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

Second draft statement on the potential risks from polybrominated diphenyl ethers (PBDEs) in the infant diet

Introduction

- 1. The Committee on Toxicity (COT) has been asked to consider aspects related to the toxicity of chemicals in the infant diet, 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. The polybrominated diphenyl ethers (PBDEs) are a group of BFRs comprising 209 structurally-related congeners. A scoping paper (TOX/2014/19) was presented to Members in May 2014, and a first draft statement was discussed in September 2014 (TOX/2014/27).
- **2.** Annex A contains a second draft COT statement summarising the available information, taking into account the previous discussions.

Questions on which the views of the Committee are sought

3. Members are invited to comment on the content of the second draft statement.

Secretariat
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TOX/2014/32 Annex A

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

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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. SACN asked COT to review the risks of toxicity from chemicals in the infant diet.
- 2. This statement gives an overview of the potential risks from polybrominated diphenyl ethers (PBDEs) in the infant diet. PBDEs are brominated flame retardants (BFRs), which are used in the manufacture of a range of products to increase their fire-related safety. None of Government's current dietary recommendations for infants and young children relates to PBDEs.
- 3. PBDEs comprise two phenyl rings linked by an ether group with bromine atoms substituting different combinations of ring hydrogens. Their generic structure is shown in Figure 1. They include ten homologues with a total of 209 isomeric congeners (Table 1).

$$\operatorname{\mathsf{Br}}_{\mathsf{m}}$$
 $\operatorname{\mathsf{Br}}_{\mathsf{n}}$ $\operatorname{\mathsf{Br}}_{\mathsf{n}}$

Where (m) plus (n) equal between 1 and 10 bromine atoms

Figure 1: Generic structure of the PBDEs

Table 1: PBDE homologues and congeners (from EFSA, 2011)

Homologues	Chemical	Molecular	Isomeric congeners	Number of
	formula	mass		congeners
monoBDEs	C ₁₂ H ₉ BrO	249.1	BDE-1 to BDE-3	3
diBDEs	C ₁₂ H ₈ Br ₂ O	328.0	BDE-4 to BDE-15	12
triBDEs	C ₁₂ H ₇ Br ₃ O	406.9	BDE-16 to BDE-39	24
tetraBDEs	C ₁₂ H ₆ Br ₄ O	485.8	BDE-40 to BDE-81	42
pentaBDEs	C ₁₂ H ₅ Br ₅ O	564.7	BDE-82 to BDE-127	46
hexaBDEs	C ₁₂ H ₄ Br ₆ O	643.6	BDE-128 to BDE-169	42
heptaBDEs	C ₁₂ H ₃ Br ₇ O	722.5	BDE-170 to BDE-193	24
octaBDEs	C ₁₂ H ₂ Br ₈ O	801.4	BDE-194 to BDE-205	12
nonaBDEs	C ₁₂ HBr ₉ O	880.3	BDE-206 to BDE-208	3
decaBDE	C ₁₂ Br ₁₀ O	959.2	BDE-209	1

- 4. Technical mixtures of PBDEs have been widely used as additive flame retardants in polymers and textiles, construction materials, furniture, and electrical equipment. Because PBDEs are not chemically bound to the materials in which they are incorporated, they can be dispersed into the environment and enter the food chain.
- 5. Table 2 lists the 8 congeners that were present in the largest amounts in commercial technical mixtures of pentaBDE, octaBDE and decaBDE (EFSA, 2011). International agreements on bans and regulations on production and use of technical mixtures of PBDEs have been introduced since 2004, leading to declining levels in the environment (EFSA, 2011). However, there are still some uses of commercial decaBDE.

Table 2: Predominant congeners in commercial technical mixtures of PBDEs (EFSA, 2011)

Congener	Bromine substitution	CAS number
BDE-28	2,2',4-triBDE	41318-75-6
BDE-47	2,2',4,4'-tetraBDE	5436-43-1
BDE-99	2,2',4,4',5-pentaBDE	60348-60-9
BDE-100	2,2',4,4',6-pentaBDE	189084-64-8
BDE-153	2,2',4,4',5,5'-hexaBDE	68631-49-2
BDE-154	2,2',4,4',5,6'-hexaBDE	207122-15-4
BDE-183	2,2',3,4,4',5',6-heptaBDE	207122-16-5
BDE-209	2,2',3,3',4,4',5,5',6,6'-decaBDE	1163-19-5

6. PBDE congeners are susceptible to photolysis, reductive debromination and free radical reactions in the environment. The chemical stability of the PBDE congeners varies with their individual structure but in general congeners with up to three bromine substituents and those with nine and ten bromine substituents are more susceptible to abiotic transformation.

7. In 2004, the COT published a statement on PBDE residues in fish from two rivers in England¹. Subsequently in 2006, the COT published a risk assessment for PBDE residues in a broader range of fish and shellfish². The EFSA Panel on Contaminants in the Food Chain issued a comprehensive opinion on PBDEs in 2011 (EFSA, 2011). This statement draws on information from the EFSA review and from more recent publications. Literature searches were conducted from January 2011 to July 2014 using the term "PBDE" together with the terms "neurodevelopment", "neurotoxicity", "infant" and "neonatal", focussing on studies relevant to infants.

Previous evaluations by COT and EFSA

COT

- 8. In its 2004 Statement, the COT noted that toxicity studies had been conducted mainly on commercial mixtures of PBDEs, the compositions of which were unclear and likely to differ from the profile of congeners in food and the environment. Because of the inadequacies of the toxicological databases it was not possible to establish a tolerable daily intake, and a Margin of Exposure (MoE) approach was adopted. The most sensitive effect of pentaBDE was considered to be neurodevelopmental, with a lowest observed adverse effect level (LOAEL) of 600 µg/kg bw, obtained from a study in which BDE-99 was administered by a single oral dose to mice on postnatal days (PNDs) 3 or 10. However, the focus of the 2004 Statement was on exposure to PBDEs from fish, and the available data did not allow an assessment of exposure to infants at a comparable developmental stage (up to one month). Therefore an MoE could not be calculated for neurodevelopmental effects.
- 9. Based on studies described in an EU Risk Assessment Report (European Commission, 2000), the COT concluded that liver toxicity was the most relevant and sensitive effect in older children and adults. The European Commission (2000) had reported that the effects of pentaPBDE included increases in liver weight, hepatocytomegaly, induction of a range of liver enzymes, and disturbances in the synthesis of cholesterol and porphyrin. The COT agreed with the no observed adverse effect level (NOAEL) for liver effects induced by a pentaBDE formulation in the rat (450 µg/kg bw/day) that had been identified in the EU Risk Assessment Report, and used that NOAEL as a reference point (point of departure).
- 10. In 2006, the COT considered exposure to PBDEs in fish and shellfish (using data collected during 2003-2004 (Fernandes, 2005a)), and from the rest of the diet (using data from the 2003 Total Diet Study (Fernandes, 2005b)). An MoE approach was again taken, with the same reference point for liver effects.

