TOX/2014/40

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

First draft statement on polybrominated biphenyls (PBBs) 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 (BRFs) should be considered as part of that body of work. The polybrominated biphenyls (PBBs) are a group of BFRs comprising 209 structurally-related congeners. A scoping paper (TOX/2014/31) was presented to Members in October 2014.

2. Annex A contains a first draft COT statement summarising the available information on PBBs. This has been written taking into account the discussion of the scoping paper in October 2014. As requested further information is provided on the rationale behind the selection of specific congeners observed in the literature, and a statement that a meaningful risk assessment was not deemed possible based on the currently available information.

Questions on which the views of the Committee are sought

3. Members are invited to comment on the structure and content of the first draft statement.

Secretariat

November 2014

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

Draft statement on polybrominated biphenyls (PBBs) 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 a part of that group.

Polybrominated biphenyls

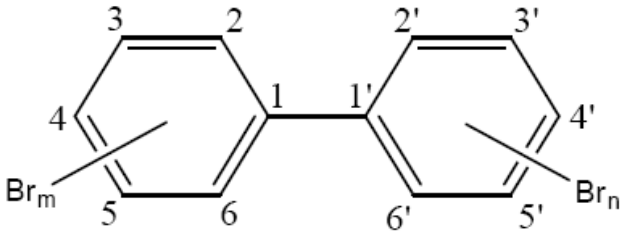
2. Polybrominated biphenyls (PBBs) are a class of BFRs formerly used in the production of synthetic fibres and polymers. They are additive flame retardants and thus are not chemically bound to the polymers to which they are added. Production and use of PBBs has been increasingly restricted throughout the world over the past four decades. There are no EU regulations to specifically limit the levels in foods.

3. In Michigan in 1973, PPBs in the form of FireMaster were accidentally incorporated into animal feed, leading to the wide-spread contamination at more than 500 farms. FireMaster was a PBB mixture predominantly comprised of 2,2',3,4,4',5,5'-hexabromobiphenyl (PBB-153: 60-80%) and 2,2',3,4,4',5,5'-heptabromobiphenyl (PBB-180: 12-25%), with lesser amounts of lower brominated compounds. As a consequence of the feed contamination, thousands of cattle and other livestock, and their produce, were destroyed including 1.5 million chickens. The local population were exposed via the food chain i.e. meat, cheese, milk and eggs (MDHC, 2011). In exposed individuals exposures were found to be several orders of magnitude higher than the general population (WHO/IPCS, 1994).

4. PBBs have a basic biphenyl structure with a varying number of bromine atoms attached. Their basic structure is provided in Figure 1. There are potentially

209 different congeners. PBBs have been used commercially as technical mixtures, differing in formulation depending on the manufacturer.

Figure 1: General structure of PBB congeners (Br_m = 1-5, Br_n = 0-5)



5. The position of the bromine atoms determines whether the configuration is planar or non-planar: Br atoms at the ortho-positions, 2, 2', 6, and 6', cause a rotation in the bridge between the two phenyl groups due to the large Br atom size. Planar congeners have structures similar to 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) and are likely to cause toxicity via aryl hydrocarbon receptor (AhR) activation, whereas non-planar congeners are more likely to cause toxicity via the activation of nuclear receptors such as the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR). The congener type, degree of bromination and associated nomenclature are given in Table 1.

Table 1: The types of PBB congeners, number of isomers and nomenclature.

Congener type	Total number of isomeric congeners	PBB Congeners	
		Non-planar (ortho)	Planar (non-ortho)
MonoBBs	3	PBB-1	PBB-2, -3
DiBBs	12	PBB-4 to -10	PBB-11 to -15
TriBBs	24	PBB-16 to -34	PBB-35 to -39
TetraBBs	42	PBB-40 to -76	PBB-77 to -81
PentaBBs	46	PBB-82 to -125	PBB-126, -127
HexaBBs	42	PBB-128 to -168	PBB-169
HeptaBBs	24	PBB-170 to -193	-
OctaBBs	12	PBB-194 to -205	-
NonaBBs	3	PBB-206 to -208	-
DecaBB	1	PBB-209	-

6. As the bromine content of the PBB structure increases, their low vapour pressure and water solubility further decrease. The PBBs are known to be chemically stable, persistent and bio-accumulative in the environment, and the profile of congeners in the environment differs from those in the commercial technical mixtures. It has been suggested that the higher brominated compounds may undergo debromination in the environment (IPCS/WHO, 1994).

7. This statement draws primarily on information from a review of the European Food Safety Authority (EFSA, 2010), summarises the toxicological and epidemiological studies that have been published more recently, summarises the sources of exposure and considers the prospects for risk assessment.

Toxicokinetics of PBBs

8. From the limited studies available, there is an indication of a high degree of absorption of PBBs. Initial distribution is widespread but over time the PBBs are redistributed, with the highest accumulations found in adipose tissue and high fat content tissues. The half-life of PBB-153 is between 9 and 69 weeks in rats. Epidemiological studies suggest that the half-life could be between 10 and 30 years in humans depending on the PBB or PBBs measured (EFSA, 2010). There is a lack of data on the toxicokinetics of most of the PBB congeners.

