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SCIENTIFIC OPINION

Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food[1]

EFSA Panel on Contaminants in the Food Chain (CONTAM)[2, 3]

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ABSTRACT

EFSA was asked by the European Commission to deliver a scientific opinion on polybrominated diphenyl ethers (PBDEs) in food. PBDEs are additive flame retardants which are applied in plastics, textiles, electronic castings and circuitry. PBDEs are ubiquitously present in the environment and likewise in biota and in food and feed. Data from the analysis of 19 PBDE congeners in 3,971 food samples were provided to EFSA by 11 European countries. Eight congeners were considered by the Panel on Contaminants in the Food Chain (CONTAM Panel) to be of primary interest: BDE-28, -47, -99, -100, -153, -154, -183 and -209. The highest dietary exposure is to BDE-47 and -209. Toxicity studies were carried out with technical PBDE mixtures or individual congeners. Main targets were the liver, thyroid hormone homeostasis and the reproductive and nervous system. PBDEs cause DNA damage through the induction of reactive oxygen species. The Panel identified effects on neurodevelopment as the critical endpoint, and derived benchmark doses (BMDs) and their corresponding lower 95 % confidence limit for a benchmark response of 10 %, $BMDL_{10}$s, for a number of PBDE congeners: 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. Due to the limitations and uncertainties in the current database, the Panel concluded that it was inappropriate to use these BMDLs to establish health based guidance values, and instead used a margin of exposure (MOE) approach for the health risk assessment. Since elimination characteristics of PBDE congeners in animals and humans differ considerably, the Panel used the body burden as starting point for the MOE approach. The CONTAM Panel concluded that for BDE-47, -153 and -209 current dietary exposure in the EU does not raise a health concern. For BDE-99 there is a potential health concern with respect to current dietary exposure.

[1] On request from the European Commission, Question No EFSA-Q-2009-00684, adopted on 9 May 2011.

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[4] The term “intra-species” has been replaced by “inter-species” in the Summary and in Chapter 9.1.

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KEY WORDS
Polybrominated diphenyl ethers, PBDE, food, human exposure, body burden, kinetics, metabolism, toxicity, risk assessment, margin of exposure (MOE)

SUMMARY

The European Commission asked the European Food Safety Authority (EFSA) to deliver a scientific opinion on polybrominated diphenyl ethers (PBDEs) in food. PBDEs are a class of brominated hydrocarbons with a basic structure consisting of two phenyl rings linked by an oxygen atom. There are 209 possible compounds, commonly referred to as PBDE congeners, which differ in the number and position of the bromine atoms in the two phenyl rings. Three commercial technical mixtures of PBDEs, PentaBDE, OctaBDE and DecaBDE, have been marketed under different trade names. They are composed of a mixture of congeners, and named according to their average bromine content. PBDEs constitute an important and widely used group of additive flame retardants generally used at concentrations between 5 and 30 % by weight in many different materials, e.g. plastics, textiles, electronic casings and circuitry. As they are mixed into polymers and not chemically bound to the plastic or textiles, they might separate or leach from the products into the environment. PBDEs have been in use since the early 1970s and they were demonstrated to be environmental contaminants already several years after their introduction. International agreements on regulation and use of some PBDEs have been introduced since 2004.

The chemical stability of the PBDE congeners varies with the individual structure. In general PBDE congeners with up to three bromine substituents and those with nine or ten bromine substituents are more sensitive to abiotic transformations. PBDE congeners with four to eight bromine substituents show the highest stability. PBDE congeners are particularly susceptible to photolysis, reductive debromination and radical reactions whereas they are less susceptible to oxidation and hydrolysis. In general, PBDE congeners are persistent and bioaccumulative with the exception of BDE-209 bioaccumulative properties of which seem to be species dependent. BDE-209 undergoes debromination reactions both in the abiotic environment and in biota, leading to formation of PBDE congeners containing seven to nine bromine atoms.

Based on the composition of the technical PBDE mixtures, occurrence in the environment and in food, the Panel on Contaminants in the Food Chain (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.

Following an advice of the CONTAM Panel, a monitoring program was carried out starting in 2006 and results obtained from the analysis of 19 PBDE congeners on 3,971 food samples were provided to EFSA by 11 European countries, covering the period from 2001 to 2009. The dominant food category is “Fish and other seafood (including amphibians, reptiles, snails and insects)”, 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”. Less than 80 samples were reported for the remaining food categories. The data were characterised 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 (“Fish and other seafood (including amphibians, reptiles, snails and insects)”, “Meat and meat products”, “Animal and vegetable fats and oils”, “Milk and dairy products”, “Eggs and egg products”, “Products for special nutritional use”,”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 (including amphibians, reptiles, snails and insects)” and “Food for infants and small children”, where BDE-47 was the congener with the highest levels.

For the food category "Eggs and egg products" the concentration (mean upper bound (UB)) of the PBDE congeners ranges from 0.07 ng/g fat for BDE-183 to 3.98 ng/g fat for BDE-209. For "Milk and dairy products" the highest UB mean concentration was measured for BDE-209 (1.69 ng/g fat), while the lowest level was measured for BDE-28 (0.06 for ng/g fat). Within the food category "Meat and meat products (including edible offal)", the mean UB concentration of the PBDE congeners ranges from 0.08 ng/g fat for BDE-183 to 2.83 ng/g fat for BDE-209. For "Animal and vegetable fats and oils", the mean UB concentration measured for the PBDE congeners varies from 0.12 to 1.50 ng/g fat. The highest frequency of analytical results was reported for the food category "Fish and other seafood (including amphibians, reptiles, snails and insects)". The highest mean lower bound (LB) and UB levels were reported for BDE-47 (1.30 and 1.32 ng/g wet weight (w.w.), respectively) followed by BDE-100 (0.33 and 0.36 ng/g w.w., respectively). For BDE-209, the corresponding mean LB and UB levels were 0.04 and 0.40 ng/g w.w., respectively. In a specific study on the sub-category of "Fish meat", the results indicate a relationship between the PBDEs levels and the fat content of the different fish. In the case of "Products for special nutritional use", the highest UB mean values were measured for BDE-47 (1.79 ng/g w.w.) and BDE-209 (2.73 ng/g w.w.). The levels of BDE-47 and -209 in "Food for infants and small children" are the highest among the different congeners analysed with UB means of 0.21 and 0.13 ng/g w.w., respectively.

The highest dietary exposure is due to BDE-47 and -209. The estimated mean chronic dietary exposure for average consumers across the dietary surveys in European countries ranges from 0.29 (minimum LB) to 1.91 ng/kg body weight (b.w.) per day (maximum UB) for BDE-47, and from 0.35 (minimum LB) to 2.82 (maximum UB) ng/kg b.w. per day for BDE-209. In the case of BDE-153 and -154 the minimum LB and maximum UB dietary exposure estimates are 0.03 and 0.42 ng/kg b.w. per day and 0.03 and 0.51 ng/kg b.w. per day, respectively. For high consumers (95^{th} percentiles) the minimum LB and maximum UB dietary exposure estimates of BDE-47 are 1.1 and 4.51 ng/kg b.w. per day, and for BDE-209 0.7 and 4.58 ng/kg b.w. per day, respectively. In the case of BDE-153 and -154 the minimum LB and maximum UB intake for high consumers are estimated as 0.07 and 0.67 ng/kg b.w. per day, and as 0.1 and 0.85 ng/kg b.w. per day, respectively.

For a specific population group consisting of high and frequent consumers of fatty fish meat (≥8 % fat) the mean dietary UB intake of BDE-47 (maximum UB across European surveys) is 7.27 ng/kg b.w. per day, followed by BDE-100 (2.77 ng/kg b.w. per day) and BDE-99 (1.40 ng/kg b.w. per day).

Supplements, such as fish oil, e.g. cod liver oil, are another source of PBDE exposure. Assuming a maximum daily intake of 15 ml of oil, the highest estimates of the total average daily exposure to individual PBDE congeners can reach up to 2.53 and 4.27 ng/kg b.w. per day, respectively for BDE-47 and -209 (maximum UB across European surveys).

As contamination of food samples of plant origin is generally lower than that of food samples of animal origin, it can be assumed that the dietary exposure to PBDEs for vegetarians is lower than that for people consuming a mixed diet.

The average concentrations of the predominant PBDE congeners in human milk show a comparable mean contamination across various European countries. BDE-47 was generally the predominant congener with mean concentrations across countries of 0.14-3.0 ng/g fat. The average concentrations across European countries for BDE-99 and BDE-153 were found to be <0.03-1.1 ng/g fat and 0.10-2.4 ng/g fat, respectively. However, the individual contamination may differ considerably as indicated by the wide concentration ranges for several PBDEs from various countries. For BDE-209 mean concentrations between 0.21 and 2.9 ng/g fat were reported for seven European countries.

