EFSA's RISK ASSESSMENT ON BROMINATED FLAME RETARDANTS (BFRs)

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Introduction

The European Food Safety Authority (EFSA) was established in January 2002 as an independent body providing scientific advice and communication on risks associated with the food chain (Regulation (EC) No 178/2002). As a risk assessor, EFSA produces scientific opinions and advice to provide a sound foundation for European policies and legislation and to support the European Commission (EC), European Parliament and EU Member States in taking effective and timely risk management decisions.

The European Commission requested EFSA to assess the risks to human health related to the presence of brominated flame retardants (BFRs) in food, considering the following classes of BFRs in five different scientific opinions: (1) polybrominated biphenyls (PBBs), (2) polybrominated diphenyl ethers (PBDEs), (3) hexabromocyclododecanes (HBCDDs), (4) tetrabromobisphenol A (TBBPA) and other phenols and (5) other BFRs, including emerging BFRs. EFSA has been asked to consider all relevant toxicological information and to carry out a dietary exposure assessment for the general population and specific groups of the population. Biomonitoring data for these compounds will also be taken into account, and potential data gaps for the BFRs should be identified.

This task was allocated to the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) and a Working Group was established for this purpose. The scientific opinions on PBBs and PBDEs have been adopted by the CONTAM Panel and published in September 2010 and May 2011, respectively. The opinions on HBCDDs, TBBP-A and other phenols, and other BFRs will be published during 2011.

In this paper the methodology used for the risk assessment will be laid out and the outcome of the scientific opinions on PBBs and PBDEs in Food reported.

Materials and methods

The assessment of the risk is done following the risk assessment paradigm: hazard identification, exposure assessment, hazard characterization and risk characterization.

The exposure assessment combines the data on human consumption for the different food categories with the occurrence data on BFRs in the respective food categories. A range of intake/exposure scenario estimates are foreseen so that special subgroups of the population (e.g. infants and children, vegetarians) that may be considered as high consumers are covered. For the purpose of these series of opinions on BFRs, the occurrence data from the EU-wide monitoring recommended by the EC in 2006 based on the outcome of the EFSA's advice on BFRs to be monitored in food and feed[1] was made available to EFSA. In addition, to ensure that human exposure assessment was as comprehensive as possible, EFSA launched a call for data in 2009, which is now closed.

Food consumption at the individual level is usually estimated through food consumption surveys. EFSA established in 2010 the "Comprehensive European Food Consumption Database", built on existing information for adults and children at a detailed level. Twenty two different European countries provided food consumption

data at the individual level to EFSA collected within the most recent national dietary surveys. Detailed information on the 32 dietary surveys included in the Comprehensive European Food Consumption Database can be found in the recently published Guidance of EFSA on the "Use of the EFSA Comprehensive European Food Consumption Database in exposure assessment"[2]. All food consumption data were codified according to the FoodEx classification system which has been developed by the EFSA Unit on Dietary and Chemical Monitoring (DCM, former DATEX Unit) in 2009. Within the Comprehensive European Food Consumption Database, detailed food consumption data for children are also included.

For the estimation of the PBDE exposure for infants from human milk and infant formula, a mean consumption of 800 mL per day and a high consumption of 1,200 mL per day are used in these opinions.
Specific groups of the population such as high and frequent fish consumers and consumers of food supplements, especially fish oil capsules or fish liver oil, were considered separately, due to the comparatively elevated PBB and PBDE levels in these commodities. In order to estimate the dietary intake of PBDEs for the specific population who might consume fish every day, a daily consumption of 2.6 g/kg b.w. fish meat eaten by the European population was used, based on data from the Comprehensive European Food Consumption Database. For food supplements the consumption recommended on the package varies according to the different brands (e.g. one teaspoon or one tablespoon). Therefore, the CONTAM Panel assumed a maximum daily consumption of 15 mL of fish oil for the exposure estimate to cover a worst case scenario.

For the hazard characterization, available toxicological and toxicokinetics studies in the open literature until the publication of the opinions were considered.

Results and discussion:

Scientific opinion on PBBs in Food[3]

Data from the analysis of 16 PBB congeners in 794 food samples were provided to EFSA by 6 European countries, covering the period from 2003 to 2009. The CONTAM Panel reviewed the available data on composition of technical mixtures, occurrence in food and toxicology of the various PBB congeners. Based on the reported data on occurrence in food, the Panel put special emphasis on the PBB congeners BB-3, -15, -29, -49, -52, -77, -80, -101, -103, -126, -153, -169, -180, -194, -206 and -209. The food category "fish and other seafood" dominated the total samples, followed by "meat and meat products (including edible offal)" and "animal and vegetable fats and oils" and "milk and dairy products". The data were characterized by a high proportion of non-detects for the various congeners (overall more than 80 %), with some food categories, i.e. "animal and vegetable fats and oils", "milk and dairy products", close to 100 % non-detects. The lowest proportion of non-detects was reported for the food category of "fish and other seafood".

