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

Statement on the 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 bears on the Government's dietary recommendations for infants and young children. The review will identify new evidence that has emerged since the Government's current recommendations were formulated, and will appraise that evidence to determine whether the advice should be revised. The recommendations cover diet from birth to age five years, but will be considered in two stages, focussing first on infants aged 0 – 12 months, and then on advice for children aged 1 to 5 years. SACN is examining the nutritional basis of the advice, and has asked that evidence on possible adverse effects of diet should be considered by other advisory committees with relevant expertise. In support of this review, the COT was asked to review the risks of toxicity from chemicals in the infant diet.

2. This statement gives an overview of the potential risks from 1,2,5,6,9,10-hexabromocyclododecanes (HBCDDs, sometimes also abbreviated as HBCDs) in the infant diet. None of Government's current dietary recommendations for infants and young children relates to HBCDDs.

3. HBCDDs have a molecular structure in the form of a 12-carbon ring substituted with 6 bromine atoms. All HBCDDs share the same chemical formula but differ from one another in the arrangement of bromine atoms around the 12-carbon ring. There are 16 structural isomers, which can be grouped into 8 diastereomeric pairs of enantiomers. Technical mixtures of HBCDDs have been widely used as additive flame retardants in fabrics and in polystyrene products in the building and electronics industries.

4. Technical HBCDD comprises mainly the three diastereomeric pairs of enantiomers, designated α, β and γ (Figure 1), in the approximate proportions, 9-13% α, <0.5-12% β and 72-90% γ (EFSA, 2011). However, in environmental media and biological material, the relative proportions are altered, with the α isomer predominating at the expense of the γ. This isomeric shift is partly a consequence of the heating process that is used when HBCDDs are applied to the material which they are to protect, but other mechanisms such as differential absorption and metabolism cannot be ruled out.

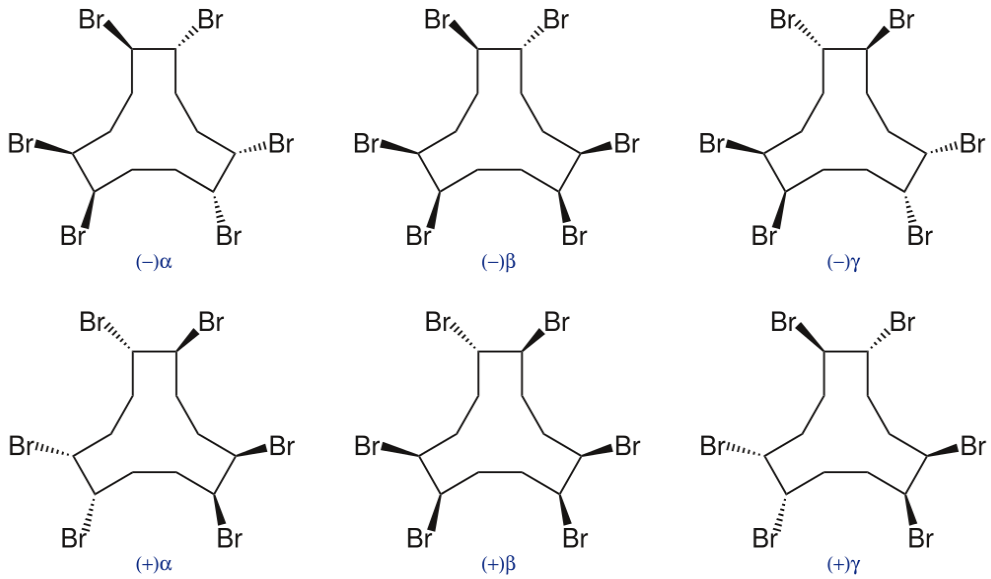

Figure 1: Structures of the main isomers in technical HBCDD

5. The physicochemical properties of HBCDDs, especially their stability and lipophilicity, along with their large volume of annual production, ubiquitous use and the fact that they do not bind to the materials in which they are incorporated, have all contributed to their becoming widely distributed in the environment and entering the food chain. HBCDDs have been added to Annex A of the Stockholm Convention on Persistent Organic Pollutants and their use for all but construction purposes was banned on 26th November 2014. (C.N.934.2013.TREATIES-XXVII.15 (Depositary Notification)) However since they were already widely distributed in the environment and consumer products, human exposure will persist beyond the ban.