For breast-fed infants with average human milk consumption the mean daily exposure of BDE-47, -99 and -153 across countries ranges from 0.64-13.8, <0.14-5.05 and 0.46-11.0 ng/kg b.w. For BDE-209 the exposure scenario based on average human milk consumption results in a range of 0.96-13.3 ng/kg b.w. per day. For infants with a high human milk consumption the respective mean daily exposure across European countries for BDE-47, -99 and -153 ranges from 0.96-20.6, <0.14-7.57 and 0.69-16.5

ng/kg b.w. For BDE-209 the exposure scenario based on high human milk consumption amounts to 1.44-20.0 ng/kg b.w. per day.

Elimination characteristics of PBDE congeners in animals and humans differ considerably, with elimination half-lives for individual congeners in rats ranging from about 2 to 20 days, whereas for humans maximum values of 926 days (BDE-47) to about 4,530 days (BDE-153) have been reported. This large difference in kinetics hampers the extrapolation of animal data to humans.

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 system.

The activation of CAR (NR1I3/Nr1i3)- or PXR (NR1I2/Nr1i2)-dependent gene expression, leading to disruption of thyroid hormone homeostasis, is considered to be associated with neurodevelopmental and behavioural effects, and might also be responsible for effects on reproduction.

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 (ROS).

There are no long-term toxicity/carcinogenicity studies for individual PBDE congeners or technical mixtures, with the exception of decaBDE. For decaBDE there is some evidence for an increase in liver adenoma in rats and liver adenoma and carcinoma in mice, but in the view of the CONTAM Panel this might be related to a secondary mode of action.

Most epidemiological studies suggested an association between PBDEs with (sub)clinical hyperthyroidism, and with neuropsychological functioning (motor, cognitive and behavioural performance, and mental and physical development in children). The CONTAM Panel noted however, that the observed effects on thyroid hormone levels were not always consistent, and that exposure to other halogenated contaminants could have confounded the outcome of these studies.

Based on the information from animal experiments on the disturbance of thyroid hormone homeostasis and neurodevelopment, which can affect behaviour, 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. Effects on liver were not included in the assessment because the lowest lowest-observed-effect levels (LOELs)/no-observed-effect levels (NOELs) were observed for induction of microsomal liver enzymes (e.g. CYP1A, CYP2B). The Panel was of the opinion that these early indicators, which are not adverse, should not form the basis for the human health risk assessment of PBDEs.

Of the eight PBDE congeners (BDE-28, -47, -99, -100, -153, -154, -183 and -209) considered by the CONTAM Panel to be of primary interest for dietary exposure, 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 end-point 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.

It has been noted that, 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 provides a more appropriate dose metric for a direct

comparison of effects in animals and humans. Based on the calculated $BMDL_{10}$ values for BDE-47, -99 and -153 as derived from studies using a single oral dose, and considering an oral absorption of these congeners in rodents of 75 %, body burdens at the $BMDL_{10}$ of 232, 9 and 62 µg/kg b.w. for BDE-47, -99 and -153, respectively, were derived.

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 data base on PBDEs, the derivation of a health based guidance value was not appropriate. Instead, the Panel used a margin of exposure (MOE) approach for the risk characterization of PBDE congeners, by comparing the minimum LB and maximum UB dietary intake for the different PBDE congeners with the estimated human intake associated with the body burden at the $BMDL_{10}$.

For BDE-47, the maximum UB dietary intake for average and high consumers results in MOEs of 90 and 38, respectively. For high and frequent fish consumers the MOE is 24, when considering the maximum UB dietary intake. For young children (1-3 years) with an average and high consumption, the maximum UB dietary intake results in MOEs of 27 and 11, respectively.

For BDE-99, the maximum UB dietary intake for average and high consumers results in MOEs of 6.5 and 3.9, respectively. For high and frequent fish consumers the MOE is 3, when considering the maximum UB dietary intake. For young children (1-3 years) with an average and high consumption, the maximum UB dietary intake results in MOEs of 1.4 and 0.7, respectively. The CONTAM Panel noted that the presence of one sample in the category "Food for infants and small children" with a high concentration of BDE-99 could have led to overestimation of the exposure of the age group of young children (1-3 years old) to BDE-99.

For BDE-153, the maximum UB dietary intake for average and high consumers results in MOEs of 23 and 14, respectively. For high and frequent fish consumers the MOE is about 11, when considering the maximum UB dietary intake. For young children (1-3 years old) with an average and high consumption, the maximum UB dietary intake results in MOEs of 6 and 3, respectively.

Since for BDE-209 the elimination half-life in animals and humans does not differ markedly the external $BMDL_{10}$ (1,700 µg/kg b.w.) can be used to be compared with the estimated human dietary intake. For the subgroup of the population with the highest maximum UB intake, children of 1-3 years old, the MOE is about 97,000.

Usually a MOE of 100, covering uncertainties and variability with respect to kinetic and dynamic differences between animal species and humans (factor $4 \times 2.5 = 10$) and within the human population (factor $3.2 \times 3.2 = 10$), is considered sufficient to conclude that there is no health concern. Since the MOE approach is based on a body burden comparison between animals and humans, the potential kinetic differences have been accounted for. Equally, by focussing on the body burden associated with a $BMDL_{10}$ for neurobehavioural effects in mice induced during a relevant period for brain development, and applying this body burden to the entire life span in humans, individual difference in susceptibility has been covered. Therefore, the calculated MOE should be sufficient to cover inter-species differences in sensitivity for the effects observed. This implies that an MOE larger than 2.5 might indicate that there is no health concern.

With the exception of the MOE of BDE-99 for young children (1-3 years), the calculated MOEs for the other PBDE congeners for the other population groups are larger than a value of 2.5. For BDE-209 the MOE is even much larger. The CONTAM Panel concluded that current dietary exposure to BDE-47, -153 and -209 in the EU does not raise a health concern. With respect to BDE-99 the MOEs for young children (1-3 years old) are smaller than a value of 2.5. 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. On the other hand it was recognised that the MOEs for the other

population groups are not much larger than 2.5. Therefore the CONTAM Panel concluded that there is a potential health concern with respect to current dietary exposure to BDE-99.

For breast-fed infants with average human milk consumption the highest reported values of the estimated mean daily exposure of BDE-47, -99, -153 and -209 across European countries are about 13.8, 5.1, 11.0 and 13.3 ng/kg b.w., respectively. For infants with high human milk consumption the values are respectively 20.6, 7.6, 16.5 and 20.0 ng/kg b.w. For BDE-47, -99 and -153 the MOE with the intake associated with the $BMDL_{10}$ is 12, 0.8 and 2.5 for infants with average human milk consumption. For infants with high human milk consumption, the MOEs are 8, 0.6 and 1.45, respectively. For BDE-209, the MOE is about two orders of magnitude. The CONTAM Panel concluded that the intake of BDE-47 and -209 by breast-fed infants does not constitute a health risk. For BDE-99 and -153, the MOE is equal or smaller than a factor of 2.5 and thus exposure of breast-fed infants might pose a potential health concern. The CONTAM Panel noted, however, that the highest mean exposure estimates across European countries were used for the MOE calculation and that the lowest estimated mean values for average and high consumption of human milk for BDE-99 and -153 are respectively about 40 and 25 times lower. In addition, the CONTAM Panel noted that it takes 3-4 half-lives to reach steady state, i.e. 10 or more years for BDE-99 and -153 in humans. Hence, the MOEs for these PBDEs calculated by the CONTAM Panel for breast-fed infants based on the body burden would be an overestimation of the risk. Therefore, the CONTAM Panel concluded that MOEs for BDE-99 and -153 in human milk are unlikely to raise health concern to breast-fed infants.

Since human half-lives of PBDEs have not been directly measured, but estimated based on assumption of steady state intake and concentration in humans, the CONTAM Panel also considered information on biomarkers of exposure to assess the possible health risk of exposure to PBDE congeners. The CONTAM Panel identified information on PBDE concentrations in adipose tissue as being most relevant, because they best reflect long-term exposure to PBDE congeners. Average concentrations in adipose tissue are therefore converted into body burden concentrations assuming a fat content of 25 % for the human female adult body, and these body burdens are then compared with the body burden at the $BMDL_{10}$. For BDE-47, -99 and -153 similar margins are found as in the MOE approach, supporting the conclusions on the health risk for these PBDE congeners.