Due to the high proportion of non-detects for certain food categories and certain congeners, occurrence information was driven by the reported limits of detection (LODs) or limits of quantification (LOQs). Therefore, the CONTAM Panel decided to focus only on the food categories "fish and other seafood", "meat and meat products", "animal and vegetable fats and oils", "milk and dairy products" and "food for infants and small children". To avoid an unrealistic exposure estimate, the exposure estimation was performed only on those congeners in the respective food categories where the proportion of non-detects was less than 80 %.

The toxicological studies on PBBs date back decades, reflecting the phase-out of the manufacture and use of PBBs. Oral toxicity studies were carried out with technical PBB mixtures of which the exact composition of congeners is not known. Main targets were the liver, the reproductive system, thyroid hormone homeostasis and the nervous and immune systems. *In vitro* and *in vivo* genotoxicity studies indicate that PBBs are not directly genotoxic.

In considering the available toxicological information, the CONTAM Panel selected the hepatic carcinogenic effects of PBBs as the critical effect for the derivation of a reference point for gauging the potential health risk of dietary exposure to PBBs. The no-observed-effect level (NOEL) for this end-point is 0.15 mg/kg body weight

(b.w.). Since this NOEL was obtained in a study with a technical PBB mixture, the congener profile of which differs from that currently found in food, the CONTAM Panel concluded that it was inappropriate to use this NOEL to derive a health based guidance value.

High and frequent consumers of fatty fish is the subgroup with the highest dietary exposure to PBBs (0.15 ng/kg b.w. per day). This is 6 orders of magnitude less than the NOEL of 0.15 mg/kg b.w. The estimated mean intake for breast-fed infants with high human milk consumption was 1.4 ng/kg b.w. per day, i.e. 5 orders of magnitude less than the NOEL. Therefore, the CONTAM Panel concluded that the risk to the European population from exposure to PBBs through the diet is of no concern. Since PBBs are no longer produced or used in Europe and due to the low and declining environmental concentrations, it was concluded that PBBs are a low priority for further research or monitoring efforts.

Scientific opinion on PBDEs in Food[4]

Data from the analysis of 19 PBDE congeners in 3,971 food samples were provided to EFSA by 11 European countries covering the period from 2001 to 2009. Based on the composition of the technical PBDE mixtures, occurrence in the environment and in food, the CONTAM Panel considered the following eight PBDE congeners to be of primary interest: BDE-28, -47, -99, -100, -153, -154, -183 and -209, which are relevant for dietary PBDE exposure. The dominant food category was "fish and other seafood", followed by "meat and meat products (including edible offal)" and "animal and vegetable fats and oils", "milk and dairy products" and "eggs and egg products". The data were characterized by a high proportion of non-detects, therefore only those food categories per each individual congener where the sample size was greater than 50 observations (or there were more than 25 positive samples), and when the percentage of non-detects was less than 80 % were considered for the exposure assessment, i.e. "fish and other seafood", "meat and meat products", "animal and vegetable fats and oils", "milk and dairy products", "eggs and egg products", "products for special nutritional use" and "food for infants and small children". The levels of BDE-209 were the highest in almost all the food categories except for "fish and other seafood" and "food for infants and small children", where BDE-47 was the congener with the highest levels.

Most toxicological studies with individual PBDE congeners or technical mixtures thereof have been carried out using different experimental designs with single or repeated dosing during gestation, postnatally or in adulthood. Most of the studies were carried out with a limited number of dose groups, and not according to appropriate guidelines. Main targets for PBDE toxicity were the liver, thyroid hormone homeostasis, and the reproductive and nervous systems. The available genotoxicity studies indicate that PBDEs do not induce gene mutations, but that they can cause DNA damage through the induction of reactive oxygen species.

Based on the information from animal experiments on the disturbance of thyroid hormone homeostasis and neurodevelopment, which can affect behavior, the CONTAM Panel derived benchmark doses (BMDs) and their corresponding lower 95 % confidence limit, the BMDLs, for the most sensitive effects of the various individual PBDE congeners.

Of the eight PBDE congeners considered by the CONTAM Panel to be of primary interest for dietary exposure (see above), relevant toxicity data were only available for BDE-47, -99, -153 and -209. Therefore a risk assessment could only be carried out for these four individual PBDE congeners.