Previous evaluations by COT and EFSA

COT

6. COT, in a statement on brominated flame retardants in fish from the Skerne-Tees rivers system (2004)[1], concluded that uncertainties and deficiencies in the toxicological databases for HBCDDs precluded specification of tolerable daily intakes (TDIs), and therefore adopted a Margin of Exposure (MOE) approach to risk assessment. The Committee observed that all toxicological studies of HBCDDs had been conducted using technical (commercial) mixtures, and that the composition of the material used in many of the studies was unclear and likely to differ from the mixture of isomers encountered in food and the environment. HBCDDs were noted to be hepatotoxic, but there had been no evidence of developmental toxicity in routine studies. One study, available only in abstract form, indicated that HBCDDs might cause neurodevelopmental effects but there was insufficient detail for the finding to be used in quantitative risk assessment. A lowest observed adverse effect level (LOAEL) of 100 mg/kg, for increased liver weight and disturbances in thyroid hormones, was used as a point of departure in the calculation of MOEs.

[1] http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2004/cotstatementbfrfish2004

EFSA

7. EFSA (2011) noted that orally administered HBCDDs were readily absorbed, but with some differences between stereoisomers. α-HBCDD was reported to concentrate in adipose tissue. Debromination and hydroxylation were the major routes of metabolism. Stereoisomerisation of γ-HBCDD to the α- and β-isomers was observed in mice, but stereoisomerisation of α–HBCDD had not been reported. Elimination half-lives in mice varied from 3-4 days for γ-HBCDD to 17 days for α-HBCDD. The elimination half-life for HBCDDs (expressed as the sum of the α, β and γ isomers) in humans was estimated to be 64 days (range 23-219 days).

8. Data concerning the toxicity of individual stereoisomers were available only from an *in vitro* cytotoxicity study (Zhang *et al.,* 2008). This indicated that that the (+)-isomers were generally more toxic than the (-)-isomers in the order (+)γ >= (+)β > (+)α >(-)γ > (-)α = (-)β. EFSA concluded that the relevance of these findings to the *in vivo* toxicity of HBCDDs was unclear, but that in general they appeared to support the low acute toxicity of the compounds tested.

9. The main targets for HBCDD toxicity in experimental animals were the liver, thyroid hormone homeostasis, and the immune, reproductive and nervous systems. The two available epidemiological studies did not show any association between levels of HBCDDs in blood and bone mineral density in elderly women, or between HBCDDs in human milk and neonatal blood levels of thyroid stimulating hormone (TSH). Like COT, EFSA concluded that because of limitations and uncertainties in the database, the derivation of a TDI was not appropriate, and instead an MOE approach was adopted (EFSA 2011). Since all in vivo toxicity studies had been carried out with technical HBCDD mixtures, risk assessments for individual stereoisomers were not possible.

10. EFSA noted that most studies showed effects on the regulation of thyroid hormones, and that the investigation showing effects at the lowest doses was a 28-day study of HBCDDs in rats by van der Ven *et al* (2006). The most sensitive effect was increased relative thyroid weight in female rats. There was no clear dose-response relationship, but a lower 95% confidence limit for a benchmark response of 10 % ($BMDL_{10}$) of 1.6 mg/kg bw per day could be derived. Reduction in blood levels of total thyroxine (T4), increased immunostaining for TSH in the pituitary, and increased pituitary weight were observed at higher doses (100 – 200 mg/kg bw), and were restricted to females. which was consistent with a finding of higher liver concentrations of HBCDDs in females than in males. EFSA noted that extrapolation of effects on thyroid hormone homeostasis observed in rodents to humans was complicated by species differences in transport systems and feedback regulation. There were indications that HBCDDs might act via mechanisms involving the constitutive androstane receptor (CAR) and pregnane X receptor. EFSA concluded that, because thyroid hormone insufficiency could lead to neurodevelopmental effects, both in experimental animals and in humans, the rodent data concerning effects of HBCDDs on thyroid hormone levels and signalling might be of relevance to the assessment of health risks in humans.