PBDEs in house dust and cars, particularly BDE-209, can be an important additional source of exposure for young children, and is estimated to be in the range of 0.5-80 ng/kg b.w. The CONTAM Panel noted that exposure from dust is far below the $BMDL_{10}$ for BDE-209 of 1.7 mg/kg b.w. per day, and therefore of no health concern.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Brominated flame retardants (BFRs) are anthropogenic chemicals that are added to a wide variety of consumer/commercial products in order to improve their fire resistance. There are 5 major classes of BFRs: brominated bisphenols, diphenyl ethers, cyclododecanes, phenols and phthalic acid derivatives.

Concern has been raised because of the occurrence of several chemical compounds from the group of BFRs in the environment, including feed and food, and in human biota. This has led to bans on the production and use of certain formulations of polybrominated diphenyl ethers (PBDEs).

EFSA concluded in its advice on a request from the Commission related to relevant chemical compounds in the group of brominated flame retardants for monitoring in feed and food of 24 February 2004 that the available occurrence data on brominated flame retardants in feed and food did not allow a comprehensive assessment of contamination in all feeds and foods and identified the following compounds as the most important ones to be monitored based on the analytical feasibility to measure the chemical compounds routinely in accredited laboratories, the production volumes, the occurrence of the chemical compounds in food and feed, their persistence in the environment and their toxicity:

- polybrominated diphenyl ethers (PBDEs): BDE congeners #28, 47, 99, 100, 153, 154, 183 and 209.
- hexabromocyclododecane (HBCD): total amount (isomer specific analysis of a limited number of samples and/or pools in case of significantly elevated levels or increasing trends).
- polybrominated biphenyls (PBBs): BB congener #153.

Optionally, the following brominated flame retardants were recommended to be monitored:

- TBBP-A and other phenols
- decabromodiphenyl ethane
- hexabromobenzene
- bis(2,4,6-tribromophenoxy)ethane

Subsequently EU-wide monitoring of these compounds was organised as of October 2006. Monitoring results will be made available to EFSA.

In order to assess the need for regulatory measures as regards BFR in food, EFSA is requested to assess the risks related to the presence of BFR in food.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Art 29 (1) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority for a scientific opinion on the risks to human health related to the presence of polybrominated diphenyl ethers (PBDEs) in food.

In particular, the opinion should

- evaluate the toxicity of the PBDEs for humans considering all relevant toxicological information available and identify the PBDEs congeners of toxicological relevance with particular reference to the congeners occurring in food;

- carry out an exposure assessment on the basis of the occurrence data obtained in the monitoring exercise and other occurrence data that may be available;

- consider the exposure situation for specific groups of the population (e.g. infants and children, people following specific diets, etc.) and indicate the relative importance from other non-dietary sources;

- take into account, if available, biomonitoring data when assessing the exposure and compare the results with the calculated exposure;

- explore whether individual compounds can be used as markers for dietary exposure to this specific groups of BFRs;

- Identify potential data gaps for this specific group of BFRs.

ASSESSMENT

1. Introduction

1.1. Introduction

Flame retardants include a broad and diverse group of compounds used to prevent fires or at least to slow down the development of a fire. There are three main categories of chemical flame retardants: halogenated hydrocarbons, organophosphorus compounds and inorganic products often based on metallic hydroxides (Vos et al., 2003; WHO, 1997). Within the halogenated hydrocarbons, the group of the Brominated Flame Retardants (BFRs) consist of different chemicals with a variety of physicochemical properties and uses. The main BFRs are the polybrominated (i) neutral aromatic, (ii) neutral cycloaliphatic, (iii) phenolic (including neutral derivatives), (iv) aromatic carboxylic acid esters and (v) trisalkyl phosphate compounds. The major individual groups of BFRs within these five classes are tetrabromobisphenol A (TBBPA), polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDDs[5]), decabromodiphenyl ethane (DBDPE), bis(2,4,6-tribromophenoxy)ethane (BTBPE) and 2,4,6-tribromophenol (WHO, 1997; Örn and Bergman, 2004; Harju et al., 2009). A set of 10-20 other BFRs makes up a group of miscellaneous brominated compounds. The polybrominated biphenyls (PBBs) have been phased out, first low and medium brominated biphenyls, most recently the DecaBB that was withdrawn from commercial production in the early 2000s (ATSDR, 2004).

The present opinion focuses on PBDEs. The three commercial technical mixtures of PBDEs are: PentaBDE, OctaBDE and DecaBDE. These have been produced in the past in large volumes (up to about 80,000 tonnes annually) and have been widely used in polymers and textiles, construction materials, furniture and electric and electronic equipment. PBDEs are additive flame retardants and as such they are not chemically bound to the polymers; and they can therefore leach into the environment (Talsness, 2008). A series of legislative and voluntary actions must have led to major changes in the production volumes of PBDE products, but no up-to-date data are available.

Based on the composition of the technical PBDE mixtures, occurrence in the environment and available data on toxicity, the Panel on Contaminants in the Food Chain (CONTAM Panel) considered the following eight PBDE congeners to be of primary interest: BDE-28, -47, -99, -100, -153, -154, -183 and -209, which can be used as markers for dietary PBDE exposure.

1.2. Previous risk assessments

The European Chemicals Bureau (ECB) published three risk assessment reports on the risks to the environment and human health from exposure to pentabromodiphenyl ether (PentaBDE) (ECB, 2001), octabromodiphenyl ether (OctaBDE) (ECB, 2003) and decabromodiphenyl ether (DecaBDE) (ECB, 2002; 2004).

The only information on the effects of repeated oral exposure (up to 90 days) to PentaBDE comes from studies in rats and mice following administration of commercial mixtures. In the risk assessment report on PentaBDE a no-observed-adverse-effect level (NOAEL) of 0.45 mg/kg per day was identified from a 30-day study in rats given technical PentaBDE, taking into account a maximum oral absorption of 90 % (ECB, 2001). Because of the short duration of this study and given the

[5] HBCDDs is used as the abbreviation for hexabromocyclododecanes (CAS No 3194-55-6) instead of HBCD in this document, to avoid misunderstandings. HBCD is occasionally used as an abbreviation of hexabromocyclodecane (CAS No 25495-98-1).

bioaccumulative nature of PentaBDE it was questioned whether this NOAEL would be appropriate for assessing longer term exposures. No data were available on reproductive toxicity, but studies with pregnant rats did not indicate developmental effects. Results of *in vitro* studies indicated that technical PentaBDE is not genotoxic. The report noted that the direct exposure of consumers to PentaBDE is negligible, since in the European Union (EU) it is used only in polyurethane foam enclosed in products. Regarding indirect exposure via the environment, the report concluded that although the risk to human health is likely to be minimal, further information should be obtained on the effects of long-term exposure. For breast-fed infants, a margin of safety (MOS) of about 47,000 was calculated compared with the NOAEL of 0.45 mg/kg per day. Although this value was considered rather large, a number of uncertainties, such as the limited toxicological database and the proportion of PentaBDE present in human milk, precluded the reassurance of little or no risk for this particular group. The report indicated that a similar MOS could be expected for infants fed cow's milk. It was concluded that there was a need for further information and/or testing, such as toxicokinetics studies and toxicological studies on liver toxicity in young and adult animals.

The report on OctaBDE (ECB, 2003) concluded that the repeated oral dose studies (13 weeks) in rats identified the liver as the target organ, with an increase in weight and cellular microscopic changes at the lowest dose level (about 7 mg/kg body weight (b.w.)). Effects on the thyroid gland were also observed suggesting an increase in thyroid gland stimulation. No studies on chronic toxicity or carcinogenicity were identified. No specific studies on fertility were identified, but the available repeated dose studies did not provide evidence of effects on reproductive organs. From the neurotoxicity studies no firm conclusion could be drawn. A NOAEL of 2 mg/kg per day was derived from a developmental toxicity study in rabbits treated orally. OctaBDE was considered to be not genotoxic on the basis of negative results obtained in various *Salmonella* tests and cytogenetic assays. The estimated regional human intake via the environment was about 0.42 µg/kg b.w. per day. Comparison with the NOAEL of 2 mg/kg b.w. derived from the developmental studies resulted in a MOS of about 4,700. As there were no reliable data on the levels of OctaBDE in human milk and in cows' milk, the risk characterization for infants could not be carried out. The report concluded that further information on the effects of long-term exposure and data on the excretion of OctaBDE into human and cows' milk were needed.