9. Bramwell *et al.* (2014) reported serum levels of PBB-15, -49, -52, -80, -101, -153, and -209 in samples from 10 UK couples. PBB-153 was quantified in 40% of samples with a median value of 0.04 ng g^{-1} lipid weight (lw) (range of <0.01-0.9 ng/g lw). All other PBBs were below the limit of detection (LOD). Levels were within the range reported for a number of countries (EFSA, 2010).

Toxicology of PBBs

10. Interpretation of the toxicology studies is hampered by the variability in the test material used, which was often technical mixtures with no compositional information. However the available data suggest that the liver, reproductive system, thyroid hormone homeostasis, the nervous and immunological systems are the primary targets.

11. The International Agency for Research on Cancer (IARC) concluded in 2013 that PBBs should be classified as Class 2A, *probably carcinogenic to humans*, due to their similarity to polychlorinated biphenyls (PCBs), which were classified as Class 1, *carcinogenic to humans* (Lauby-Secretan *et al.,* 2013).

12. EFSA identified five key areas of human data; ‘immunological dysfunction and thyroid and hormone disruption’, ‘neurodevelopmental effects’, ‘cancer’, ‘diabetes and metabolic syndrome’ and ‘effects on fertility and offspring’. No consistent effects

were found in any of these areas and EFSA highlighted the potential confounding impact of co-exposures to other environmental contaminants, lifestyle factors and study designs. However, EFSA did state that there was an indication that PBBs are associated with neurodevelopmental effects, cancer at specific sites and effects on fertility and offspring. (EFSA, 2010).

13. Of the scientific literature published since EFSA (2010), an *in vitro* study by Ibhazehiebo *et al.* (2011) adds support to the evidence that PBBs, in the form of FireMaster BP-6, may have effects on the thyroid and the nervous system. No other relevant studies were found.

14. Since EFSA (2010), Jamieson *et al.* (2011) and Yard *et al.* (2011) have published epidemiological studies based on follow-up assessments for the original participants of the Michigan Long-Term PBB; a cohort of individuals exposed to FireMaster from the environment and food chain at the time of the Michigan incident. Jamieson *et al.* (2011) investigated abnormal Papanicolaou (Pap) test[1] results in a subset of the cohort (n = 103). No significant association between PBB exposure (based on PBB-153) and the risk of reporting an abnormal Pap test result was found. The data suggested that breastfeeding could be associated with a decrease in positive Pap test results in those with serum PBB-153 levels of >13 µg/L. Yard *et al.* (2011) found no increased incidence of thyroid disease in men and women (n = 3333), although incidence in women was 5 times higher than in men, and women were observed to have a decreased age at the time of diagnosis of thyroid disease.

15. With regards to a point of departure, EFSA (2010) identified hepatocarcinogenicity as the critical endpoint for PBBs, with a no observed effect level (NOEL) of 0.15 mg FireMaster /kg bw/day. This was based on a National Toxicology Programme (NTP) 2-year carcinogenicity study of a technical PBB mixture of FireMaster, which included pre- and perinatal exposure of the dams (NTP, 1993). The composition of this technical mixture was not consistent with the PBB profiles found in food. Therefore EFSA concluded that it was not appropriate to derive a health-based guidance value from this NOEL, and instead used the NOEL as the reference point in a margin of exposure (MOE) approach. EFSA considered the planar PBBs to potentially have dioxin-like activity.

16. The COT concluded that PBBs would be expected to have modes of action (MOA) similar to PCBs, with the effects of planar molecules mediated via the AhR and occurring at exposure levels lower than those of non-planar molecules, which were likely to be ligands for the CAR and pregnane X receptor (PXR). The COT had previously concluded that the World health Organisation (WHO) toxicity equivalency factors (2005 WHO-TEFs) assigned to the chlorinated dioxins and PCBs could be applied to the non-*ortho*-brominated (planar) congeners, to determine toxicity

equivalences (TEQs) for comparison with the TDI for dioxin-like compounds. This would be considered a conservative approach as the corresponding chlorinated congeners were expected to be more toxic than their brominated counterparts[2,3,4].

17. Thus the COT concluded that for the planar PBBs, the toxicity equivalences (TEQs) should be added to those for the chlorinated compounds to give an estimate of total intake of chemicals with dioxin-like properties for comparison with the TDI of 2 pg WHO-TEQ/kg bw/day. For the non-planar molecules, the tumour incidence in the NTP carcinogenicity study, although possibly CAR-related, could be used to provide a reference point for the purposes of risk characterisation.

Sources of PBB exposure

18. Due to the persistent nature of PBBs in the environment, humans can be exposed to PBBs via food, dust, air and water.