11. EFSA (2011) identified neurodevelopmental effects as the critical end-point and derived a $BMDL_{10}$ from a study by Eriksson *et al* (2006). Eriksson *et al*. administered a single oral gavage dose of HBCDDs (α-, β- and γ-HBCDD in relative proportions of 3 %, 8 % and 89 %) at either 0.9 or 13.5 mg/kg bw to mouse pups at the age of 10 days, which is the peak time of brain growth in mice. At 3 months of age the mice were tested for effects on locomotion and memory. The mice treated with HBCDDs at the higher dose initially scored lower than controls and low dose animals in the tests of locomotion, but maintained their level of activity such 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. They noted limitations of the single-administration protocol, but concluded that use of this $BMDL_{10}$ in the risk assessment was justified because the observed effects occurred at the lowest doses that had been associated with developmental effects on behaviour and covered a relevant neurodevelopmental period in the experimental animals.

12. The much slower rate of elimination in humans than in rodents led EFSA to take differing toxicokinetics into account by estimating the daily human intake which, after attainment of steady state, would produce the same body burden as might occur in rodents following a single dose by gavage at the $BMDL_{10}$ (assuming 85% uptake from the gut). Using the longest estimated human half-life of 219 days, this intake was calculated to be 3 µg/kg bw/day, which was then used as the reference point in the MOE approach.

13. EFSA also noted that effects on bone mineral density were observed in a one generation reproductive study in rats, with a $BMDL_{10}$ of 0.056 mg/kg bw (van der Ven *et al*., 2009), but that the ratio between the $BMDL_{10}$ and the benchmark dose upper confidence limit ($BMDU_{10}$) indicated "a large variation in the dose response data"[2]. EFSA therefore concluded that the $BMDL_{10}$ for effects on bone mineral density should not be used as the reference point for the MOE, and that further studies were needed to confirm the effect.

New toxicological and epidemiological data

Toxicokinetics

14. Toxicokinetic data published since EFSA (2011) indicate that ≥ 85% of an oral dose of β-HBCDD was absorbed in mice, with a T_{max} (time to peak serum concentration) of 3 hours (Sanders *et al*., 2013). Of this, absorbed dose, approximately 90% was excreted in urine and faeces within 24h, primarily as β-HBCDD-derived metabolites, but 9% was excreted in the faeces as γ-HBCDD. An in vitro human colon model yielded similar results for a mixture of isomers (α 92%, β 80% and γ 72% bioaccessibility) from domestic dust (Abdallah *et al*., 2012). Other studies have confirmed the widespread distribution of HBCDDs in the body, with metabolism by debromination and hydroxylation. Hakk *et al*. (2012) dosed female

[2] COT noted that it would be more accurate to say that this reflects large statistical uncertainty

mice with ^{14}C- labelled α– or γ– HBCDD and identified hydroxylated debrominated metabolites from each isomer in urine, faeces and tissue. Malarvannan *et al*. (2013) found predominantly α-HBCDD in human visceral and subcutaneous fat from obese individuals. In Canadian studies, low but measurable concentrations of HBCDDs were reported in human sera (geometric mean 0.851 μg/kg lipid) (Rawn *et al.,* 2014a) and in placenta (median 48 μg/kg lipid) and fetal liver (median 29 μg/kg lipid) (Rawn *et al*., 2014b).

Toxicity

15. Newly reported studies of toxicity have used mixtures of HBCDDs purchased from bulk chemicals companies, with unspecified isomeric proportions.

16. Following exposure of pregnant dams to >1000 – 10 000ppm HBCDDs in the diet, changes were observed in neuronal migration in the dentate gyrus of rat pups (Saegusa *et al.,* 2012), and in rat fetal glial cell development (Fujimoto *et al.,* 2013), possibly resulting from effects on the thyroid gland. Rasinger *et al.* (2014) fed juvenile BALB/c mice a diet containing 1300 ppm HBCDDs that resulted in a dose of 200 mg/kg bw per day for 28 days. HBCDD induced 90 genes in the brain and the authors hypothesised that the overall effect would be alterations in calcium and zinc homeostasis leading to excitotoxicity. Dietary administration of HBCDDs to mice at 199 mg/kg bw/day for 28 days resulted in increased liver weight and fat content (Maranghi *et al*., 2013). Sensitivity to this effect appeared to be increased when dietary fat content was higher, leading to significant increases in liver- and body-weight following weekly bolus gavage doses of 35 or 700 μg/kg/week (Yanagisawa *et al*., 2014).