The report on DecaBDE (ECB, 2002) concluded that repeated dose studies by the oral route indicated low systemic toxicity in mice or rats, especially when the degree of purity was high. A NOAEL of 1,120 mg/kg b.w. per day was identified for neoplastic effects in a 2-year toxicity/carcinogenicity study in rats. DecaBDE was considered not to be mutagenic, on the basis of negative results obtained in *Salmonella* tests and the absence of cytogenetic effects neither *in vitro* nor *in vivo*. The maximum human intake from environmental sources was estimated to be 8-12 µg/kg b.w. per day, dietary intake accounted for more than 95 % of the total intake. Considering the maximum intake of 12 µg/kg b.w. per day, a MOS of about 93,000 was derived and compared with the above mentioned NOAEL. This MOS was considered to represent no health concern. The update of the report was published in 2004 (ECB, 2004), it addressed only the risk to the environment and not to human health.

In 2004, the Committee on Toxicity (COT) issued a statement on BFRs in fish from the Skerne-Tees river system (COT, 2004). For the toxicological profile, the Committee based its assessment on the information provided in ECB risk assessment and on studies published subsequently. The statement concluded that the uncertainties and deficiencies in the toxicological PBDEs databases prevented the establishment of a tolerable daily intake (TDI), and a margin of exposure (MOE) approach was then used in the risk assessment. A NOAEL of 0.45 mg/kg b.w. per day for effects of PentaBDE on the liver in rats was considered, and a target MOE of 1,000 above which risks to health would not be expected was suggested, taking into consideration uncertainty factors (UFs) to allow for inter- and intraspecies differences in toxicokinetics and toxicodynamics (100) and limitations in the database such as study duration and gaps in the data (up to 10). The MOE for intake of PBDEs from the consumption of one portion of fish from the Skerne-Tees river system per week would be about

10,000. The conclusion of the assessment was that the estimated intakes were unlikely to pose a health risk.

In 2004, the Agency for Toxic Substances and Disease Registry (ATSDR) issued a toxicological profile for PBBs and PBDEs (ATSDR, 2004). For PentaBDE, a minimal risk level of 0.03 mg/kg b.w. per day for acute oral exposure was derived from a NOAEL of 1 mg/kg b.w. per day for reduced serum levels of thyroxine (T4) hormone in foetal rats exposed to a commercial PentaBDE mixture (Zhou et al., 2002). For intermediate-duration oral exposure, a minimal risk level of 0.007 mg/kg b.w. per day was derived from a minimal lowest-observed-adverse-effect level (LOAEL) of 2 mg/kg b.w. per day for effects on the liver in rats exposed to a technical PentaBDE in a 90-day study (WIL Research Laboratories, 1984, in ATSDR, 2004). A chronic-duration oral minimal risk level was not derived for lower brominated diphenyl ethers because of insufficient data. For DecaBDE, the ATSDR derived a minimal risk level of 10 mg/kg b.w. per day for intermediate-duration oral exposure, from a NOAEL of 1,000 mg/kg b.w. per day for developmental toxicity in rats exposed to technical DecaBDE for 19 days during gestation (Hardy et al., 2002). No acute- or chronic-duration oral minimal risk levels were derived for DecaBDE because of insufficient data.

In 2004, Health Canada issued a screening health assessment on PBDEs (tetra-, penta-, hexa-, hepta-, octa-, nona- and decaBDE congeners) (Health Canada, 2006). Most of the data identified as relevant to the evaluation related to commercial mixtures, whereas less information was available on individual congeners. The critical effects were identified to occur on the liver and on neurobehavioral development. A conservative lowest-observed-effect level (LOEL) of 0.8 mg/kg b.w. for PentaBDE was considered, based on neurodevelopmental effects in mice exposed neonatallly (Eriksson et al., 1998; 2001). It was considered that this LOEL would also be protective for the small increase in the incidence of liver tumours observed in mice and the increase in neoplastic nodules observed in rats chronically administered higher doses of DecaBDE, in view of the lack of evidence for the genotoxicity of PBDEs. The critical effect level was compared with the intake of total PBDEs (tetra- to decaBDEs congeners) of breast-fed infants of 2.6 µg/kg b.w. per day (upper-bound estimate), who were considered to be the group with the highest exposure. This resulted in a MOE of approximately 300. The report acknowledged that the health assessment was conservative and recognized the need for a thorough evaluation of the available data and more meaningful information on human exposure to PBDEs.

PBDEs were evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2005 (FAO/WHO, 2006). That Committee noted that it was not possible to establish a common mechanism of action that would allow the use of a single congener as a surrogate for total exposure to PBDEs. Furthermore, a no-observed-effect level (NOEL) could not be defined due to the lack of a systematic toxicity database on the main PBDE congeners in food. Many of the adverse effects reported were suggested to be confounded by the presence of impurities that caused adverse effects, e.g. activation of the aryl hydrocarbon receptor (AhR). The committee considered that "the more toxic PBDE congeners" would be unlikely to have adverse effects when consumed at doses below 100 µg/kg b.w. per day. The MOE appeared to be large in relation to the estimated dietary intake of approximately 0.004 µg/kg b.w. per day for the adult population and up to 0.1 µg/kg b.w. per day for breast-fed infants. The Committee concluded that, although the data on toxicity and the intake estimates were not adequate, dietary intake of PBDEs was unlikely to be a significant health concern.

In 2006, the French agency for food, environmental and occupational health safety (ANSES, former AFSSA) evaluated the risk related to the presence of BFRs in food (AFSSA, 2006). Owing to the lack of information on the individual congeners, the assessment was based on the technical PBDE mixtures. The exposure of the French population to PBDEs was estimated to be 2.5-7.2 ng/kg b.w. per day for infants and 1.0-2.2 ng/kg b.w. per day for adults. For high fish consumers, the estimated dietary exposure was 2.5-3.7 ng/kg b.w. per day. The food groups that contributed most to the PBDE intake were fish and sea food products, followed by milk and dairy products and meat and meat products. The report concluded that the available toxicokinetic and toxicological studies were insufficient to derive a toxicological reference level.

In 2006, the COT issued a statement on organic and brominated contaminants in shellfish, and in farmed and wild fish (COT, 2006). From the 17 PBDE congeners analysed, BDE-47, -209, -100 and -49 were the most abundant ones. Dogfish contained the higest concentration of the sum of the measured PBDEs (8.71 µg/kg fresh weight) followed by eel (5.4 µg/kg fresh weight). The estimated upper bound intake from the diet (taking into account both the non-fish and the fish part of the diet) was 8.5 ng/kg b.w. per day. When compared with the target MOE of 1,000 (COT, 2004), the MOE for this intake level was approximately 53,000. In relation to the reference dose proposed by JECFA at which adverse effects were not expected (100 µg/kg b.w. per day) (FAO/WHO, 2006), the Committee concluded that consumption of one weekly portion of dogfish would result in a MOE of approximately 11,000.

In 2007, the Food Standards Australia New Zealand (FSANZ, 2007) carried out a study of PBDE-concentrations in foods in Australia and performed a dietary exposure assessment for different groups of the population as well as a risk characterization. The majority of the samples analysed were reported to be non detects (69 %). The mean dietary intake estimated for adults was 49 and 54 ng/kg b.w. per day (upper bound estimates), for male and females, respectively. An independent review of available toxicological data concurred with the threshold dose of 100 µg/kg b.w. per day proposed by JEFCA (FAO/WHO, 2006) below which adverse effect would be unlikely to occur. This dose was used as a reference point for determining the magnitude of the margin of exposure (MOE) for PBDEs. The MOEs for the majority of the population was at or above 1,000 and it was concluded that the intakes of PBDE through diet in Australia were unlikely to be a significant health concern.

In 2007, the Swedish National Food Administration (NFA) conducted a risk assessment of persistent chlorinated and brominated environmental pollutants in food (NFA, 2007). The estimated mean dietary intake of PBDEs in Sweden was reported to be about 0.7 ng/kg b.w. per day. Critical effects were found to occur during early development, consisting of effects on neuromotor function, hormone levels and on the morphology and function of reproductive organs. For BDE-99, a LOAEL for male reproduction and motor activity of 0.06 mg/kg was derived from a study in rats (Kuriyama et al., 2005), while for neurotoxicity a LOAEL of 0.6-0.8 mg/kg was derived (Eriksson et al., 2001; Branchi et al., 2002). For BDE-47, a LOAEL for neurotoxicity of 0.7 mg/kg was derived (Kuriyama et al., 2004a). The report concluded that when the estimated human dietary intake was compared with the lowest intake that had negative health effects on animals, the margin was approximately 100,000 for PBDEs.