¹ http://cot.food.gov.uk/pdfs/bfrstatement.pdf

² http://multimedia.food.gov.uk/multimedia/pdfs/cotstatementfishsurveys.pdf

EFSA

- 11. EFSA noted that following oral exposure, BDE-209 was absorbed to a limited extent (<25% of dose), whereas absorption of other congeners for which data were available was higher (50-80%), with distribution primarily into fatty tissues. Debromination and hydroxylation were the major metabolic pathways. Elimination half-lives for individual congeners in the rat ranged from about 2 to 20 days, whereas much larger values had been reported in humans for lower brominated congeners (e.g. 926 days for BDE-47, 4,530 days for BDE-153). The elimination half-life of BDE-209 was reported as 2.5-8.6 days for rats, and about 15 days for humans. (EFSA, 2011).
- 12. The main targets of PBDE toxicity were identified as the liver, thyroid hormone homeostasis, and the reproductive and nervous systems. EFSA (2011) reviewed a number of epidemiological studies relating tissue levels of PBDEs to levels of thyroid hormones, neurodevelopmental effects, cancer, diabetes and metabolic syndrome, and effects on fertility and offspring. Limitations in the study designs, inconsistencies between the outcomes of different studies, and co-exposure to other halogenated contaminants prevented firm conclusions.
- 13. EFSA concluded that relevant toxicological data were available for only four individual congeners (BDE-47, BDE-99, BDE-153 and BDE-209) of the eight identified as being predominant in PBDE technical mixtures (Table 2). From studies of neurodevelopmental behavioural changes, mainly in mice, following a single administration by gavage in neonatal animals, EFSA calculated benchmark dose lower confidence limits for a 10% increase in different outcome measures (BMDL₁₀s). The critical neurodevelopmental effect of BDE-47 was on locomotor activity, whilst those for BDE-99, -153 and -209 were on total physical activity.
- 14. For BDE-47, -99 and -153, the much slower rate of elimination in humans compared to 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 BMDL₁₀ (assuming 75% uptake from the gut). In the case of BDE-209, the elimination half-life did not differ markedly between humans and rodents, and therefore the BMDL₁₀ value was applied without adjustment for body burden. These estimated human intakes corresponding to the BMDL₁₀s for BDE-47, -99 and -153, and the external dose for BDE-209, were used as the reference points (see Table 3) in an MoE approach.

Table 3: BMDLs and references points derived by EFSA (2011)

Congener	Critical endpoint	BMDL ₁₀ (µg/kg bw)	Body burden at BMDL ₁₀ (μg/kg bw)	Reference point (µg/kg bw/day)	Reference
BDE-47	Locomotion (mouse, PND 10)	309	232	172 ⁶	Eriksson et al. (2001)
BDE-99	Total activity (mouse, PND 10)	12	9	4.2 ^b	Viberg, et al. (2004)
BDE-153	Total activity (mouse, PND 10)	83	62	9.6 ^b	Viberg et al. (2003)
BDE-209	Total activity (rat, PND 3)	1700	n/r ^a	1700	Viberg et al. (2007)

n/r: not reported because the elimination half-life in rodents and humans is similar, and therefore the external dose was used as the reference point ^b Daily human intake estimated to result in the body burden occurring at the BMDL₁₀.

- 15. EFSA expressed some reservations about the methods of the studies in neonatal animals and the relevance of their findings. Limitations included the use of only a single dose, not taking into account litter effects, and that most studies were conducted in a single laboratory with no independent verification. However, EFSA also noted that the studies identified the lowest doses that had been found to cause neurobehavioural effects, covered a relevant neurodevelopmental period in experimental animals, and that the half-lives and the lipophilic nature of a number of PBDE congeners were such that even a single dose would maintain internal exposures for an appreciable period of time. Thus on balance, EFSA considered it appropriate to use the studies for their risk assessment.
- The potential for additive toxicity of PBDEs was considered by EFSA (2011) but the limited information that was available indicated divergent effects. Thus, it was not possible to identify a common mode of action between congeners, and a cumulative risk assessment was not performed.

New toxicological and epidemiological data

The literature search for 2011-14 found one new toxicological study of neurodevelopmental effects of BDE-47 that had been published since those included in the EFSA evaluation. Groups of nine male and nine female 10-day old rats were given a single administration by gavage of 1, 5 or 10 mg/kg bw BDE-47 (He et al., 2011). Serum/plasma concentrations of BDE-47 and thyroid hormones, organ to body weight ratios and performance in tests for learning and memory were assessed when the rats were two months old. Relative uterine weights were significantly decreased at all doses of BDE-47, relative ovarian weights were increased at 5 and 10 mg/kg bw and relative thyroid weight was decreased at the top dose. Plasma thyroxine (T4) concentration was significantly increased at 5, but not 1 or 10 mg/kg bw BDE-47. Tri-iodothyronine (T3) and thyroid stimulating hormone (TSH) did not differ

significantly from control. BDE-47 was detected in the serum of control animals at the age of 2 months, but was significantly higher in those that received doses of 5 and 10 mg/kg bw. Performance in learning and memory tests was reported to be impaired at all doses. The lowest dose in this study was higher than the BMDL calculated by EFSA.