17. Recent *in vitro* studies have provided information on possible modes of action for HBCDDs, including oestrogenic activity (Dorosh *et al*., 2011), generation of reactive oxygen species (An *et al*., 2014) and inhibition of calcium transport in the smooth endoplasmic reticulum (Al-Mousa & Michaelangeli, 2014). HBCDDs reduced splenocyte viability but enhanced the differentiation of bone marrow cells into dendritic cells (Koike *et al*., 2013). HBCDDs inhibited cAMP production and the expression of several cAMP-dependent steroidogenesis genes in rat Leydig cells, but increased basal steroidogenesis (Fa *et al*., 2013). HBCDDs potentiated FSH-stimulated EGF receptor phosphorylation and activated ERK1/2 and PKB (AKT), but decreased FSH-induced luteinizing hormone receptor expression (Fa *et al*., 2014). Both An *et al.* (2014) and Fa *et al*. (2013) found that HBCDDs reduced mitochondrial membrane potential in cells in vitro. All of these effects were observed at HBCDD concentrations in the range of 15 nM to 40μM. The lowest concentration at which HBCDDs were seen to have an effect *in vitro* was 0.1nM, which produced suppression of thyroid hormone (TH)-stimulated transcription and dendrite arborisation of new-born rat Purkinje cells (Ibhazehiebo *et al*., 2011a). Ibhazehiebo *et al*. (2011b) also observed inhibition of TH-induced neurite extension of cerebellar granule cells by 0.1nM HBCDDs, possibly through reduced production of bone-derived neurotrophic factor, which promotes granule cell development.

Epidemiological studies

18. Kim & Oh (2014) reported a statistically significant ($p < 0.05$) negative correlation between serum levels of HBCDDs and the level of triiodothyronine (T3) in the mothers of children with congenital hypothyroidism. The 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 confirm the results.

19. The total HBCDD concentration in house dust has been correlated ($p = 0.004$, Spearman's $r = 0.46$, $n = 28$) with decreased sex hormone binding globulin and increased free androgen index in men (Johnson *et al*., 2013), but exposures were not estimated. Meijer *et al*. (2012) found HBCDDs at 0.7 μg/kg fat in the serum of 34 women at the 35th week of pregnancy, but no correlation with the testicular volume or penile length of their infants postnatally.

COT evaluation

20. COT noted that the female specificity of effects in the 28-day study of technical HBCDD (α 10.3%, β 8.7%, γ 81.0%) in rats by van der Ven *et al*. (2006) contrasted with the findings of Chengelis *et al*. (2001), who reported similar effects in both sexes. Germer *et al*. (2006) found induction of cytochrome P450 in the livers of juvenile Wistar rats after 28 days of oral dosing with technical HBCDD (10.3% α / 8.7% β / 81.0% γ). CYP2B1/2B2 were induced in the livers of treated animals of both sexes at 100-200mg HBCDD/kg bw/day, and CYP3A1/3A2 at 3 – 200 mg HBCDD/kg bw/day in female rats only. Van der Ven *et al* (2006) speculated that induction of CYP isozymes by HBCDDs, as observed by Germer *et al.* (2006), might be functionally linked to induction of T4-uridinediphosphate-glucuronosyltransferase (T4-UGT), COT considered it possible that the effects of HBCDDs on the thyroid hormone axis were secondary to increased hepatic clearance of T4 via glucuronidation.

21. The study by Maranghi *et al*. (2013) suggested that obese individuals might be more sensitive to HBCDDs than leaner people, but did not provide a suitable basis from which to derive a reference point for the characterisation of risk.

22. The new in vitro toxicity data suggest that technical mixtures of HBCDDs have a range of effects on different cell types, but give little insight into the toxic effects observed in vivo. Regarding the epidemiological studies, COT noted limitations in the reporting and agreed that further studies would be needed to verify the findings that had been reported.

23. Overall, the new data did not demonstrate a mode of action for HBCDDs or provide an improved basis for extrapolation of experimental animal data to the human situation. Thus, they did not offer an alternative approach to the reference point identified by EFSA from the study by Eriksson *et al*. (2006), which remained the best available starting point for risk assessment.

Sources of exposure to HBCDDs

24. HBCDDs have been found in air, indoor dust, soil, food and breast milk. No consistent temporal trends in concentrations have been apparent (Law *et al*., 2014; Dietz *et al*., 2013).