In 2008, the United States Environmental Protection Agency (US-EPA) issued health assessments of four individual PBDE congeners, BDE-47, -153, -99 and -209, within its Integrated Risk Information System (IRIS) program. These four congeners were identified as those most commonly found in the environment and in human biological media, and for which toxicological studies suitable for dose-response assessments were available.

For BDE-47, in the absence of consensus on the level that is considered to be adverse, US-EPA selected a benchmark response (BMR) as a change in the parameter observed equal to one standard deviation (1 SD) of the mean of the control group ($BMDL_{1SD}$). A reference dose (RfD) of 0.1 µg/kg b.w. per day was derived from a benchmark dose lower confidence limit ($BMDL_{1SD}$) of 0.35 mg/kg b.w. based on changes in habituation ratios in adult mice (Eriksson et al., 2001), with application of a total UF of 3,000 to account for interspecies variability, human variability, extrapolation from a single dose (on postnatal day (PND) 10) to chronic exposure and for database deficiencies. It was noted that there was inadequate information to assess the carcinogenic potential of BDE-47 (US-EPA/IRIS, 2008a).

For BDE-99, a RfD of 0.1 µg/kg b.w. per day was derived from a $BMDL_{1SD}$ of 0.29 mg/kg b.w. per day, based on the effects on spontaneous motor behaviour in mice (Viberg et al., 2004a), with application of a total UF of 3,000 to account for interspecies variability, human variability, extrapolation from a single dose (on PND10) to chronic exposure and for database deficiencies. There was inadequate information to assess the carcinogenic potential of BDE-99 (US-EPA/IRIS, 2008b).

For BDE-153, neurobehavioral developmental toxicity was identified as the critical endpoint and a RfD of 0.2 µg/kg b.w. per day was derived from a NOAEL of 0.45 mg/kg b.w. (Viberg et al., 2003a) with application of a total UF of 3,000 to account for interspecies variability, human variability, extrapolation from a single dose (on PND10) to lifetime exposure and for database deficiencies. It was noted that there was inadequate information to assess the carcinogenic potential of BDE-153 (US-EPA/IRIS, 2008c).

For BDE-209**,** a RfD of 7 µg/kg b.w. per day was derived from a NOAEL of 2.22 mg/kg b.w. for neurobehavioral changes observed in mice (Viberg et al., 2003a), with application of an UF of 300 to account for the interspecies uncertainty, intraspecies variation and extrapolation of a single dose (on PND10) to a lifetime exposure. Based on two chronic rodent studies, it was considered that there was "suggestive evidence of carcinogenic potential" of BDE-209. The doses that resulted in excess cancer risks of 10^{-4}, 10^{-5} and 10^{-6} were approximately 100, 10 and 1 µg/kg b.w. per day, respectively (US-EPA/IRIS, 2008d).

1.3. Chemical characteristics

PBDEs are a class of brominated aromatic compounds with a basic structure consisting of two phenyl rings linked by an ether bond. There are 209 possible compounds, referred to as PBDE congeners, which differ in the number and position of the bromine atoms in the two phenyl rings (Figure 1). PBDEs form the same number of congeners and the substitution patterns are identical to the congeners of polychlorinated biphenyls (PCBs). Hence, the PBDEs share the same congener numbering system as proposed for PCBs (Ballschmiter et al., 1993). PBDEs exist in twist to skew conformations (Teclechiel, 2008) but not in planar conformations (Figure 2). The more bromine substituents there are in the PBDE congener, the more skewed is the conformation.

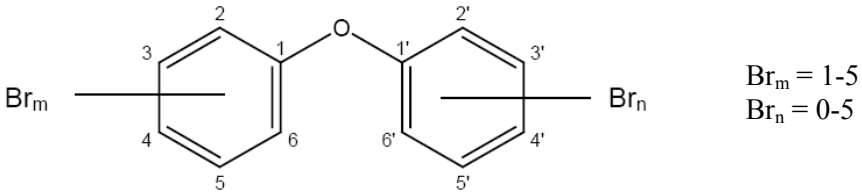

Figure 1: General structure of the PBDE congeners.

Figure 2: Theoretical conformations of diphenyl ethers (planar and butterfly) and the actual conformations of PBDEs, skew and twist.

The molecular masses of PBDE congeners range from 249 g/mole for monoBDEs to 959 g/mole for BDE-209 (see Table 1 for number of isomers within each degree of bromination and for molecular masses (g/mole)). Table 2 shows the octanol-water partitioning coefficients (log K_{ow}) (measured and modelled by Chemical Abstract) for the congeners in the homologue series. The high log K_{ow}

constants imply poor water solubilities. PBDEs are non-ionizable compounds with low volatility (Table 2). Ultraviolet (UV) absorption spectra of PBDE congeners were published by Eriksson et al. (2004).

The chemical stability of the PBDE congeners vary with the individual structure, but in general, PBDE congeners with a low number of bromine substituents and those with nine and ten bromine substituents are the most vulnerable, while PBDE congeners with four to eight bromine substituents are the ones showing the highest stability. PBDE congeners may undergo photolysis (Eriksson et al., 2004; Christiansson et al., 2009) and reductive debromination (Eriksson et al., 2004; Granelli et al., 2010) but are less sensitive to nucleophilic aromatic substitution (NAS) and oxidations (Rahm et al., 2005; Moreira Bastos et al., 2008). However, BDE-209 undergoes NAS. The PBDE congener sensitivity to metabolic transformations is addressed in Chapter 4.

Based on the physicochemical and reactivity properties, PBDEs are often generalized as persistent even though individual PBDE congeners show differences in degrees of persistency, due to their structures.

Table 1: Homologues, number of isomers for each homologue group and nomenclature for PBDEs.

Homologues	Chemical formula (Molecular mass)	Number of isomeric congeners	Congeners
monoBDEs	$C_{12}H_9Br_1O$ (MW: 249.1)	3	BDE-1 to BDE-3
diBDEs	$C_{12}H_8Br_2O$ (MW: 328.0)	12	BDE-4 to BDE-15
triBDEs	$C_{12}H_7Br_3O$ (MW: 406.9)	24	BDE-16 to BDE-39
tetraBDEs	$C_{12}H_6Br_4O$ (MW: 485.8)	42	BDE-40 to BDE-81
pentaBDEs	$C_{12}H_5Br_5O$ (MW: 564.7)	46	BDE-82 to BDE-127
hexaBDEs	$C_{12}H_4Br_6O$ (MW: 643.6)	42	BDE-128 to BDE-169
heptaBDEs	$C_{12}H_3Br_7O$ (MW: 722.5)	24	BDE-170 to BDE-193
octaBDEs	$C_{12}H_2Br_8O$ (MW: 801.4)	12	BDE-194 to BDE-205
nonaBDEs	$C_{12}H_1Br_9O$ (MW: 880.3)	3	BDE-206 to BDE-208
decaBDE	$C_{12}Br_{10}O$ (MW: 959.2)	1	BDE-209

Table 2: Some physicochemical properties of the PBDE congeners considered.

PBDE congener	Homologue series	Log K_{ow}		Volatility
		Observed[(a)]	Predicted[(b)(c)]	Vapour pressure
BDE-28	triBDE	5.94±0.15	5.96/6.7	2.32×10^{-5}
BDE-47	tetraBDE	6.81±0.08	6.76/7.4	4.19×10^{-6}
BDE-99	pentaBDE	7.32±0.14	7.27/8.2	2.46×10^{-7}
BDE-100	pentaBDE	7.24±0.16	7.49/8.0	9.57×10^{-7}
BDE-153	hexaBDE	7.90±0.14	7.58/9.0	1.35×10^{-8}
BDE-154	hexaBDE	7.82±0.16	7.89/8.8	5.64×10^{-8}
BDE-183	heptaBDE	8.27±0.26	8.35/9.5	2.69×10^{-9}
BDE-209	decaBDE	nr	12.11[(d)]/9.4	1.64×10^{-12}

nr: not reported; log K_{ow}: octanol-water partitioning coefficients
(a): Experimental data for log K_{ow} for the PBDEs indicated using slow-stir method (Braekvelt et al., 2003).
(b): Predicted log K_{ow} for PBDEs homologues (Li et al., 2008).
(c): Calculated using Advanced Chemistry Development (ACD/Labs) Software v9.04 (1994-2010 ACD/Labs).
(d): Result from the EPI estimation program (ECB, 2001).