The CONTAM Panel identified effects on neurodevelopment, which affect behaviour, in mice as the critical endpoint and derived the following $BMDL_{10}$ (lower 95 % confidence limit for a benchmark response of 10 %) values: BDE-47: 309 µg/kg b.w.; BDE-99: 12 µg/kg b.w.; BDE-153: 83 µg/kg b.w.; BDE-209: 1,700 µg/kg b.w. Except for BDE-209, the elimination kinetics of PBDEs in rodents and humans differ considerably. Therefore, external dose levels of PBDE congeners associated with toxic effects in animals are not an appropriate dose metric for the extrapolation to humans for the risk assessment. Instead, the internal dose or body burden was used. Body burdens at the $BMDL_{10}$ were derived from studies using a single oral dose, considering an oral absorption in rodents of 75 %. These values were 232, 9 and 62 µg/kg b.w. for BDE-47, -99 and -153,

respectively. These body burden estimates could in principle be used as the basis to establish a human health based guidance value, e.g. a tolerable daily intake. The CONTAM Panel concluded, however, that due to the limitations and uncertainties in the current toxicological database on PBDEs, the derivation of a health based guidance value was not appropriate. Therefore, a margin of exposure (MOE) approach was used for the risk characterization, by comparing the minimum lower bound (LB) [i.e. non-detects were assumed to be zero] and maximum upper bound (UB) [i.e. non-detects were assumed to be at the LOD] dietary intake for the different PBDE congeners with the estimated human intake associated with the body burden at the $BMDL_{10}$. The MOEs for maximum UB dietary intake of different population groups are given in Table 1.

Table 1. Margin of exposure (MOE) for individual PBDE congeners for various population groups based on maximum UB dietary intake.

PBDE congeners	Children (1-3 years od), average consumers	Children (1-3 years old), high consumers	Adults, average consumers	Adults, high consumers	Adults, high fish consumers
BDE-47	27	11	90	38	24
BDE-99	1.4	0.7	6.5	3.9	3
BDE-153	6	3	23	14	11

Usually a MOE of 100 will cover uncertainties and variability in kinetic and dynamic differences between animal species and humans ($4 \times 2.5 = 10$) and within the human population ($3.2 \times 3.2 = 10$). By applying a body burden comparison for PBDEs between animals and humans and focusing on the most sensitive period of brain development, the MOE need only be sufficient to cover intra-species differences in sensitivity, the other differences have been accounted for. Thus an MOE larger than 2.5 indicates that a health concern is unlikely.

With the exception of the MOEs of BDE-99 for young children (1-3 years old), the calculated MOEs for the other PBDE congeners for the various population groups are all larger than 2.5. For BDE-209 the MOEs are even much larger. The CONTAM Panel concluded that for BDE-47, -153 and -209 the MOEs do not indicate a health concern with respect to current dietary exposure to these PBDEs in the EU.

The MOEs for BDE-99 for young children (1-3 years old) with an average and high consumption (maximum UB), are 1.4 and 0.7, respectively. These MOEs are smaller than 2.5, and thus indicate a potential health concern. The CONTAM Panel noted that the use of UB intake estimates, and the application of the longest reported half-life in humans for the calculation of the dietary intake associated with the body burden at the $BMDL_{10}$, would have resulted in an overestimation of the risk for this specific age group. In addition, the presence of one sample in the category "Food for infants and small children" with a particularly high concentration of BDE-99 could have led to overestimation of the exposure. On the other hand it was recognized that the MOEs for the other population groups are not much larger than a value of 2.5. These observations, therefore, support the conclusion for a potential health concern of current dietary exposure to BDE-99.

Acknowledgements:
EFSA wishes to thank the members of the EFSA CONTAM Panel. EFSA and the CONTAM Panel acknowledge all the European countries that provided BFR occurrence data in food and supported the consumption data collection for the Comprehensive European Food Consumption Database.

References:
1. Advice of the CONTAM Panel on a request from the Commission related to relevant chemical compounds in the group of brominated flame retardants for monitoring in feed and food. (2006); *EFSA Journal* 328, 1-4.
2. Guidance of EFSA. Use of the EFSA Comprehensive European Food Consumption Database in exposure assessment. (2011); *EFSA Journal* 9(3): 2097.
3. EFSA Panel on Contaminants in the Food Chain; Scientific Opinion on Polybrominated Biphenyls (PBBs) in Food. (2010); *EFSA Journal* 8(10): 1789.
4. EFSA Panel on Contaminants in the Food Chain; Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. (2011); *EFSA Journal* 9(5): 2156.