA in interpreting the margin of exposure?

iv) It is noted that the BMDL was derived from a study in which the test material was predominantly γ-HBCDD, whereas the estimated exposures are higher for α-HBCDD, than for the other isomers. How should this be taken into account?

v) Do Members have comments on whether there is concern about infants' exposure to HBCDDs?

Secretariat
August 2014

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

COT STATEMENT ON BROMINATED FLAME RETARDANTS IN FISH FROM THE SKERNE-TEES RIVER SYSTEM

Available at: http://cot.food.gov.uk/pdfs/bfrstatement.pdf

STATEMENT ON ORGANIC CHLORINATED AND BROMINATED CONTAMINANTS IN SHELLFISH, FARMED AND WILD FISH

Available at:
http://multimedia.food.gov.uk/multimedia/pdfs/cotstatementfishsurveys.pdf

TOX/2014/24 Annex B

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

Scoping paper on the potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet

EFSA (European Food Safety Authority) (2011). Scientific Opinion on Hexabromocyclododecanes (HBCDDs) in Food. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal 9(7):2296.
For copyright reasons this document is not reproduced on the COT website. It is available at http://www.efsa.europa.eu/en/efsajournal/doc/2296.pdf

TOX/2014/24 Annex C

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

Scoping paper on the potential risks from hexabromocyclododecanes (HBCDDs) in the infant diet

Search Strategy

Websites interrogated –
EFSA
IARC
COT
FSA
JECFA
WHO

Scientific publications literature search. Databases interrogated –
PubMed
Web of Science

Specific search terms:

Milk AND (HBCDDs OR HBCDDs)
Search Dates (From/To) – 2011 - 2014
Exclusion Criteria –
Studies where HBCDDs levels in breast milk were below the LOD/LOQ
Studies which did not measure the levels of HBCDDs in breast milk
PubMed –17 hits
Web of Science –3 hits

Infant formula* AND (HBCDDs OR HBCDDs)
Search Dates (From/To) – 2011 - 2014
Exclusion Criteria –
Studies where HBCDDs levels in infant formula were below the LOD/LOQ
Studies which did not measure the levels of HBCDDs in infant formula
PubMed – 0 hits
Web of Science – 0 hits

Baby food AND (HBCDDs OR HBCDDs)
Search Dates (From/To) – 2011 - 2014
Exclusion Criteria –
Studies where HBCDDs levels in baby food were below the LOD/LOQ
Studies which did not measure the levels of HBCDDs in baby food
PubMed – 0 hits
Web of Science – 0 hits

Food packaging AND (HBCDDs OR HBCDDs)
Search Dates (From/To) – 2011 - 2014

Exclusion Criteria –
Studies where HBCDDs levels in food packaging were below the LOD/LOQ
Studies which did not measure the levels of HBCDDs in food packaging
PubMed – 0 hits
Web of Science – 0 hits

Drinking water AND (HBCDDs OR HBCDDs)
Search Dates (From/To) – 2011 - 2014
Exclusion Criteria –
Studies where HBCDDs levels in drinking water were below the LOD/LOQ
Studies which did not measure the levels of HBCDDs in drinking water
PubMed – 0 hits
Web of Science – 0 hits

Air AND (HBCDDs OR HBCDDs)
Search Dates (From/To) – 2011 - 2014
Exclusion Criteria –
Studies where HBCDDs levels in air were below the LOD/LOQ
Studies which did not measure the levels of HBCDDs in air
PubMed – 19 hits
Web of Science – 4 hits

Dust AND (HBCDDs OR HBCDDs)
Search Dates (From/To) – No limit
Exclusion Criteria –
Studies where HBCDDs levels in dust were below the LOD/LOQ
Studies which did not measure the levels of HBCDDs in dust
PubMed – 22 hits
Web of Science –16 hits

Literature searches for absorption, distribution, metabolism, excretion and toxicology for HBCDDs since 2010. These would include epidemiology studies related to the topics of interest.

Two databases are routinely used to perform searches; PubMed and Web of Science. The number of hits next to the database is the number of hits that come back in relation to the request put in. The list below does not take into account overlap of search results between databases or between search terms.