- 18. Two main modes of action have been proposed for the neurodevelopmental effects of PBDEs: an indirect effect mediated by modulation of thyroid hormone homeostasis; and direct interaction of PBDEs with nerve cells (Dingemans *et al.*, 2011; Gilbert *et al.*, 2012; Costa *et al.*, 2013).
- 19. A recent developmental neurotoxicity study, conducted according to international guidelines, found no evidence of adverse effects of BDE-209 on neurodevelopment following repeated administration by oral gavage to dams from gestation day 6 to weaning, at doses of 0, 1, 10, 100 and 1000 mg/kg bw/day. No treatment-related neurobehavioural changes were observed in detailed clinical observations, startle response, learning and memory tests, or assessments of motor activity up to 6 months of age. Furthermore, there were no treatment-related neuropathological or morphometric alterations, and the authors concluded that the NOAEL was 1000 mg/kg bw/day, the highest dose tested (Biesemeier *et al.*, 2011). It should be noted that this NOAEL applies to a maternal dose, whereas the BMDL₁₀ of 1700 μ g/kg bw/day relates to direct exposure of the neonatal animal, and is therefore more relevant to the assessment of risk from the infant diet.
- 20. Roth and Wilks (2014) conducted a systematic review of the epidemiological literature since January 2006 relating neurodevelopmental and neurobehavioural outcomes to exposure to polybrominated and polyfluorinated chemicals. The review identified 10 reports concerning PBDEs that met the specified inclusion criteria. The studies addressed various endpoints including reduced head circumference, motor function, cognitive development, attention and hyperactivity disorders, internalising and externalising behaviour, socio-emotional skills, and social competence. The authors noted the difficulty in appraising the body of evidence for specific neurodevelopmental and neurobehavioural outcomes because of inconsistencies across studies. However, they concluded that the epidemiological evidence currently did not support a strong causal association between PBDEs and adverse neurodevelopmental or neurobehavioural outcomes in infants and children.
- 21. The literature search did not identify any additional epidemiological studies concerning post-natal exposure (via breastfeeding) to PBDEs that were not included in either the systematic review of Roth and Wilks (2014) or the EFSA opinion.
- 22. Overall, the COT concluded that the new data did not call into question the reference points identified by EFSA for BDE-47, BDE-99, BDE-153 and BDE-209, and did not provide a basis on which to establish reference points for other congeners.

Sources of exposure to PBDEs

Environmental occurrence of PBDEs

- 23. Because of their low vapour pressure, PBDEs preferentially partition to dust in the indoor environment (Law *et al.*, 2014). Concentrations of PBDEs have been measured in dust sampled from homes, offices and cars in the UK. Results have varied widely depending on the specific compounds measured and the location of sampling, but generally have shown higher levels of BDE-209 and the nonaBDEs than of other congeners. For most compounds, concentrations were in the order cars > offices ≥ homes. It is likely, however, that the levels of specific PBDE congeners have changed over time due to progressive reductions in usage of PBDE products and environmental degradation.
- 24. Table 4 presents results from samples of dust that were vacuumed from carpets or bare floors in UK homes. Household dust is likely to be more relevant to the long-term exposures of infants than dust in offices or cars. Particularly highly concentrations of BDE-209 were found in the dust from two homes (0.22 and 0.14%). In an effort to verify the second highest concentration of 1,400,000 µg/kg, dust was resampled approximately nine months after the original sample had been taken. There was only a slight decline in concentration to 900,000 µg/kg BDE-209. Between the two sampling times, the furniture, television, video recorder, and DVD player had been replaced, which suggests that these were not the source of the elevated BDE-209 levels. The origin appeared to be either two items of electronic equipment (a music system and a digital television receiver) that had been present in the room at both times, or the carpet or curtains. These results indicate that high concentrations of BDE209 can occur in the dust of UK homes, but their prevalence is uncertain.

Table 4: Concentrations of eight PBDEs in dust (30 samples) collected in UK homes during 2006 (Harrad *et al.*, 2008)

Congener	PBDE concentrations in dust (μg/kg)				
3.7 3.7	Median	Mean	Range		
BDE-28	<0.5 ^a	0.70	<0.5 - 2.10		
BDE-47	10	15	1.2 - 58		
BDE-99	20	36	2.8 – 180		
BDE-100	3.4	5.6	<0.5 - 17		
BDE-153	5.0	14	<0.5 - 110		
BDE-154	2.8	4.4	<0.5 - 16		
BDE-183	4.2	71	<2 – 550		

Sum of tri-hexa-BDE ^b	46	77	7.1 – 250
BDE-209	8100	260,000	12 - 2,200,000

Thirty samples were analysed for tri-hexa-BDEs; 18 samples were analysed for tri-deca-BDEs, DBDPE, and TBE.

25. The median summed concentration of BDEs 28, 47, 49, 66, 99, 100, 153, and 154, in air sampled in the 31 UK homes (reported in 2006), was 24 pg/m³ (range 4-245 pg/m³), which was higher than in outdoor air (median 0.49, range 8.7-30 pg/m³). Concentrations of BDE-209 were not reported (Harrad *et al.*, 2010).

Dietary occurrence of PBDEs

Breast milk

- 26. Fürst (2006) noted that PBDE levels in milk samples collected in the early 2000s were approximately 60% higher than those sampled 10 years earlier. A review by Costa *et al.* (2008) reported that levels of PBDEs in breast milk had increased in the past 20-30 years, along with serum levels in the general population, although a slight decline had started to emerge towards the end of the period. The more recent review by EFSA did not find a consistent trend (EFSA, 2011).
- 27. Data from two studies of breast milk sampled in the UK during 2010-12 are summarised in Table 5. BDE-47 was the congener with the highest reported concentrations in both studies. In contrast to the findings in dust and food (tables 4 and 7), BDE-209 was not detected at markedly higher levels than the other congeners, which is consistent with its being less bioaccumulative.