Environmental occurrence of HBCDDs

Air, dust and soil

25. Abdallah *et al.* (2008) found a mean concentration of 250 pg total α+β+γ HBCDD/m^3 (range 67 – 1300 pg/m^3) in indoor air from 45 homes in Birmingham UK. This study used a passive air sampler to collect vapour phase compounds with high efficiency, together with a substantial proportion of particle-associated HBCDDs (Abdallah *et al* , 2008 (Supplementary Information): Harrad, 2015). As the HBCDDs were encountered predominantly in the vapour phase, the vast majority of the airborne material should have been sampled. The mean concentration of HBCDDs in indoor dust in the same study was 8300 μg/kg (range 140 – 140000 μg/kg). Both air and dust showed isomeric proportions that had shifted from those in technical HBCDD (α:β:γ 3:8:89), air containing 22% α: 11% β: 65% γ and dust containing 33% α: 11% β: 56% γ. Table 1 shows measurements of HBCDDs in dust from UK houses and cars.

Table 1. HBCDDs in dust from houses and cars in the UK

Sampling date where given	Environment	Total α+β+γ HBCDD concentration (μg/kg)	Reference
March – December 2007	House (n = 21) Car (n = 12)	228 – 140774 (range) 10021 (mean) 194 – 55822 (range) 18488 (mean)	Abdallah *et al*., 2009
	House (n = 45)	140 – 140000 (range) 8300 (mean)	Abdallah *et al.,* 2008
	House (5 samples from each of 3 houses)	170 – 19000 (range)	Harrad *et al*., 2009
2009	Car (n = 14)	9200 (median)	Harrad and Abdallah., 2011

26. A study investigating spatial and temporal enantiomeric shifts in HBCDDs in household dust revealed a rapid photolytically-mediated shift from γ-HBCDD to α-HBCDD that was complete after one week of exposure to daylight, and a slower degradative loss of HBCDDs through elimination of HBr. With exposure to light, the decay in total HBCDD concentration 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. The total α+β+γ HBCDD concentration in dust was 540,000 μg/kg inside the TV, 24,000 μg/kg at 1 metre, and fell to 5,700 μg/kg at 4 metres. In one room, a significant negative correlation was observed between concentrations of total HBCDDs and dust loading (g dust/m^2 floor), implying that "dilution" occurred at higher dust loadings (Harrad *et al*., 2009).

27. Data have been reported on levels of HBCDDs in soil at polluted industrial sites in China and other Far Eastern countries, but no information is available about soil levels in the UK.

Dietary occurrence of HBCDD

Breast milk

28. A study conducted in Birmingham, UK, found HBCDDs in 34 samples of human milk (collection period unspecified). The mean total concentration of α+β+γ HBCDDs was 5.95 ng/kg lipid weight, which is equivalent to 208 pg/kg whole weight (assuming 3.5% fat content). The α-isomer accounted for 62-95% of the measured HBCDDs while β- and γ-HBCDD made up 2-18% and 3-33% respectively (see Table 2). Enantioselective enrichment of (-)-α-HBCDD (average enantiomer fraction = 0.29) was observed, indicating possible differences between enantiomers in absorption, metabolism and/or excretion (Abdallah & Harrad, 2011). The measured concentrations were in broad agreement with findings from a study in Ireland that measured HBCDDs and other halogenated flame retardants in breast milk, and found a mean summed concentration of HBCDD enantiomers of 3.52 ng/kg lipid weight, with α-HBCDD making up over 70% of the total (Pratt *et al*., 2013).

Table 2. HBCDD in 34 samples of breast milk from the UK.

Reference	Isomer	HBCDD concentrations in breast milk (ng/kg whole weight) [a]			
		Arithmetic Mean	Minimum	Median	Maximum
Abdallah & Harrad 2011	α	0.17	0.026	0.11	0.69
	β	0.011	0.0028	0.011	0.26
	γ	0.026	0.0046	0.020	0.080
	Sum	0.21	0.036	0.13	0.78

[a] Data converted to whole milk basis from fat weight basis assuming breast milk contains 3.5% fat.
Sum = sum of α + β + γ

Infant formula and complementary foods

29. No measurements of HBCDDs in infant formula or commercially produced infant foods are available from the UK.

30. In data submitted to EFSA by EU countries, HBCDDs were not found in 3 samples of infant formula (limit of detection not stated in the EFSA report) but could be measured in 38% of 13 samples described as "Ready-to-eat meal for infants and small children". The lower and upper bounds[3] (LB and UB) of the mean for these 16 samples were 0.01 and 0.03 μg/kg respectively EFSA (2011)

Food

31. The most recent measurements of HBCDDs in foods sampled in the UK are for the composite food groups of the 2012 Total Diet Study (TDS) (Fernandes *et al*., 2012). The three major diastereomers were each measured individually. Levels were mostly below the limits of detection, as shown in Table 3.