The three commercial technical mixtures of PBDEs are: PentaBDE, OctaBDE and DecaBDE. They are composed of a mixture of congeners, and are named according to their average bromine content. To avoid confusion, names in capital letters will be used throughout the opinion when referring to the commercial technical mixtures (e.g. PentaBDE), whereas lowercase letters will refer to the homologues itself (e.g. pentaBDEs). The composition of PBDE products have been addressed by several authors (La Guardia et al., 2006) (see Chapter 4).

The present opinion is focused on the eight PBDE congeners shown in Figure 3. Congener, bromine substitution and Chemical Abstracts Service (CAS) numbers are given in Table 3. These eight PBDE congeners are the most abundant compounds present in the three commercial mixtures mentioned above, i.e. PentaBDE, OctaBDE and DecaBDE.

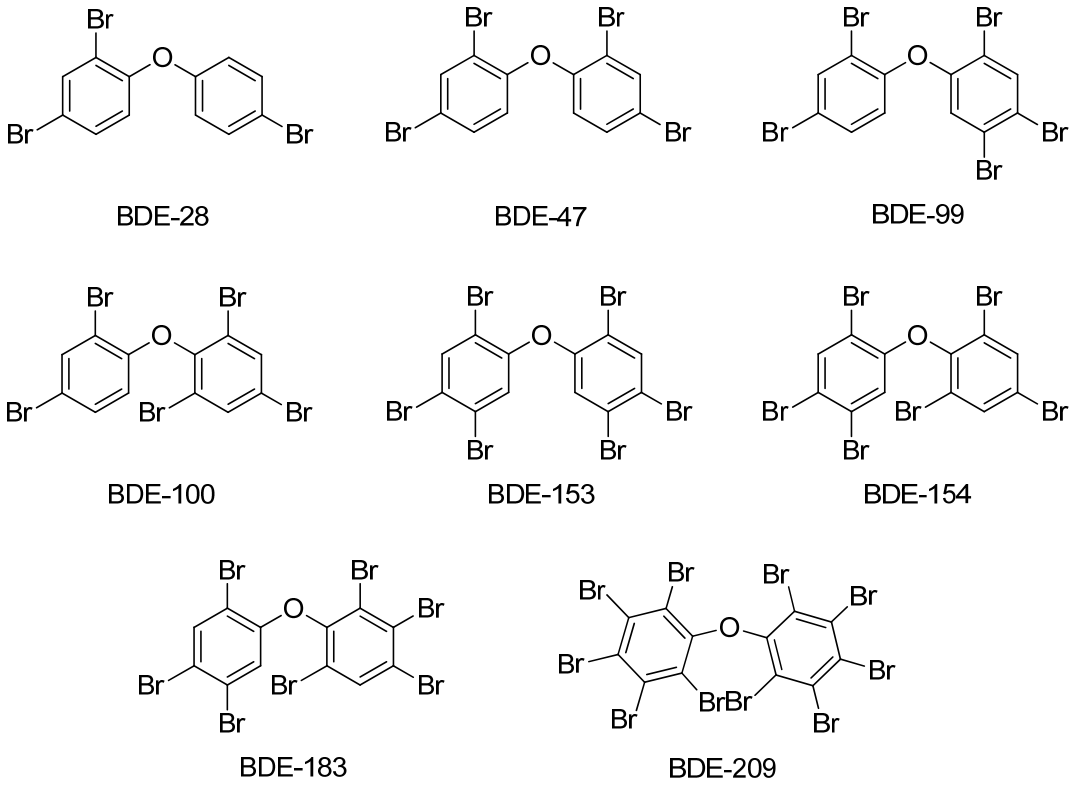

Figure 3: Structure of the eight PBDE congeners considered.

Table 3: Congener, bromine substitution and CAS number of the eight PBDE congeners considered.

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

2. Legislation

In order to protect public health, Article 2 of Council Regulation (EEC) No 315/93[6] of 8 February 1993 laying down Community procedures for contaminants in food stipulates that, where necessary, maximum tolerances for specific contaminants shall be established. While a number of maximum tolerances are currently laid down in Commission Regulation (EC) No. 1881/2006[7] of 19 December 2006 setting maximum levels (MLs) for certain contaminants in foodstuffs, e.g. dioxins, dioxin-like PCBs and benzo[*a*]pyrene, PBDE are neither regulated so far under this Regulation nor under another EU regulation.

Commission Directive 2002/32 regulates undesirable substances in animal feed. While maximum contents are set for a number of inorganic and organic contaminants in various feed materials, PBDEs are not regulated so far by the European Commission under this Directive.

In 2001 and 2002, the European Commission adopted Recommendations in the framework of Regulation (EEC) No 793/93 for a risk reduction strategy for PentaBDE[8] and OctaBDE[9] providing for restrictions on marketing and use to control risks to the environment. As a consequence, Directive 2003/11 of the European Parliament and of the Council of 6 February 2003 amending for the 24th time Council Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (pentabromodiphenyl ether, octabromodiphenyl ether)[10] ruled that PentaBDE and OctaBDE may not be placed on the market or used as substances or as constituents of substances or of preparations in concentrations higher than 0.1 % by mass. Moreover, articles may not be placed on the market if they, or flame-retarded parts thereof, contain PentaBDE and OctaBDE in concentrations higher than 0.1 % by mass. With effect from 1 June 2009, Regulation 1907/2006 (REACH) repeals and replaces Directive 76/769/EEC. The conditions of PentaBDE and OctaBDE restrictions are now set in ANNEX XVII to this Regulation.

DecaBDE (1163-19-5) is on the list that the European Chemicals Agency (ECHA) has published of substances that companies need to register under the Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH) Regulation in 2010. The list is based on feedback received from companies and registrations already submitted.

Directive 2002/95/EC[11] of the European Parliament and of the Council of 27 January 2003 on the restriction of the use of certain hazardous substances (RoHS) in electrical and electronic equipment stipulates that Member States shall ensure that, from 1 July 2006, new electrical and electronic equipment put on the market does not contain PBDEs. Specifically exempted from the requirements was the application of DecaBDE in polymeric applications. In January 2006, however, the European Parliament and Denmark launched legal proceedings against the European Commission for the exemption of DecaBDE from the RoHS Directive. On 1 April 2008, the European Court of Justice annulled the Commission Decision on the basis that procedural errors were made when establishing the exemption. As of July 2008, therefore, DecaBDE can no longer be used in electronics and electrical applications as decided by the European Court of Justice.[12]

According to Article 5(1)(a) of Directive 2002/95/EC a maximum concentration value of 0.1 % of PBDEs by weight in homogeneous materials shall be tolerated.

[6] OJ L 37, 13.2.1993, p. 1-3.
[7] OJ L 364, 20.12.2006, p. 5-24.
[8] OJ L 69, 10.3.2001, p. 30.
[9] OJ L 249, 17.9.2002, p. 27.
[10] OJ L 42, 15.2.2003, p. 45.
[11] OJ L 37, 13.2.2003, p. 19-23.
[12] OJ C 116, 9.5.2008, p. 2-3.

Directive 2002/96/EC[13] of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE) stipulates that plastic containing brominated flame retardants has to be removed from any separately collected WEEE and treated separately.

Directive 2000/60/EC[14] of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy classifies pentabromodiphenylether as a priority hazardous substance (to be phased out) and the other brominated diphenylethers as priority substances (to be monitored or reviewed for identification as potentially hazardous substances).

Since 1 July 2006, Norway has a ban on DecaBDE in electrical and electronic equipment. From 1 April 2008 it is forbidden in Norway to manufacture, import, export, sell and use DecaBDE as a substance or in preparations containing 0.1 weight percent or more of this compound. It is also forbidden to manufacture, import, export, and sell products or flame retardant parts of products that contain 0.1 weight percent or more DecaBDE.

PBDEs are regulated in both the global Stockholm Convention and the United Nations Economic Commission for Europe (UNECE) Protocol to the 1979 Convention on Long-Range Transboundary Air Pollution on Persistent Organic Pollutants (LRTAP POPs). More specifically, the regulation covers commercial Penta- and OctaBDE by the inclusion of hexabromodiphenyl ether and heptabromodiphenyl ether as well as, tetrabromodiphenyl ether and pentabromodiphenyl ether in the respective annexes listing substances scheduled for elimination. In both conventions "*Hexabromodiphenyl ether and heptabromodiphenyl ether*" means *2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153, CAS No: 68631-49-2), 2,2',4,4',5,6'-hexabromodiphenyl ether (BDE-154, CAS No: 207122-15-4), 2,2',3,3',4,5',6 heptabromodiphenyl ether (BDE-175, CAS No: 446255-22-7), 2,2',3,4,4',5',6-heptabromodiphenyl ether (BDE-183, CAS No: 207122-16-5) and other hexa- and heptabromodiphenyl ethers present in commercial OctaBDE* and "*Tetrabromodiphenyl ether and pentabromodiphenyl ether"* means *2,2',4,4'-tetrabromodiphenyl ether (BDE-47, CAS No: 40088-47-9) and 2,2',4,4',5-pentabromodiphenyl ether (BDE-99, CAS No: 32534-81-9) and other tetra- and pentabromodiphenyl ethers present in commercial PentaBDE*.