Table 5. PBDE congeners in breast milk sampled in the UK in 2010 (Abdallah and Harrad, 2014) and 2011-2012 (Bramwell *et al.*, 2014)

Location Sampling date	Congener	Concentration in breast milk (ng/kg whole weight) ^a			
(number of samples) Reference	(% >LOD)	Median	Minimum	Maximum	
	BDE-47 (100)	98	5.95	513	
Birmingham	BDE49 (20)	<1.75	<1.75	15.8	
Jan-Feb 2010	BDE-85 (45)	<1.75	<1.75	29.1	
Jan-1 eb 2010	BDE-99 (94)	24.2	<2.1	120	
(n=35)	BDE-100 (89)	13.3	<1.75	65.1	
	BDE-153 (97)	31.9	<2.1	156	
Abdallah and Harrad, 2014	BDE-154 (77)	7.35	<2.1	389	
	SumTri-hexa ^b (100)	175	<7	914	

^a below the limit of detection (LOD) - number of samples <LOD not reported

^b Sum of BDEs 28, 47, 85, 99, 100, 153, 154.

	BDE-209 (69)	8.75	<2.1	32.2
	DBE28 (100)	3.15	0.7	10.9
North Foot Footond	BDE-47 (100)	67.2	11.2	458
North-East England	BDE-49 (67)	1.05	<0.7	<3.85
April 2011-Feb 2012	BDE-66 (67)	1.05	<1.05	4.55
7,5 2011 1 00 2012	BDE-85 (83)	1.4	< 0.35	12.3
(n=6)	BDE-99 (100)	30.8	4.2	131
	BDE-100 (100)	22.4	2.45	76.7
Bramwell et al., 2014	BDE-138 (100)	0.7	< 0.35	1.4
	BDE-153 (67)	35.4	24.5	58.8
	BDE-154 (100)	2.45	0.35	6.3
	BDE-183 (100)	1.75	0.7	8.05
	Sum exc 209 ^c	173	44.8	736
	BDE-209 (100)	18.2	<7	36.4

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

Infant formulae and complementary foods

28. Table 6 presents mean occurrence data for eight PBDE congeners in foods classified as being "for infants and small children", as reported by EFSA (2011). These were derived from 42 samples, of which 29 were ready-to-eat meals for infants and young children, eight were infant and follow-on formulae, two were cereal-based foods for infants and young children, and one was unspecified. Data are not available for infant formula or commercially-produced infant foods purchased in the UK.

Table 6: Mean concentrations of eight PBDEs in foods "for infants and small children" reported in EFSA (2011)

		Mean occurrence (ng/kg whole weight)						
	BDE-	BDE-	BDE-	BDE-	BDE-	BDE-	BDE-	BDE-
	28	47	99	100	153	154	183	209
Lower bound ^a	1	207	76	21	2	5	2	115
Upper bound ^a	2	208	78	23	6	7	5	127

a In the lower and upper bound, <LOD is treated as 0 and the LOD, respectively

Food

29. The most recent measurements of PBDEs in food sampled in the UK are for the composite food groups of the 2012 Total Diet Study (TDS) (Fernandes *et al.*, 2012). The congeners measured in the 2012 TDS were BDE-17, -28, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -153, -154, -183 and -209. Table 7 shows the concentrations of the PBDE congeners for reference points are available.

^b Sum of BDEs 28, 47, 85, 99, 100, 153, 154.

^c Sum of all measured congeners except BDE-209

Table 7. Levels of selected and summed PBDE congeners in food expressed on a whole weight basis

		PBDE o	oncentratio	ons in food (ng/kg food) ^a	
Food group	BDE-47	BDE-99	BDE-153	Total excluding BDE-209 ^b	BDE-209
Bread	5.38	5.71	1.66	23.0-25.0	<200°
Canned vegetables	0.65	0.47	<0.14	1.34-2.07	20.1
Carcase meat	17.9	22.5	7.06	61.4-62.1	<130
Cereals	6.31	7.63	2.07	20.9-22.6	<190
Dairy products	23.1	25.4	5.83	64.8-66.9	21.0
Eggs	12.8	16.2	4.97	45.0-45.7	89.8
Fats+oils	36.9	34.7	8.12	97.4-103	<391
Fish	134	22.7	7.08	304	170
Fresh fruit	1.22	0.91	0.24	3.19-3.66	142
Fruit products	1.25	0.99	0.41	2.86-4.42	30.2
Green vegetables	1.54	1.48	0.16	4.07-4.21	50.2
Meat products	17.7	19.2	4.01	52.0-52.8	<140
Milk	1.79	1.95	0.49	5.30-54.8	120
Nuts	5.86	4.60	1.26	13.4-20.1	100
Offal	7.34	8.83	2.98	25.4-27.4	<120
Other vegetables	5.13	7.75	1.37	21.1-21.2	50.2
Potatoes	4.67	5.19	0.67	12.9-13.4	49.8
Poultry	5.34	5.86	1.39	18.0-19.0	220
Sugar and preserves ^d	121	62.1	7.08	263	1948

^a Concentrations in food were calculated from values for concentrations in fat and for the fat content of food, which were both reported in Fernandes *et al.*, 2012.

^b Total BDE-17, -28, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -153, -154, -183,

Drinking water

30. Concentrations of PBDEs in water were not reported in EFSA (2011). In a series of international studies (Crookes *et al.*, 2009), the only findings for PBDEs in water in the EU were from Sweden, and all were below the limits of detection (LOD), which ranged from 0.6 to 2.9 ng/L for different congeners. If PBDEs occur in water, levels are likely to be low because of their lipophilicity.

Exposure to PBDEs

31. The assessments that are presented in this section are for external exposures from dust, air and the diet. Data on bodyweights were taken from the UK Dietary and Nutrition Survey of Infants and Young Children (DNSIYC) (DH, 2013), with average values of 7.8, 8.7 and 9.6 kg for infants aged >4.0-

^b Total BDE-17, -28, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -153, -154, -183, Where a range is given it represents lower bound to upper bound (treating values <LOD as 0 and the LOD, respectively)

^cBelow the limit of detection (LOD), which varied with food group and congener.

^d Includes sugar, sugar confectionery, jam, syrup, honey, jelly and chocolate.

6.0, >6.0-9.0 and >9.0-12.0 months, respectively. Since DNSIYC did not include infants younger than 4 months, a value of 5.9 kg for infants aged 0-3 months from an earlier survey (DH, 1994), was assumed for infants aged 0-4 months.