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

Food group	Mean 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

Values prefixed by "<" were below limits of detection

32. EFSA (2011) reported that the LB and UB of the mean for the sum of the three major HBCDD stereoisomers in ten fish oil samples were 1.21 and 1.86 μg/kg fat, with a high proportion of the total being α-HBCDD. The α isomer was detected more frequently than the β or γ. Three samples were described as fish oil bottled and seven as fish oil in capsules. The liquid fish oil contained up to ten times higher concentrations of α-HBCDD than the capsules (LB and UB of the mean 2.83 and 2.99 μg/kg respectively).

[3] The lower bound for the mean was calculated with the assumption that unmeasurable concentrations were zero, and the upper bound with the assumption that they were at the limit of detection.

Drinking Water

33. No measurements of HBCDDs in drinking water in the UK are available.

Exposure to HBCDDs

34. The assessments presented here are for external exposures from air, dust and the diet. Data on bodyweight 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 respectively. Since DNSIYC did not include infants younger than 4 months, in this statement a value of 5.9 kg for infants aged 0 – 3 months from an earlier survey (DH, 1994) is assumed for infants aged 0 – 4 months.

Environmental Exposure to HBCDDs

Air and Dust

35. Potential exposures of UK infants to HBCDDs in air, assuming a ventilation rate of 3 m^3/day (US EPA, 1989), and the mean reported occurrence of 250 pg/m^3 for the sum of HBCDDs in domestic air (paragraph 25), are 0.127, 0.096, 0.086 and 0.078 ng/kg bw/day at ages 0-4, 4-6, 6-9 and 9-12 months respectively

36. Assuming daily ingestion of 100 mg of dust (WHO, 2007), and the values for HBCDD in house dust from Abdallah *et al*. (2009) in Table 1, infants aged 9-12 months (who are more likely to come into contact with floors and other surfaces than those in younger age groups) would be exposed on average to 104 ng/kg bw/day HBCDDs, with a range of 2.4 – 1466 ng/kg bw/day.

Dietary exposure to HBCDDs

Breast milk

37. Table 4 shows estimated exposures of exclusively breast-fed infants based on the median and maximum concentrations in the study by Abdallah and Harrad (2011), and assuming average (800 mL) or high-level (1200 mL) daily consumption of breast milk.

Table 4. Estimated exposures of UK infants to HBCDDs from exclusive breastfeeding.

Isomer	Exposure ng/kg bw/day							
	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	0.015	0.094	0.011	0.071	0.023	0.140	0.017	0.106
β	0.001.4	0.0036	0.0011	0.0027	0.0021	0.0054	0.0016	0.0041
γ	0.0027	0.011	0.002	0.0082	0.0040	0.016	0.0030	0.012
Sum	0.018	0.11	0.014	0.080	0.027	0.159	0.021	0.120

Exposure values calculated from occurrence data from Abdallah and Harrad, 2011.

Sum = sum of $\alpha + \beta + \gamma$

Food

38. No data are available on concentrations of HBCDDs in infant formula and commercially-produced infant food in the UK. EFSA (2011) did not estimate infants' exposure to HBCDDs from infant formula and "ready-to-eat meals for infants and small children" because the available data were too limited.

39. Table 5 summarises upper bound mean and high-level estimates[4] of infant dietary exposure to HBCDDs, calculated using measurements for the 19 composite food groups analysed in the 2012 TDS (see Table 3) in combination with data on consumption of those foods from DNSIYC (DH, 2013). Since HBCDDs were not detected in most of the food groups, it is possible that the upper bound estimates are substantially higher than actual exposures. Estimates for individual food items are presented in Annex 1.

