TOX/2015/06

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

Second 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 (BFRs) 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, and a first draft statement was discussed in December 2014 (TOX/2014/40).

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 agree the second draft statement.

Secretariat

January 2015

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

Second draft statement on polybrominated biphenyls (PBBs) 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. 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 biphenyls (PBBs) in the infant diet. PBBs are brominated flame retardants (BFRs), which have been 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 PBBs.

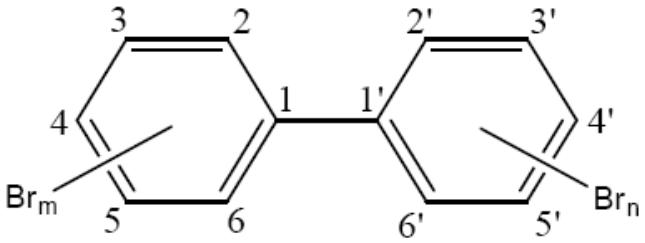
Polybrominated biphenyls

3. Polybrominated biphenyls (PBBs) are a class of BFRs formerly used in the production of synthetic fibres and other polymers. They are additive flame retardants and thus are not chemically bound to the polymers to which they are added. Over the past four decades, the production and use of PBBs has been restricted progressively across the world. Within the EU, there are no specific regulatory limits for levels of PBBs in foods.

4. PBBs have a biphenyl structure, to which bromine atoms are attached in varying numbers and positions that distinguish 209 possible congeners (Figure 1).

Commercially, they have been produced as technical mixtures, which have differed in their mix of individual congeners.

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: Bromine 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 size of the bromine atom. Planar congeners have structures similar to 2,3,7,8-tetrachloro-p-dibenzodioxin (TCDD) and are likely to cause toxicity through activation of the aryl hydrocarbon receptor (AhR), whereas non-planar congeners are more likely to cause toxicity through activation of nuclear receptors such as the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR). The classification of congeners and associated nomenclature is summarised in Table 1.

Table 1: The types of PBB congeners, numbers 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 PBBs increases, their vapour pressure and water solubility reduce. They are chemically stable, persistent and bio-accumulative in the environment, where the profiles of congeners differ from those in commercially produced 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 by the European Food Safety Authority (EFSA, 2010), summarises the toxicological and epidemiological studies that have been published more recently, reviews the sources of exposure, and considers the scope for risk assessment.

Toxicokinetics of PBBs

8. From the limited research that has been conducted, there is an indication that PBBs are readily absorbed from the gut. Initial distribution is widespread, but over time they are redistributed, with the greatest accumulation in adipose tissue and other tissues with high fat content. The half-life of PBB-153 in rats is between 9 and 69 weeks. Epidemiological studies suggest that in humans, half-lives for PBBs could be between 10 and 30 years, according to congener (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 fat (range of <0.01-0.9 ng/g fat). All other PBBs were below the limit of detection (LOD). The findings were consistent with those reported from a number of other countries (EFSA, 2010).

Toxicology of PBBs

10. Interpretation of toxicological research on PBBs is hampered by variability in the test materials used, studies often having been conducted with technical mixtures of unspecified composition. However the information that is available suggests that the primary targets are the liver, reproductive system, thyroid hormone homeostasis, and the nervous and immunological systems.

11. Epidemiological data have come principally from follow-up of an incident in Michigan in 1973, in which a product called FireMaster was accidentally incorporated into animal feed, leading to contamination at more than 500 farms. FireMaster was a PBB mixture comprising mainly 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 congeners. As a consequence of the contamination, it was necessary to destroy thousands of cattle, 1.5 million chickens, other livestock, and derived produce. Despite this action, the local population was exposed through

consumption of contaminated meat, cheese, milk and eggs (MDHC, 2011), the exposures being several orders of magnitude higher than in the general population (WHO/IPCS, 1994).

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

13. In 2010 EFSA noted indications from epidemiological research that PBBs are associated with neurodevelopmental effects, cancer (digestive tract, lymphoma and breast) and adverse reproductive effects on fertility and offspring. However no consistent evidence was found for any of these outcomes. (EFSA, 2010).

14. As regards a point of departure for risk assessment, EFSA (2010) identified hepatocarcinogenicity as the critical endpoint for PBBs, with a no observed effect level (NOEL) of 0.15 mg/kg bw/day for the mix of congeners in FireMaster. This came from a National Toxicology Programme (NTP) 2-year carcinogenicity study in rats, which included pre- and perinatal exposure of the dams (NTP, 1993). The composition of the technical mixture in Firemaster differed from the profiles of PBBs found in food. Therefore EFSA concluded that it was not appropriate to derive a health-based guidance value from the NOEL, and instead used it as a reference point in a margin of exposure (MOE) approach.