Environmental exposure to PBDEs

Dust

32. Table 8 shows potential exposures of infants to PBDEs through ingestion of dust, assuming ingestion of 100 mg dust/day (WHO, 2007), and based on the occurrence data in Table 4. The assessment focuses on infants aged 9-12 months because they are likely to have more contact with floors and other surfaces than younger infants. Since the dust was sampled in 2006, and there have been changes in usage of PBDEs since then, it is possible that these estimates are not representative of current exposures.

Table 8: Potential exposures of infants aged 9-12 months to PBDEs in dust in UK homes

	Dotontial evenou	uros to DDDE from			
	Potential exposures to PBDE from				
	consumption of dust				
Congeners	(ng/kg	bw/day)			
Congeners	Congener present at	Congener present at			
	mean measured	maximum measured			
	concentration	concentration			
BDE-28	0.007	0.022			
BDE-47 ^a	0.16	0.60			
BDE-99	0.38	1.88			
BDE-100	0.058	0.18			
BDE-153	0.15	1.15			
BDE-154	0.046	0.17			
BDE-183	0.74	5.73			
Sum of BDE-28 to -183	1.53	9.72			
BDE-209	2,700	22,900			

^a Congeners for which reference points have been derived are highlighted in bold

33. Potential exposures of UK infants to PBDEs in air, assuming a ventilation rate of 3 m³/day (US EPA, 1989), and the median reported occurrence of 0.24 pg/m³ for the sum of BDEs 28, 47, 49, 66, 99, 100, 153, and 154 in domestic air (paragraph 24), are 0.12, 0.09, 0.08 and 0.08 ng/kg bw/day at ages 0-4, 4-6, 6-9 and 9-12 months respectively.

Dietary exposure to PBDEs

Breast milk

34. Table 9 shows estimated exposure to PBDEs from exclusive breastfeeding by infants, based on the maximum concentrations identified from the data of Abdallah and Harrad (2014) and Bramwell *et al.* (2014), and assuming average (800 mL) or high-level (1200 mL) daily consumption of breast milk.

Table 9 PBDE exposure (µg/kg bw/day) from exclusive breastfeeding by infants, estimated for average and high-level consumption of breast milk

Congonor(a)	Exposures to PBDE from exclusive breastfeeding (ng/kg bw/day)					
Congener(s) (concentration in	Ages 0-4.0	Ages 0-4.0	Ages >4-6.0	Ages >4-6.0		
µg/L whole weight)	months	months	months	months		
μg/ε whole weight)	(800 mL	(1200 mL	(800 mL	(1200 mL		
	milk)	milk)	milk)	milk)		
BDE-28 (10.9) b	1.47	2.21	1.11	1.67		
BDE-47 ^a (513) ^c	69.5	104	52.6	78.9		
BDE-49 (15.8) ^c	2.14	3.20	1.62	2.42		
BDE-66 (4.55) b	0.62	0.93	0.47	0.70		
BDE-85 (29.1) ^c	3.94	5.91	2.98	4.47		
BDE-99 (131) ^b	17.8	26.6	13.4	20.1		
BDE-100 (76.7) b	10.4	15.6	7.86	11.8		
BDE-138 (1.4) b	0.19	0.28	0.14	0.22		
BDE-153 (160) ^c	21.7	32.5	16.4	24.6		
BDE-154 (389) ^c	52.7	79.0	39.9	59.8		
BDE-183 (8.05) b	1.09	1.64	0.83	1.24		
Sum of Tri-hexa ^c	124	186	93.7	141		
Sum exc 209 ^d (736) ^b	99.8	150	75.5	113		
BDE-209 (36.4) b	4.94	7.40	3.73	5.60		

^a Congeners for which reference points have been derived are highlighted in bold

Food

35. No UK Data on PBDE in infant formula and commercially-produced infant foods are available. Table 10 summarises upper bound total infant dietary exposures to PBDEs, estimated using the 19 composite food groups of the 2012 TDS (see Table 7) together with consumption data from the DNYSIC (DH, 2013). The detailed data are presented in Annex 1. The food groups contributing most to total exposure vary by age group.

Table 10: Estimated exposure of infants to PBDEs from food

	Upper bound dietary exposure to PBDEs (ng/kg bw/day)							
Congener(s)	Age 4-6 months	Age 6-9 months	Age 9-12 months					

^b Bramwell *et al.* (2014)

^c Abdallah and Harrad (2014)

^d Sum of all measured congeners except BDE-209

	(n=102 b)		(n=6	(n=602 b)		(n=684 ^b)	
	Mean	P97.5 ^c	Mean	P97.5 ^c	Mean	P97.5 °	
BDE-47	1.00	3.39	1.04	3.29	1.00	2.48	
BDE-99	1.10	3.73	1.10	3.51	1.01	2.66	
BDE-153	0.251	0.856	0.25	0.833	0.23	0.612	
Sum exc 209 d	2.94	9.83	3.14	9.57	3.21	7.25	
BDE-209	1.55	4.16	2.94	7.71	4.48	10.9	

^a Treating occurrence data < LOD as the LOD

Risk characterisations for PBDEs

36. Table 11 shows MoEs for exclusively breastfed infants, calculated as the ratio of the reference point (Table 3) to estimated exposure, for each congener. The reference point used for the sum of all measured congeners except BDE-209, was 4.2 μ g/kg bw/day – i.e. the lowest of the available reference points (which was for BDE-99). This was a pragmatic approach taken to allow for the congeners for which reference points were unavailable because of a lack of relevant toxicity data. Insofar as other congeners are less toxic than BDE-99, it will represent a worst case. BDE-209 was excluded from this combined assessment since it is less toxic and has a much higher reference point than the other congeners.