Table 5 Estimated dietary exposure of infants to HBCDDs 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
Sum	3.24	9.29	3.63	10.2	3.81	8.24

P97.5 = 97.5th percentile

Sum = sum of $\alpha + \beta + \gamma$

40. Although dietary supplements like cod liver oil are not recommended for children under 3 years of age, there were four recorded cases in the DNSIYC in which infants aged 4 to 12 months were given daily doses of 9 to 62 mg fish oil /kg bw, either by spoon or as capsules. The small number of consumers in DNSIYC 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, However,

[4] These estimates all assume that unmeasured concentrations were at the limit of detection. Mean values represent the average intake with this assumption, and high-level values the 97.5th centile of the distribution of intakes.

assuming the highest UB concentration of HBCDDs reported by EFSA, 62 mg fish oil /kg bw would lead to an exposure of 0.19 ng HBCDDs /kg bw.

Risk Characterisation for HBCDDs

41. MOEs were calculated as the ratio of the reference point of 3 μg/kg bw/day, derived from a study on a technical mixture of HBCDDs (Eriksson *et al*., 2006), to estimates of exposures to HBCDDs. For exposure of infants from air, MOEs based on the mean reported airborne concentration of HBCDDs, were in the range 5280 – 103400 according to age group. For dust, the MOEs based on the range of reported HBCDD concentrations were 2.0 – 1260.

42. Table 6 shows that the MOEs for exposure to HBCDDs in exclusively breastfed infants, calculated from the maximum reported concentration of HBCDDs in breast milk, are 19,000 or higher.

Table 6. MOEs for exposure to HBCDDs in exclusively breastfed infants in the UK.

Isomer	**MOE for HBCDDs in breast milk**			
	Average consumer 800 mL/day		High consumer 1200 mL/day	
	Age 0 - 4 months	Age >4 – 6 months	Age 0 - 4 months	Age >4 – 6 months
α	32,000	42,000	21,000	28,000
β	830,000	1,100,000	570,000	750,000
γ	280,000	370,000	180,000	240,000
Sum	28,000	37,000	19,000	25,000

Sum = sum of α + β + γ

43. Table 7 shows MOEs for infant exposures to HBCDDs via the diet. The MOEs for the sum of α-, β- and γ-HBCDDs are in the region of 300 or higher.

Table 7. MOEs for dietary exposure of infants to HBCDD

HBCDD isomer	**MOEs for upper bound dietary exposure to HBCDD isomers**					
	4 – 6 months		6 – 9 months		9 – 12 months	
	Mean	P97.5	Mean	P97.5	mean	P97.5
α	2200	680	1900	670	1700	810
β	3300	1000	3000	1100	2900	1300
γ	3200	1000	3000	1100	2900	1300
Sum	930	320	830	290	790	364

P97.5 = 97.5th percentile

Sum = sum of α + β + γ

44. For fish oil, the MOE for the highest level of consumption is 15800.

45. EFSA (2011) noted that usually an MOE of 100 is considered to provide adequate reassurance that there is no health concern regarding the toxic effect on which it is based. A margin of this magnitude covers uncertainties regarding toxicokinetic and toxicodynamic differences between experimental animals and humans (factor 4 x 2.5 = 10), and within the human population (factor 3.2 x 3.2 = 10). This breakdown of the uncertainty factors is consistent with the COT Report on Variability and Uncertainty in Toxicology (COT, 2007)[1]. Since for HBCDDs the MOE approach was based on a body burden comparison between animals and humans, using the higher end of the reported range for elimination half-life in humans, EFSA (2011) considered that the potential for kinetic differences between species had been taken into account. Similarly, by focusing on the body burden associated with a $BMDL_{10}$ for neurobehavioural effects in mice induced during a relevant period for brain development, and applying that body burden to the entire life span in humans, EFSA (2011) took the view that individual differences in susceptibility had been covered. EFSA thus concluded that in their risk assessment for HBCDDs, the calculated MOEs needed to cover inter-species differences in dynamics (factor 2.5) and the uncertainties in the elimination half-life in humans (factor 3.2). This implied that an MOE greater than 8 (2.5 x 3.2) would indicate that there was no concern for health

46. 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.

47. From the above evaluation, the MOE values for HCDDs in air, breast milk and food are all substantially in excess of 8, but for dust the highest estimated exposure gives an MOE below this value.