Sources of PBB exposure

Breast milk

19. In the EFSA (2010) opinion the only European breast milk data were from Germany (published in 1988), and from Denmark and Finland (published in 2008). Since EFSA (2010) one study by Bramwell *et al.* (2014) has reported PBB levels in UK-based females. Of these studies, the only PBB that was measured in all four studies was PBB-153. Mean levels of PBB-153 were found to be 0.2 ng/g fat (range 0.04 - 1.5 ng/g fat), and 0.134 ng/g fat (range 0.03 - 1.21 ng/g fat), in Danish (n = 65) and Finnish (n = 65) samples respectively. In the German study samples (n = 25) PBB-153 had a mean level of 1.03 ng/g fat (range 0.29 - 2.8 ng/g fat, median 0.75 ng/g fat). In the UK a median concentration of 0.08 ng/g fat (range 0.06 – 0.79 ng/g fat) was reported from 6 individuals.

20. Comparison of the levels of PBBs in these studies is complicated by the panel of PBBs measured and that even for PBB-153 there is a mixture of mean and median data (summarised in Table 2). The data suggest that levels of PBB-153 have reduced during the time between these studies, but it is not possible to draw robust conclusions from the limited data available.

Table 2: PBB-153 levels in breast milk (ng/g fat).

[2] COT (2006). http://cot.food.gov.uk/sites/default/files/cot/cotstatementfishsurveys.pdf
[3] COT (2010). http://cot.food.gov.uk/sites/default/files/cot/cotstatementhalogenatedioxins201002.pdf

Country	Number of samples	Mean	Median	Range	Year study published
Germany	25	1.03	0.75	0.29 - 2.8	1988
Finland	65	0.13	-	0.03 - 1.20	2008
Denmark	65	0.2	-	0.04 - 1.5	2008
UK	6	-	0.08	0.06 - 0.79	2014

Food

29. Two recent studies have reported on PBBs in food in the UK. The non-*ortho* PBB-77, -126 and -169 were detected in white and oily fish, sampled in 2013 and 2014 (table 3) (FERA unpublished, 2014). The non-*ortho* PBB-77, -126 and -169, and the ortho PBBs -15, -49, -52, -80, -101, -153 and -209 were measured in the 2012 Total Diet Study (TDS) (Fernandes *et al.,* 2012) and were predominantly below the limits of detection with the exception of some low levels quantified in fish and some specific congeners in bread, eggs and sugars and preserves. Selection of the congeners for measurement was mainly based on availability of standards for the analysis.

Table 3: Mean levels of PBB congeners in oily and white fish (ng/kg fish).

	PBB-77		PBB-126		PBB-169		Sum	
	LB	UB	LB	UB	LB	UB	LB	UB
Oily fish	0.022	0.023	0.000	0.005	0	0.006	0.022	0.034
White fish	0.006	0.008	0.001	0.004	0.002	0.005	0.008	0.017

Dust

21. No data are available on dust sampled in the UK. Levels of PBBs -4, -10 and -209 in home dust sampled in Pretoria, South Africa were mostly below the LOD. Detectable levels of PBB-4 and -209 were reported in a small fraction of samples, with maxima of 21.3 and 20.4 ng/g of dust, respectively. The authors considered that the congeners PBB-4 and -10 were not environmentally relevant and also noted that they were not present in technical PBB mixtures.

Conclusions

22. In line with its previous conclusions, the Committee concluded that the key overall endpoint of PBBs is liver carcinogenicity, but that planar and non-planar PBBs need separate consideration. Planar PBBs are expected to behave in a manner similar to that of dioxins, via the AhR. The PCB 2005 WHO-TEFs can be conservatively assigned to the planar PBBs in order to calculate TEQs for comparison to the TDI for dioxin-like compounds. For the non-planar PBBs, the carcinogenicity data, although of uncertain human relevance, could provide a basis for deriving a reference point for risk characterisation. However the technical mixture tested in the carcinogenicity study was not representative of the profile of PBBs that humans could be exposed to from the environment and foodstuffs.

23. The available data on PBB sources is limited in terms of the number of congeners measured, which vary between different studies, the small number of samples analysed within the UK and knowledge of how representative they are. Thus a meaningful estimate of infants' exposure to PBBs is not possible. Hence the Committee concluded that a meaningful risk assessment cannot be performed.

24. The Committee noted that further research on the toxicity of PBBs was not likely to be a high priority since their use is now restricted, and exposures are likely to decrease further over time. However, it would be useful to obtain more data on levels of the planar congeners in foods, taking into account their relative potency (as estimated from those of the corresponding PCBs).

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ABBREVIATIONS

AhR	Aryl hydrocarbon receptor
BFRs	Brominated flame retardants
CAR	Constitutive androstane receptor
CI	Confidence Intervals
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
EFSA	European Food Safety Authority
HR	Hazard ratio
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
LB	Lower bound
LOD	Limit of detection
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NTP	National Toxicology Programme
OR	Odds ratio
PBBs	Polybrominated biphenyls
PCBs	Polychlorinated biphenyls
PXR	Pregnane X receptor
SACN	Scientific Advisory Committee on Nutrition
TCDD	2,3,7,8-tetrachloro-p-dibenzodioxin
TDI	Tolerable Daily Intake
TDS	Total Diet Study
TEF	Toxicity Equivalence Factor
TEQ	Toxicity equivalency
UB	Upper bound
WHO	World Health Organization