"**Absorption AND (HBCDDs OR HBCDDs)**"
PubMed 19
Web of Science 10

"**Uptake AND (HBCDDs OR HBCDDs)**"
PubMed 9
Web of Science 11

"**Distribution AND (HBCDDs OR HBCDDs)**"
PubMed 45
Web of Science 60

"**Metabolism AND (HBCDDs OR HBCDDs)**"
PubMed 120
Web of Science 99

"**Elimination AND (HBCDDs OR HBCDDs)**"

PubMed 11
Web of Science 12

"**Excretion AND (HBCDDs OR HBCDDs)**"
PubMed 5
Web of Science 6

"**Tox* AND (HBCDDs OR HBCDDs)**"
PubMed 97
Web of Science 94

Develop* AND (HBCDDs OR HBCDDs) 2009-2014
PubMed 2
Web of Science (Topic) 92

Neuro* AND (HBCDDs OR HBCDDs) 2009-2014
PubMed 4
Web of Science (Topic) 19

Hepato* AND (HBCDDs OR HBCDDs) 2009-2014
PubMed 5
Web of Science (Topic) 6

Cardio* AND (HBCDDs OR HBCDDs) 2009-2014
PubMed 0
Web of Science (Topic) 3

Repro* AND (HBCDDs OR HBCDDs) 2009-2014
PubMed 26
Web of Science (Topic) 29

Endocrine AND (HBCDDs OR HBCDDs) 2009-2014
PubMed 19
Web of Science (Topic) 23

Renal AND (HBCDDs OR HBCDDs) 2009-2014
PubMed 0
Web of Science (Topic) 0

Literature search for Toxicology *---include subheadings for in vitro, in vivo, epidemiology etc*
Carcinogenicity
Cardiovascular Toxicity
Developmental Toxicity
Endocrine Disruption
General Toxicity
Genetic Toxicity
Immunotoxicity
Neurotoxicity
Renal Toxicity
Reproductive Toxicity
Respiratory Toxicity
Mechanistic Toxicity

Dosimetric anchoring
Reviews

Upper bound mean dietary exposure of infants to HBCDD isomers in food

Food group	Number of Consumers	4.00 to 5.99 months - HBCD Mean Exposure (ng/kg bw/d)		
		Alpha	Beta	Gamma
Bread	11	0.0230	0.0153	0.0230
Canned vegetables	4	0.0193	0.0193	0.0193
Carcase meat	10	0.2076	0.0083	0.0083
Cereals	59	0.0341	0.0227	0.0227
Dairy products	76	1.6678	1.1118	1.1118
Eggs	2	0.0062	0.0062	0.0062
Fats+oils	14	0.0196	0.0037	0.0061
Fish	6	0.0925	0.0116	0.0116
Fresh fruit	36	0.0376	0.0376	0.0376
Fruit products	29	0.0882	0.0441	0.0661
Green vegetables	33	0.0219	0.0219	0.0219
Meat products	1	0.0744	0.0149	0.0149
Milk	17	0.0308	0.0308	0.0308
Nuts	0	0.0000	0.0000	0.0000
Offal	0	0.0000	0.0000	0.0000
Other vegetables	57	0.0249	0.0249	0.0249
Potatoes	36	0.0232	0.0232	0.0232
Poultry	11	0.0158	0.0158	0.0158
Sugar and preserves[3]	10	0.0045	0.0022	0.0045
Total	102	1.3868	0.9200	0.9274

Food group	Number of Consumers	6.00 to 8.99 months - HBCD Mean Exposure (ng/kg bw/d)		
		Alpha	Beta	Gamma
Bread	242	0.0366	0.0244	0.0366
Canned vegetables	131	0.0167	0.0167	0.0167
Carcase meat	217	0.3727	0.0149	0.0149
Cereals	496	0.0923	0.0615	0.0615
Dairy products	535	1.3122	0.8748	0.8748
Eggs	88	0.0128	0.0128	0.0128
Fats+oils	282	0.0300	0.0056	0.0094
Fish	175	0.0959	0.0120	0.0120
Fresh fruit	385	0.0410	0.0410	0.0410
Fruit products	235	0.0727	0.0363	0.0545
Green vegetables	338	0.0187	0.0187	0.0187
Meat products	93	0.1506	0.0301	0.0301
Milk	270	0.0559	0.0559	0.0559
Nuts	19	0.0129	0.0215	0.0129
Offal	6	0.0123	0.0041	0.0041
Other vegetables	453	0.0347	0.0347	0.0347
Potatoes	389	0.0277	0.0277	0.0277
Poultry	252	0.0111	0.0111	0.0111
Sugar and preserves[3]	172	0.0074	0.0037	0.0074
Total	602	1.6220	0.9965	1.0113