Table 11. MoEs for exclusively breastfed infants

	MoEs for PBDEs for exclusive breastfeeding for age 0-4 and 4-6 months							
Congener(s)	Ages 0-4.0 months (800 mL milk)	Ages 0-4.0 months (1200 mL milk)	Ages >4-6.0 months (800 mL milk)	Ages >4-6.0 months (1200 mL milk)				
BDE-47	2,475	1,654	3,270	2,180				
BDE-99	236	158	313	209				
BDE-153	442	295	585	390				
Sum exc BDE-209 a	42	28	56	37				
BDE-209	344,130	229,730	455,764	303,571				

^a Reference point for BDE-99 divided by upper bound sum of all measured congeners except BDE-209

37. Tables 12 and 13 show MoEs calculated for infant exposure to PBDEs via the diet and dust.

Table 12. MoEs for dietary exposure of infants

Congener(s)	Age 4-6 months	Age 6-9 months	Age 9-12 months
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^b Number of infants in the survey

^c 97.5th percentile

^d Sum of all measured congeners except BDE-209

	Mean	P97.5 ^a	Mean	P97.5 ^a	Mean	P97.5 ^a
BDE-47	172000	50737	165385	52280	172000	69355
BDE-99	3818	1126	3818	1197	4158	1579
BDE-153	38247	11215	38400	11525	41739	15686
Sum exc BDE-209 b	1429	427	1338	439	1308	579
BDE-209	1096774	408654	578231	220493	379464	155963

^a 97.5th percentile

Table 13: MoEs for exposure to PBDEs from consumption of dust in homes

	Margin of Exposure				
Congener(s)	Congener present at mean measured concentration.	Congener present at maximum measured concentration			
BDE-47	1,075,000	286,667			
BDE-99	11,053	2,234			
BDE-153	64,000	8,348			
Sum of BDE-28 to 183 ^a	2,745	432			
BDE-209	630	74			

^a Reference point for BDE-99 divided by upper bound sum of measured BDEs in the range 28-183

- 38. For non-genotoxic compounds, an MoE of 100 is normally 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 relating to possible toxicokinetic and toxicodynamic differences, both between experimental animals and humans, and within the human population. The reference points for PBDEs took into account differences in toxicokinetics between humans and animals. Therefore, in this case, an MoE somewhat < 100 (say about 30) would be acceptable.
- 39. Of the calculated MoEs, only that for the sum of congeners other than BDE-209 in infants with high daily consumption of breast milk was below 30. However, the margin was only slightly lower (28), and is conservative because it assumes that all congeners are as toxic as BDE-99 (the most toxic measured), and is based on the sum of the maximum reported concentrations. Thus COT does not consider it a cause for concern.
- 40. Occurrence data for PBDEs are limited to a relatively small proportion of the 209 possible congeners. Whilst different research groups have measured and reported different subsets of congeners, they have generally focussed on those that were most likely to be present, based on their prevalence in technical mixtures of PBDEs that have been used as BFRs. Thus, although there is a lack of toxicity data for many of the congeners, the finding that MoEs were acceptable when the sum of measured congeners,

^b Reference point for BDE-99 divided by upper bound sum of all measured congeners except BDE-209

excluding BDE-209, was compared to the lowest toxicological reference point for any single congener (BDE-99), provides some reassurance of safety for the compounds as a group.

41. On the basis of the above considerations, the COT considers that current exposures of infants in the UK to PBDEs from breastfeeding, from complementary food and from ingestion of dust, are unlikely to pose a health concern.

Uncertainties

- 42. The toxicity studies used by EFSA to derive reference points for MOEs involved a single gavage administration to neonatal mice (or rats in the case of BDE-209). There is uncertainty about the relevance of these studies to risk assessment for longer term repeated exposures in humans (see paragraph 15), but because they found neurobehavioural effects at lower doses than in other studies, and covered a relevant neurodevelopmental period in experimental animals, they could not be discounted. The long half-lives of PBDEs mean that after a single administration, systemic exposure would continue over a prolonged period. Furthermore, 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 derivation of reference points from the single dose studies conservative.
- 43. On the other hand, 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 may have overestimated the body burden needed to produce toxicity.
- 44. PBDEs have been used as technical mixtures, and the profile of congeners now present in food and the environment differs from that in the original mixtures. There is uncertainty about the full profile of exposure to PBDEs, and the effects of this combined exposure. This was addressed to some extent by comparing the sum of measured PBDEs (excluding the most prevalent and least toxic BDE-209) to the reference point for the most toxic congener for which data were available. However, the possibility cannot be ruled out that one or more of the congeners that have not been tested in toxicity studies is exceptionally hazardous.
- 45. In addition, no data were available on levels of PBDEs in infant formula and commercially produced infant foods in the UK.

Conclusions

46. There are 209 PBDE congeners, most of which have not been tested for their toxicological properties. Toxicity tests conducted with formerly

available commercial technical mixtures are of limited relevance to the profile of PBDEs in the environment and in food, due to differing persistence of individual congeners .

- 47. In animal studies, the main targets of PBDE 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 risk assessment.
- 48. The available data are insufficient to establish health-based guidance values, such as Tolerable Daily Intakes, for PBDEs. Therefore the COT adopted a Margin of Exposure (MOE) approach to risk assessment, in which estimated exposures of infants to specific PBDEs or combinations of PBDEs were compared to reference points derived from toxicity studies for those compounds.
- 49. Suitable reference points for use in the MOE approach were available for only four congeners: BDE-47, BDE-99, BDE-153 and BDE-209. These reference points were derived from studies in which neonatal rodents were given the PBDE congeners via a single gavage administration, and behavioural changes were observed in adulthood. The Committee had some reservations about the studies, but in the context of a limited database, concluded that they provided a reasonable basis for risk assessment.
- 50. In the absence of adequate toxicity data for most congeners, the COT compared exposures to the sum of all PBDEs that had been measured (excluding the most prevalent and least toxic BDE-209) with the reference point for the most toxic congener for which data were available. This analysis indicated adequate margins of exposure.
- 51. Based on the data that are available, current exposures of UK infants to PBDEs in breast milk, food and dust are unlikely to represent a health concern. However, there are uncertainties because of the limited toxicological database, and no data are available on potential exposures in the UK from infant formula and commercially produced infant foods.