3. Sampling and methods of analysis

3.1. Sampling

There are no specific guidelines for sampling of food samples to be analysed for their PBDE content. Therefore, basic rules for sampling of organic contaminants or pesticides should be followed. Respective requirements are for example laid down in Commission Regulation (EC) No 1883/2006[15] of 19 December 2006 laying down methods of sampling and analysis for the official control of levels of dioxins and dioxin-like PCBs in certain foodstuffs. This Regulation contains inter alia a number of provisions concerning methods of sampling depending on the size of the lot, packaging, transport, storage, sealing and labelling. The primary objective is to obtain a representative and homogeneous laboratory sample with no secondary contamination.

[13] OJ L 37, 13.2.2003, p. 24-39.
[14] OJ L 327, 22.12.2000, p. 1-73.
[15] OJ L 364, 20.12.2006, p. 32-43.

3.2. Methods of analysis

3.2.1. Biological methods

The knowledge on screening tests for PBDEs is quite limited. Recently, magnetic particle Enzyme Linked Immunosorbent Assays (ELISA) were developed for detection of BDE-47 in sample extracts (Ahn et al., 2009; Shelver et al., 2008; Xu et al., 2009). These assays were developed specifically for BDE-47, but some cross-reactivity with other PBDEs was observed. Little or no cross-reactivity was observed for other halogenated contaminants (Ahn et al., 2009; Shelver et al., 2008). Sensitivity (0.02-0.08 ng/mL) was similar to gas chromatogaphy-electron capture negative ionization-mass spectrometry (GC-ECNI-MS) for PBDEs up to BDE-153, but much lower for the higher brominated congeners (Shelver et al., 2008). These assays have been applied to e.g. fish and human milk, and there was a reasonable agreement between the assay and the results of the instrumental analysis (Shelver et al., 2008). Although detection is fairly simple and straightforward, the sample extraction and cleanup was similar to that of the instrumental detection. Therefore, the benefit of this test may be limited compared to the instrumental analysis where congener specific information is obtained for several congeners in one run. Future developments in this area will show the potential of application of these tests for detection of PBDEs in food samples.

Attempts have been made to use AhR-dependent activity to compare the potencies of different PBDE congeners (Behnisch et al., 2003). However, a study by van der Ven et al. (2008a) showed that a purified technical DE-71 mixture (the purified material was analyzed to contain 42 % BDE-47, 34 % BDE-99, 9 % BDE-100, 2 % BDE-153 and 2 % BDE-154) tested reproducibly negative for AhR agonist activity in the Dioxin Responsive-Chemically-Activated LUciferase eXpression (DR-CALUX) assay. The apparent responsiveness of the AhR to some congeners has now been shown to be due most likely to contamination with potent AhR agonists such as polybrominated dibenzofurans (Öberg et al., 2010). Hence, such methods are not appropriate for detection of PBDEs.

3.2.2. Chemical methods

Current analytical methods allow the determination of all 209 PBDE congeners. Although a number of calibration standards are commercially available, normally only a limited number of PBDE congeners are analysed. Most often, the analytical methods cover the BDE congeners -17, -28, -47, -66, -99, -100, -153, -154 and -183. In the past few years the analysis of BDE-209 has gained increased importance. The selection of these congeners is mainly based on their occurrence in environmental, food and human samples.

The analytical method starts with the extraction of the PBDEs from the sample. Several methods for extraction of biological samples have been proposed in the literature (Covaci et al., 2003, 2007; van Leeuwen and de Boer, 2008). For extraction of solid material, the Soxhlet procedure is used in some laboratories. This method is a time-consuming technique that, in addition, requires large quantities of organic solvent. Other techniques include supercritical fluid extraction (SFE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE) and solid-phase extraction (SPE).

Cleanup of the extract is performed to isolate the PBDEs from the co-extracted interfering compounds such as lipids and other contaminants. Co-extracted lipids can be removed in several ways such as gel permeation chromatography (GPC), alumina-oxide chromatography and multilayer silica chromatography (Covaci et al., 2003). The next step is fractionation to isolate the PBDEs from other potentially interfering compounds. This is typically done by silica column fractionation or similar (Covaci et al., 2003).

The injection of PBDEs into the gas chromatography (GC) system is a critical and important part of the chromatographic analysis. Thus, careful selection and optimization of the injection techniques have to be performed in order to reduce the discrimination of the compounds. Splitless is the most

commonly used injection technique for GC separation of PBDEs. Both the programmable temperature vaporization injector (PTV) as well as on-column injectors have been successfully used. Large-volume injections using either PTV in solvent elimination mode or the loop-type interface have also been used (Tollbäck et al., 2003).

GC separation is done on capillary columns with an apolar or slightly polar stationary phase. The column dimensions are typically 25-60 m length, 0.25 mm diameter and 0.1-0.25 µm film thickness (Covaci et al., 2003). The physicochemical properties of BDE-209 put great demands on the analytical method, including sampling, extraction and cleanup, as well as final chromatographic separation. The problems encountered during the analysis of higher brominated diphenyl ether congeners have been reviewed by Kierkegaard et al. (2009). In particular, the degradation of BDE-209 is increased with unfavourable GC conditions such as high temperatures, time spent at elevated temperatures and presence of catalytic sites. Björklund et al. (2004) also demonstrated degradation and discrimination of BDE-209 to heptaBDEs associated with different injection techniques (and parameters) and GC column characteristics, such as the column length and the stationary film thickness. For the best yield of BDE-209, these parameters should be kept as low as possible. As a consequence, the GC separation of BDE-209 is generally performed on a short column (10-15 m) (Covaci et al., 2003; de Boer and Wells, 2006).

Due to the relatively low levels of PBDEs in food, their determination requires high sensitivity combined with high selectivity. The two approaches that best fulfil these requirements are GC-electron capture negative ionization-mass spectrometry (GC-ECNI-MS) and GC-high resolution mass spectrometry (GC-HRMS) (Covaci et al., 2003; de Boer and Wells, 2006; van Leeuwen and de Boer, 2008). Brominated substances are often analysed under chemical ionization conditions, monitoring the negative ions formed by electron capture reactions (ECNI) (Buser et al., 1985). The predominant ions formed from organobromine substances under such conditions are the bromine isotopes *m*/*z* 79 and 81. This technique allows similar limits of detection (LOD) and is less costly than other alternatives, such as GC-HRMS. However, the latter technique has a higher selectivity than ECNI-MS detection of bromine isotopes, since the accurate mass of the molecular ion or fragment ion is recorded. Moreover, isotope labelled PBDEs can be used as ideal internal standards. Isotope labelled standards cannot be used with GC-ECNI-MS, except for BDE-209 where a good sensitivity and selectivity is achieved using fragment ions for the native and isotope labelled BDE-209 (Björklund et al., 2003).

Quality control (QC) and quality assurance (QA) represent important tools of the total analytical procedure. The analysis of PBDEs is laborious and complex and involves many steps. Errors are easily made in extraction, cleanup, GC determination and quantification. A number of factors determine the final accuracy and precision (i.e. the quality) of the results reported. Considerable blank contributions are easily encountered for the major congeners BDE-47, -99, -100 and -209, and therefore, blank tests must be carried out regularly. BDE-209 is present in high levels in dust and special care should be taken to avoid contamination of samples and extracts (de Boer and Wells, 2006; Covaci et al., 2003; Päpke et al., 2004). Moreover, it is essential to use separate sets of glassware and extraction and cleanup equipment for high contaminated samples and low contaminated samples.Various studies have shown that PBDEs, in particular higher brominated congeners, and other polybrominated aromatic compounds undergo photolytic debromination under laboratory conditions in the presence of UV light with a wavelength above 290 nm (Eriksson et al., 2004). Due to this fact, it is recommended that all analytical work is carried out in such a manner that UV light is kept out, e.g. treatments can be undertaken in brown glass or in glassware covered with aluminium foil.

Interlaboratory studies and certified reference materials (CRMs)

A number of interlaboratory studies have been organised for biota samples by QUASIMEME (Quality Assurance of Information for Marine Environmental Monitoring in Europe). Improvement was seen over the years for most PBDEs, although BDE-183 and -209 remain problematic (de Boer and Wells, 2006).