Food group	Number of Consumers	9.00 to 11.99 months - HBCD Mean Exposure (ng/kg bw/d)		
		Alpha	Beta	Gamma
Bread	502	0.0561	0.0374	0.0561
Canned vegetables	271	0.0230	0.0230	0.0230
Carcase meat	372	0.3916	0.0157	0.0157
Cereals	656	0.1281	0.0854	0.0854
Dairy products	661	1.0316	0.6877	0.6877
Eggs	207	0.0144	0.0144	0.0144
Fats+oils	456	0.0461	0.0086	0.0144
Fish	305	0.1193	0.0149	0.0149
Fresh fruit	574	0.0511	0.0511	0.0511
Fruit products	322	0.0835	0.0418	0.0626
Green vegetables	436	0.0181	0.0181	0.0181
Meat products	262	0.1475	0.0295	0.0295
Milk	426	0.1050	0.1050	0.1050
Nuts	29	0.0209	0.0349	0.0209
Offal	9	0.0295	0.0098	0.0098
Other vegetables	595	0.0340	0.0340	0.0340
Potatoes	546	0.0344	0.0344	0.0344
Poultry	400	0.0140	0.0140	0.0140
Sugar and preserves[3]	297	0.0091	0.0046	0.0091
Total	684	1.7447	1.0233	1.0515

Upper bound 97.5th percentile exposure of infants to HBCDD isomers in food

Food group	Number of Consumers	4.00 to 5.99 months - HBCD 97.5 Exposure (ng/kg bw/d)		
		Alpha	Beta	Gamma
Bread	11	0.0488	0.0325	0.0488
Canned vegetables	4	0.0231	0.0231	0.0231
Carcase meat	10	0.5748	0.0230	0.0230
Cereals	59	0.1265	0.0843	0.0843
Dairy products	76	4.4353	2.9569	2.9569
Eggs	2	0.0136	0.0136	0.0136
Fats+oils	14	0.0556	0.0104	0.0174
Fish	6	0.1726	0.0216	0.0216
Fresh fruit	36	0.1362	0.1362	0.1362
Fruit products	29	0.3623	0.1811	0.2717
Green vegetables	33	0.0668	0.0668	0.0668
Meat products	1	0.0744	0.0149	0.0149
Milk	17	0.1256	0.1256	0.1256
Nuts	0	0.0000	0.0000	0.0000
Offal	0	0.0000	0.0000	0.0000
Other vegetables	57	0.0779	0.0779	0.0779
Potatoes	36	0.0560	0.0560	0.0560
Poultry	11	0.0530	0.0530	0.0530
Sugar and preserves[3]	10	0.0098	0.0049	0.0098
Total	102	4.4067	2.9387	2.9387

Food group	Number of Consumers	6.00 to 8.99 months - HBCD 97.5 Exposure (ng/kg bw/d)		
		Alpha	Beta	Gamma
Bread	242	0.1308	0.0872	0.1308
Canned vegetables	131	0.0694	0.0694	0.0694
Carcase meat	217	1.5708	0.0628	0.0628
Cereals	496	0.3714	0.2476	0.2476
Dairy products	535	4.2614	2.8409	2.8409
Eggs	88	0.0536	0.0536	0.0536
Fats+oils	282	0.1218	0.0228	0.0381
Fish	175	0.3599	0.0450	0.0450
Fresh fruit	385	0.1425	0.1425	0.1425
Fruit products	235	0.3054	0.1527	0.2290
Green vegetables	338	0.0751	0.0751	0.0751
Meat products	93	0.5241	0.1048	0.1048
Milk	270	0.1787	0.1787	0.1787
Nuts	19	0.0413	0.0689	0.0413
Offal	6	0.0154	0.0051	0.0051
Other vegetables	453	0.1204	0.1204	0.1204
Potatoes	389	0.1039	0.1039	0.1039
Poultry	252	0.0454	0.0454	0.0454
Sugar and preserves[3]	172	0.0233	0.0116	0.0233
Total	602	4.5038	2.8475	2.8486

Food group	Number of Consumers	9.00 to 11.99 months - HBCD 97.5 Exposure (ng/kg bw/d)		
		Alpha	Beta	Gamma
Bread	502	0.1885	0.1257	0.1885
Canned vegetables	271	0.0860	0.0860	0.0860
Carcase meat	372	1.7640	0.0706	0.0706
Cereals	656	0.4273	0.2849	0.2849
Dairy products	661	3.0097	2.0065	2.0065
Eggs	207	0.0552	0.0552	0.0552
Fats+oils	456	0.1704	0.0319	0.0532
Fish	305	0.4385	0.0548	0.0548
Fresh fruit	574	0.1708	0.1708	0.1708
Fruit products	322	0.3985	0.1993	0.2989
Green vegetables	436	0.0826	0.0826	0.0826
Meat products	262	0.5814	0.1163	0.1163
Milk	426	0.5952	0.5952	0.5952
Nuts	29	0.0699	0.1165	0.0699
Offal	9	0.0655	0.0218	0.0218
Other vegetables	595	0.0998	0.0998	0.0998
Potatoes	546	0.1139	0.1139	0.1139
Poultry	400	0.0482	0.0482	0.0482
Sugar and preserves[3]	297	0.0330	0.0165	0.0330
Total	684	3.7047	2.2458	2.2903