Uncertainties

48. The toxicity study used by EFSA to derive the reference point for MOEs involved a single gavage administration to neonatal mice. There is uncertainty about the relevance of this study to risk assessment for longer term repeated exposures in humans. However, since the neurobehavioural effects were observed at lower doses than in other studies and covered a relevant neurodevelopmental period in experimental animals, they cannot be discounted. The long half-lives of HBCDDs mean that after a single administration, systemic exposure would continue over a prolonged period. Furthermore, it may be reasoned that when the body burden following single administration matches that in steady state from repeated exposures, most tissue concentrations are likely to be higher as there will have been limited redistribution to adipose tissue. This would tend to make the derivation of reference points from a single dose study conservative.

[1] http://cot.food.gov.uk/cotreports/cotwgreports/cotwgvut

49. Conversely, if adverse effects depended on the exposure of tissues at a critical time point which did not coincide exactly with that at which the maximum level was reached following single administration, it is possible that the single dose studies could overestimate the body burden needed to produce toxicity.

50. HBCDDs have been used as technical mixtures, and the profile of isomers now present in food and the environment differs from that in the original mixtures. There is uncertainty about the exact profile of exposure to HBCDDs, and the effects of this combined exposure. This has been addressed to some extent by calculating MOEs for exposure to the sum of measured HBCDDs. However, the possibility cannot be ruled out that toxic potency varies according to the relative concentrations of different isomers.

51. In addition, no data were available on levels of HBCDDs in infant formula or commercially produced infant foods in the UK

Conclusions

52. HBCDDs have been produced as technical mixtures containing 3 major HBCDD isomers, and there are only limited data on their individual toxicological properties. Tests of toxicity conducted with technical mixtures are of limited relevance to the profile of HBCDDs that occurs in the environment and in food, owing to differing persistence of individual isomers.

53. In animal studies, the main targets of HBCDD toxicity are the liver, thyroid hormone homeostasis, and the reproductive and nervous systems. Epidemiological data on possible adverse effects in human populations are inconsistent, and cannot be used as a basis for quantitative risk assessment.

54. The available data are insufficient to establish Tolerable Daily Intakes for HBCDDs. Therefore the COT adopted a Margin of Exposure (MOE) approach to risk assessment, in which estimated exposures of infants to HBCDDs were compared to a reference point derived from toxicity studies.

55. The reference point was determined 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. The Committee had some reservations about this study, but in the context of a limited database, concluded that it provided a reasonable basis for risk assessment.

56. In the absence of adequate toxicity data for individual congeners, the COT compared exposures to HBCDDs with this reference point. Overall the analysis indicated that estimated exposures via breast milk and food are not a cause for concern, but that high levels found in some samples of domestic dust are. Further dust sampling should be carried out to obtain a more reliable assessment of the distribution of potential exposures through ingestion of dust, and especially to establish whether levels begin to fall now that production and new usage of HBCDDs has largely ceased. New studies on the levels of HBCDDs in infant formula and commercially produced infant food would also be useful, but are of lower priority

COT Statement 2015/02
April 2015

List of Abbreviations

BMDL10	**Benchmark 95% lower confidence limit on a 10% response**
bw	**Body Weight**
cANP	**Adenosine 3',5'-Monophosphate**
COT	**Committee on Toxicology**
CYP	**Cytochrome P450**
DH	**Department of Health**
DNSIYC	**Dietary and Nutrition Survey of Infants and Young Children**
EFSA	**European Food Safety Authority**
EGF	**Endothelial Growth Factor**
ERK 1/2	**Extracellular Signal-Regulated Kinase 1 and/or 2**
FSH	**Follicle Stimulating Hormone**
g	**Grams**
HBCDDs	**Hexabromocyclododecanes**
HBr	**Hydrogen bromide**
kg	**Kilograms**
LB	**Lower Bound**
LOAEL	**Lowest Observed Adverse Effect Level**
μg	**Micrograms**
μM	**Micromolar**
MOE	**Margin of Exposure**
nM	**Nanomolar**
PKB (AKT)	**Protein Kinase B**
ppm	**Parts Per Million**
SACN	**Scientific Advisory Committee on Nutrition**
T3	**Triiodothyronine**
T4	**Thyroxine**
T4-UGT	**T4-uridinediphosphate-glucuronosyltransferase**
TDI	**Tolerable Daily Intake**
TDS	**Total Dietary Study**
TH	**Thyroid Hormone**
UB	**Upper Bound**
UK	**United Kingdom**

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Annex 1

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