Secretariat October 2014

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Abbreviations

COT Committee on Toxicity of Chemicals in Food Consumer Products

and the Environment

BDE Brominated diphenyl ether

BMDL Benchmark dose lower confidence limit

BFR Brominated flame retardant

bw Body weight

DH Department of Health

DNSIYC Dietary and Nutrition Survey of Infants and Young Children

EFSA European Food Safety Authority

FERA Food and Environment Research Agency LOAEL Lowest observed adverse effect level

LOD Limit of detection
MoE Margin of Exposure

NOAEL No observed adverse effect level PBDE Polybrominated diphenyl ether

PND Postnatal day

SACN Scientific Advisory Committee on Nutrition

T3 Tri-iodothyronine

T4 Thyroxine

TSH Thyroid stimulating hormone

Additional abbreviations can be found within Tables 1 and 2.

Annex 1

Dietary exposure to PBDEs for different foods and infant age groups

Table A1: Estimated mean dietary exposures at age 4-6 months

_	Number of	4.00		onths - PBDE (ng/kg bw/c	E Mean Expo:	sure
Food group	Consumers	BDE-47	BDE-99	BDE-153	Sum exc BDE-209	BDE-209
Bread	11	0.0041	0.0044	0.0013	0.0191	0.1531
Canned						
vegetables	4	0.0013	0.0009	0.0003	0.0039	0.0387
Carcase meat	10	0.0149	0.0187	0.0059	0.0516	0.1079
Cereals	59	0.0072	0.0087	0.0023	0.0257	0.2157
Dairy products	76	1.2842	1.412	3.241	3.7191	1.1167
Eggs	2	0.0079	0.0099	0.0031	0.0281	0.0526
Fats+oils	14	0.0045	0.0042	0.0009	0.0126	0.0478
Fish	6	1.5489	0.0262	0.0082	0.3514	0.1965
Fresh fruit	36	0.0046	0.0034	0.0009	0.0138	0.5346
Fruit products	29	0.0028	0.0022	0.0009	0.0097	0.0666
Green vegetables	33	0.0034	0.0032	0.0004	0.0092	0.1098
Meat products	1	0.0132	0.0143	0.0029	0.0393	0.1042
Milk	17	0.0055	0.006	0.0015	0.1689	0.3698
Nuts	0	0	0	0	0	0
Offal	0	0	0	0	0	0
Other vegetables	57	0.0128	0.0193	0.0034	0.0528	0.125
Potatoes	36	0.0108	0.012	0.0016	0.031	0.1154
Poultry	11	0.0084	0.0093	0.0022	0.03006	0.348
Sugar and						
preserves	10	0.0272	0.0139	0.0016	0.059	0.4374
Total	102	1.0049	1.0981	0.2514	2.9418	1.5512

Table A2: Estimated mean dietary exposures at age 6-9 months

	Number of	6.00		onths - PBDE (ng/kg bw/c	E Mean Expo	sure
Food group	Consumers	BDE-47	BDE-99	BDE-153	Sum exc BDE-209	BDE-209
Bread	242	0.0066	0.0070	0.0020	0.0305	0.2441
Canned						
vegetables	131	0.0011	0.0008	0.0002	0.0035	0.0335
Carcase meat	217	0.0267	0.0335	0.0105	0.0926	0.1938
Cereals	496	0.0194	0.0235	0.0064	0.0695	0.5847
Dairy products	535	1.0104	1.1110	0.2550	2.9261	0.9185
Eggs	88	0.0163	0.0207	0.0063	0.0584	0.1147
Fats+oils	282	0.0069	0.0065	0.0015	0.0193	0.0733
Fish	175	0.1607	0.0272	0.0085	0.3646	0.2039
Fresh fruit	385	0.0050	0.0037	0.0010	0.0150	0.5823
Fruit products	235	0.0023	0.0018	0.0007	0.0080	0.0549
Green vegetables	338	0.0029	0.0028	0.0003	0.0079	0.0938
Meat products	93	0.0267	0.0289	0.0060	0.0795	0.2108
Milk	270	0.0100	0.0109	0.0027	0.3061	0.6702
Nuts	19	0.0013	0.0010	0.0003	0.0043	0.0215
Offal	6	0.0030	0.0036	0.0012	0.0112	0.0491
Other vegetables	453	0.0178	0.0269	0.0048	0.0736	0.1742
Potatoes	389	0.0130	0.0144	0.0019	0.0372	0.1382
Poultry	252	0.0059	0.0065	0.0015	0.0211	0.2440
Sugar and						
preserves	172	0.0449	0.0231	0.0026	0.0976	0.7231
Total	602	1.0419	1.0986	0.2523	3.1433	2.9442

Table A3: Estimated mean dietary exposures at age 9-12 months

	Nli	9.00			E Mean Expo	sure
Food group	Number of			(ng/kg bw/c		
	Consumers	BDE-47	BDE-99	BDE-153	Sum exc BDE-209	BDE-209
Bread	502	0.0101	0.0107	0.0031	0.0468	0.3742
Canned						
vegetables	271	0.0015	0.0011	0.0003	0.0048	0.0463
Carcase meat	372	0.0280	0.0352	0.0111	0.0973	0.2036
Cereals	656	0.0269	0.0326	0.0088	0.0965	0.8112
Dairy products	661	0.7943	0.8734	0.2005	2.3004	0.7221
Eggs	207	0.0184	0.0233	0.0071	0.0656	0.1290
Fats+oils	456	0.0106	0.0100	0.0023	0.0297	0.1127
Fish	305	0.1998	0.0339	0.0106	0.4534	0.2535
Fresh fruit	574	0.0062	0.0046	0.0012	0.0187	0.7253
Fruit products	322	0.0026	0.0021	0.0009	0.0092	0.0630
Green vegetables	436	0.0028	0.0027	0.0003	0.0076	0.0908
Meat products	262	0.0261	0.0283	0.0059	0.0779	0.2065
Milk	426	0.0188	0.0205	0.0051	0.5756	1.2604
Nuts	29	0.0020	0.0016	0.0004	0.0070	0.0349
Offal	9	0.0072	0.0087	0.0029	0.0270	0.1182
Other vegetables	595	0.0175	0.0264	0.0047	0.0721	0.1708
Potatoes	546	0.0161	0.0179	0.0023	0.0462	0.1715
Poultry	400	0.0075	0.0082	0.0019	0.0265	0.3069
Sugar and						
preserves	297	0.0552	0.0283	0.0032	0.1200	0.8890
Total	684	1.0001	1.0136	0.2340	3.2088	4.4796