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

16. Jamieson *et al.* (2011) and Yard *et al.* (2011) have published new epidemiological research based on follow-up of the original participants in the Michigan Long-Term PBB cohort, who were exposed to PBBs at the time of the Michigan contamination incident (see above). At the time of their enrolment in 1976-78, participants completed questionnaires and their serum concentrations of PBBs and PCBs were measured. Subsequently, follow-up questionnaires and telephone interviews were used to assess health outcomes. Jamieson *et al.* (2011) investigated abnormal Papanicolaou (Pap) test[1] results in a subset of the cohort (n = 103). No significant association was found between PBB exposure (assessed by measurement of PBB-153) and report of an abnormal Pap test result. However, the data suggested that breastfeeding might be associated with a lower frequency of positive Pap test results among those with serum PBB-153 concentrations >13 µg/L at the time of the incident (a pattern that might be expected if PBBs were carcinogenic, and body burden of the chemicals were importantly reduced by

[1] Cervical screening to detect abnormal cells thought to be the early phases of neoplastic changes.

excretion in breast milk). In a nested case-control study based on the Michigan Long-Term PBB cohort, Yard *et al.* (2011) compared PBB serum concentrations in cases with thyroid disease (stated that it "could include hypothyroidism, hyperthyroidism, goiter and thyroid cancer") and controls without. After adjustment for body mass index, they found no increased risk of thyroid disease in men or women with higher serum levels of PBBs.

COT conclusions on toxicology of PBBs

17. From the evidence that is now available, the COT concludes that the planar PBBs are likely to be of greater toxicological concern than the non-planar congeners. PBBs are expected to have modes of action (MOAs) similar to polychlorinated biphenyls (PCBs), whereby the effects of planar molecules are mediated via the Ah receptor, dioxin-like in character, and occur at exposure levels lower than effects of the non-planar congeners. The non-planar congeners are expected to be ligands for the pregnane X receptor (PXR) and constitutive androstane receptor (CAR), the latter being of questionable relevance to human toxicity.

18. For planar PBBs, as previously concluded by the COT, the World Health Organization (WHO) toxicity equivalency factors (2005 WHO-TEFs) assigned to PCBs could be applied to the corresponding PBB congeners, to determine toxicity equivalences (TEQs). This would be a conservative approach since the corresponding chlorinated congeners are expected to be more toxic than their brominated counterparts due to their higher relative potencies and lower clearance[2,3].

19. The toxicity equivalences (TEQs) for planar PBBs could then be added to those for other relevant compounds to give a measure of the total intake of chemicals with dioxin-like properties, which could be compared with the TDI of 2 pg WHO-TEQ/kg bw/day.

20. With regard to 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

21. Due to the persistent nature of PBBs in the environment, human infants may be exposed to them though ingestion of dust, breast milk and other foods.

[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

Sources of PBB exposure

Dust

22. No data are available on levels of PBBs in dust sampled in the UK. Levels of PBBs -4, -10 and -209 in household dust sampled in Pretoria, South Africa were mostly below the LODs (0.16, 0.16 and 1.30 ng/g respectively). 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 (Kefeni *et al.,* 2014).

Breast milk

23. In the EFSA (2010) opinion, the only European data on PBBs in breast milk 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 measured PBB levels in breast milk in the UK. The only congener that was analysed in all four of these 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)[4], and 0.134 ng/g fat (range 0.03 - 1.21 ng/g fat), in the Danish (n = 65) and Finnish (n = 65) samples respectively. In the German study sample (n = 25), PBB-153 occurred at a mean concentration 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 in six individuals.

24. Comparison of the levels of PBBs in these studies is complicated by differences in the panel of PBBs measured, and even for PBB-153 the published findings have been summarised in different ways (either by means or by medians) (Table 2).

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

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

25. Two recent studies have measured PBBs in food in the UK. The planar PBB-77, -126 and -169 were detected in white and oily fish, sampled in 2013 and 2014

(Table 3) (FERA unpublished, 2014). The same congeners, together with the non-planar 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 LOD (which ranged between 0.01 and 208 ng/g fat). Exceptions were the findings of low levels in fish, and of some specific congeners in bread, eggs and sugars and preserves. The non-planar congeners were chosen for investigation in the TDS because they had previously been found in studies of higher marine biota, and because reliable standards were available. The inclusion of the planar congeners was because of their chemical similarity to the PCBs for which WHO-TEF values had been assigned.

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

Conclusions

26. As previously, the Committee concludes that the key effect 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 dioxins, acting via the AhR. The 2005 WHO-TEFs for PCBs can conservatively be assigned to the corresponding planar PBBs in order to calculate TEQs for comparison with the TDI for dioxin-like compounds. For the non-planar PBBs, available carcinogenicity data, although of uncertain human relevance, could be used to derive a reference point for risk characterisation. However the technical mixture tested in the carcinogenicity study was not representative of the profiles of PBBs to which people are exposed in the environment and foodstuffs.

27. Data on sources of exposure to PBBs are available for only a limited number of congeners, coverage of which has varied between studies. Moreover, few measurements have been made in the UK, and there is uncertainty about the extent to which they are representative. Thus reliable estimation of infants' exposure to PBBs is not possible, and no meaningful risk assessment can be performed.

28. The Committee considers that further research on the toxicity of PBBs is not a high priority since their use is now restricted, and exposures are likely to decrease

over time. However, it would be useful to obtain more data on levels of the planar congeners in foods in the UK.

Secretariat
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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