Table A4: Estimated high level (97.5th percentile) dietary exposures at age 4-6 months

Food group	Number of	4.00 to 5.99 months - PBDE 97.5 Percentile Exposure (ng/kg bw/d)				
Food group	Consumers	BDE-47	BDE-99	BDE-153	Sum exc BDE-209	BDE-209
Bread	11	0.0087	0.0093	0.0027	0.0407	0.3252
Canned						
vegetables	4	0.0015	0.0011	0.0003	0.0048	0.0465
Carcase meat	10	0.0412	0.0517	0.0162	0.1428	0.2989
Cereals	59	0.0266	0.0322	0.0087	0.0953	0.8009
Dairy products	76	3.4152	3.7552	0.8619	9.8907	3.1047
Eggs	2	0.0174	0.0205	0.0068	0.0622	0.1222
Fats+oils	14	0.0122	1.2000	0.0028	0.0358	0.1358
Fish	6	0.2890	0.0490	0.0153	0.6558	0.3667
Fresh fruit	36	0.0166	0.0124	0.0033	0.0498	1.9338
Fruit products	29	0.0113	0.0090	0.0037	0.0400	0.2735
Green vegetables	33	0.0103	0.0099	0.0011	0.0281	0.3355
Meat products	1	0.0132	0.0143	0.0030	0.0393	0.1042
Milk	17	0.0248	0.0245	0.0062	0.6881	1.5069
Nuts	0	0	0	0	0	0
Offal	0	0	0	0	0	0
Other vegetables	57	0.0399	0.0604	0.0107	0.1652	0.3912
Potatoes	36	0.0261	0.0291	0.0038	0.0750	0.2788
Poultry	11	0.0283	0.0310	0.0074	0.1007	1.1657
Sugar and						
preserves	10	0.0591	0.0303	0.0035	0.1285	0.9520
Total	102	3.39232	3.73067	0.85618	9.82632	4.16336

Table A5: Estimated high level (97.5th percentile) dietary exposures at age 6-9 months

_	Number of	6.00 to 8.		- PBDE 97.5 (ug/kg bw/d	5 Percentile E	Exposure
Food group	Consumers	BDE-47	BDE-99	BDE-153	Sum exc BDE-209	BDE-209
Bread	242	0.0235	0.0249	0.0072	0.1090	0.8720
Canned						
vegetables	131	0.1409	0.0723	0.0082	0.3063	2.2686
Carcase meat	217	0.0116	0.0111	0.0012	0.0316	0.3768
Cereals	496	0.0485	0.0539	0.0070	0.1392	0.5173
Dairy products	535	0.0618	0.0933	0.0165	0.2553	0.6045
Eggs	88	0.0045	0.0033	0.0010	0.0144	0.1395
Fats+oils	282	0.0174	0.0130	0.0034	0.0522	2.0237
Fish	175	0.0095	0.0076	0.0031	0.0337	0.2306
Fresh fruit	385	0.0320	0.0349	0.0088	0.9794	2.1448
Fruit products	235	3.2813	3.6080	0.8281	9.5030	2.9830
Green vegetables	338	0.0781	0.0945	0.0256	0.2798	2.3521
Meat products	93	0.0040	0.0032	0.0009	0.0138	0.0689
Milk	270	0.1125	0.1414	0.0444	0.3902	0.8168
Nuts	19	0.0038	0.0045	0.0015	0.0141	0.0618
Offal	6	0.0928	0.1006	0.0210	0.2767	0.7338
Other vegetables	453	0.0243	0.0266	0.0063	0.0863	0.9998
Potatoes	389	0.6028	0.1021	0.0318	1.3676	0.7647
Poultry	252	0.0281	0.0264	0.0062	0.0784	0.2977
Sugar and						
preserves	172	0.0687	0.0869	0.0267	0.2452	0.4817
Total	602			0.83306		
Total	002	3.29291	3.50835	1	9.56762	7.71142

Table A6: Estimated high level (97.5th percentile) dietary exposures at age 9-12 months

	Number of	9.00 to 11		s - PBDE 97. (ng/kg bw/c	5 Percentile	Exposure
Food group	Consumers	BDE-47	BDE-99	BDE-153	Sum exc BDE-209	BDE-209
Bread	502	0.0338	0.0359	0.0104	0.1571	1.2565
Canned						
vegetables	271	0.0056	0.0040	0.0012	0.4338	0.1729
Carcase meat	372	0.1263	0.1588	0.0498	0.0178	0.9173
Cereals	656	0.0899	0.1087	0.0295	0.4382	2.7064
Dairy products	661	2.3175	2.5482	0.5849	0.3219	2.1068
Eggs	207	0.0707	0.0894	0.0274	6.7116	0.4958
Fats+oils	456	0.0393	0.0370	0.0086	0.2523	0.4164
Fish	305	0.7344	0.1244	0.0388	0.1097	0.9318
Fresh fruit	574	0.0208	0.0155	0.0041	1.6662	2.4257
Fruit products	322	0.0125	0.0099	0.0041	0.0625	0.3009
Green vegetables	436	0.0127	0.0122	0.0013	0.0440	0.4148
Meat products	262	0.1029	0.1116	0.0233	0.0348	0.8139
Milk	426	0.1065	0.1161	0.0292	0.3070	7.1419
Nuts	29	0.0068	0.0054	0.0015	3.2615	0.1165
Offal	9	0.0160	0.0193	0.0065	0.0234	0.2619
Other vegetables	595	0.0512	0.0774	0.0137	0.0598	0.5011
Potatoes	546	0.0532	0.0591	0.0076	0.2116	0.5674
Poultry	400	0.0257	0.0282	0.0067	0.1527	1.0602
Sugar and						
preserves	297	0.1996	0.1024	0.0117	0.0916	3.2131
Total	684	2.4809	2.6602	0.6120	7.2518	10.9439