Since the year 2000 the Norwegian Institute of Public Health has offered interlaboratory comparison studies on POPs in food. While in the beginning these studies were limited to dioxins and PCBs, for a couple of years they have also covered PBDEs in food commodities, such as salmon, herring, eel, cod liver, pork, beef, chicken, butter, cream and others. More than 30 laboratories participated in the latest study in 2010 on the determination of PBDEs in non-spiked pork, trout and human milk specimens.[16]

Standard or Certified Reference Materials (SRM, CRM) are important tools for laboratory performance evaluation against external references. The US National Institute for Standards and Technology (NIST) issues standard reference materials (SRMs) certified for the concentrations of PBDEs in fish tissue (SRM 1947) and mussel tissue (SRM 2977), as well as in spiked and non-spiked human milk (SRM 1954 and SRM 1953, respectively) and human serum (SRM 1958 and SRM 1957, respectively). Solutions certified for 38 PBDE congeners (SRM 2257) or only for BDE-209 (SRM 2258) in 2,2,4-trimethylpentane (isooctane) are also available. No CRMs are available for PBDEs in food other than fish (van Leeuwen et al., 2006). However, the Norwegian Institute of Public Health offers surplus samples from their intercomparison studies. Although not certified, consensus values based on the proficiency tests are available for the different food matrices.

Methods for analysis of PBDE metabolites (OH-PBDEs)

The OH-PBDEs differ in relation to the PBDE congeners, by holding a phenol functional group, making these metabolites slightly acidic compounds. The OH-PBDEs are compounds with pKa values in the range of 7-9 (Malmberg, 2004) making them ionisable even at physiological pH. The analytical procedure takes advantage of the acidity of the OH-PBDEs for cleanup (Hovander et al., 2000) by partitioning between an organic solvent and an alkaline aqueous phase. The OH-PBDEs may be derivatized prior to further cleanup and instrumental analysis by GC-MS (Malmberg et al., 2005; Athanasiadou et al., 2008; Qiu et al., 2009). The OH-PBDEs are fully separated from the parent PBDE congeners during cleanup. A potentially complicating factor regarding OH-PBDEs is their origin as natural products (see Chapter 8.1.3) but this is referring to the origin of the compounds, not to their identity.

4. Sources, use and environmental fate

Flame retardants are used in many different materials e.g. plastics, textiles, electronic casings and circuitry and other materials to prevent fires by prolonging the time until the heated material will catch fire. PBDEs constitute an important and widely used group of flame retardants. They are used as additives generally at concentrations between 5 and 30 % by weight, i.e. they are mixed into polymers but are not chemically bound to the plastic or textiles. They might therefore separate or leach from the product applications into the environment.

PBDEs have been in use at least since the early 1970s. Their occurrence in commercial flame retardants were elucidated by Norström et al. (1976) and Hutzinger et al. (1976) and they were demonstrated to be environmental contaminants already in 1981 (Andersson and Blomkvist, 1981) but warning flags had been raised prior to this discovery by Norström et al. (1976). International agreements on regulation of some PBDEs have been introduced since 2004.

OH-PBDEs substituted with the hydroxy group in an *ortho* position appear to be primarily of natural origin, i.e. from biosynthesis by marine organisms (Gribble, 2000; Teuten et al., 2005; Malmvärn et al., 2005; Wan et al., 2009; Löfstrand et al., 2010; Nordlöf et al., 2010). It has also been shown that algae can produce methoxylated PBDEs (MeO-PBDEs) (cf. references given above).

[16] www.fhi.no

4.1. Formation and production

Technical PBDE products are manufactured by bromination of diphenyl ether in the presence of a Friedel-Craft catalyst in a solvent. The major technical products contain mainly pentaBDEs, heptaBDEs or decaBDE, but they also contain other PBDE congeners. A comprehensive overview of the content of six common technical mixtures (two PentaBDE products (DE-71 and Bromkal 70-5DE) two OctaBDE products (DE-79 and Bromkal 79-8DE) and two DecaBDE products (Saytex 102E and Bromkal 82-ODE) can be found in La Guardia et al. (2006) and is illustrated in Tables 4, 5 and 6.

Table 4: Composition of technical PBDE products (concentrations in %, w/w) (WHO, 1994).

Technical product	tetraBDEs	pentaBDEs	hexaBDEs	heptaBDEs	octaBDEs	nonaBDEs	decaBDE
PentaBDE	24-38	50-60	4-8				
OctaBDE			10-12	44	31-35	10-11	< 1
DecaBD						< 3	97-98

Table 5: Concentrations (%, w/w) of PBDE congeners in selected PentaBDE technical products (La Guardia et al., 2006).

PBDE congener	Technical PentaBDE products	
	DE-71	Bromkal 70-5DE
BDE-17	0.07	0.05
BDE-28/33	0.25	0.1
BDE-75	<0.02	nd
BDE-51	<0.02	nd
BDE-49	0.74	0.36
BDE-48/71	<0.02	nd
BDE-47[(a)]/74	38.2	42.8
BDE-68/42	0.53	0.21
BDE-102	0.15	nd
BDE-100	13.1	7.82
BDE-99	48,6	44,8
BDE-97/118	<0.02	0.12
BDE-85	2.96	2.16
BDE-126/155[(a)]	0.21	0.67
BDE-154	4.54	2.68
BDE-144	nd	nd
BDE-153	5.44	5.32

nd: not detected.
(a): major congener of coeluting pair.

Table 6: Concentrations (%, w/w) of PBDE congeners in selected Octa and DecaBDE technical products (La Guardia et al., 2006; Environment Canada, 2010).

PBDE congener	Commercial OctaBDE products		Commercial DecaBDE products	
	DE-79	Bromkal 79-8DE	Saytex 102E	Bromkal 82ODE
BDE-154	1.07	0.04	nd	nd
BDE-144	0.1	0.12	nd	nd
BDE-153	8.66	0.15	nd	nd
BDE-139	nd	nd	nd	nd
BDE-140	<0.02	nd	nd	nd
BDE-138	0.62	nd	nd	nd
BDE-184	<0.02	<0.02	nd	nd
BDE-175/183	42	12.6	nd	nd
BDE-191	<0.02	nd	nd	nd
BDE-180	1.7	nd	nd	nd
BDE-171	1.81	0.17	nd	nd
BDE-201	0.78	<0.02	nd	nd
BDE-197	22.2	10.5	nd	0.03 0.07
BDE-203	4.4	8.14	nd	0.07
BDE-196	10.5	3.12	nd	0.46
BDE-194	<0.02	nd	nd	nd
BDE-208	0.19	<0.02	nd	0.07
BDE-207	11.5	11.2	0.24	4.1
BDE-206	1.38	7.66	2.19	5.13
BDE-209	1.31	49.6	96.8	91.6

nd: not detected.

The predominant congeners in two PentaBDE mixtures are given in Table 5 and the predominant congeners in commercial OctaBDE and DecaBDE products are given in Table 6.

PBDEs have been produced in a number of different compositions but by only a small number of producers. Still, more than 50 different trade names have been in use and a number of these are given in Table 7.

Table 7: Some trade names of technical PBDE products.

Product category	Trade names
Commercial PentaBDE and OctaBDE containing products	Adine 404; Bromkal 70; Bromkal 70-5; Bromkal 79-8 DE; Bromkal G1; CD 79; DCD 71; DE 71; DE 71DE; DE-79; EB 8; E-60 F; FR 143; FR 1205/1215; FR-1208; Octobrombiphenyl ether; Pentabromprop[(a)]; Planetron PB501; Saytex 111; Tardex 50; Tardex 80
Commercial DecaBDE products	Adine 505; AFR 1021; Berkflam B10E; BR55N; Bromkal 81; Bromkal 82-ODE; Bromkal 83-10 DE; Caliban F/R-P 39P; Caliban F/R-P 44; Chemflam 011; DE 83; DE-83-RTM; DP 10F; EB 10FP; EBR 700; Flame Cut BR 100; FR-1210; FR 300BA; FRP-39; FRP-53; FR-PE; FR-PE(H); HFO-102; Hexcel PF1; NC-1085; NCI-C55287; Phoscon Br-250; Planelon DB 100; Saytex 102; Saytex 102E; Tardex 100

(a): According to the producer, Pentabromprop should contain tribromophenyl-dibromopropyl ether but according to Norström et al. (1976) the product mainly consisted of a mixture of tetra to hexaBDEs.

It has not been possible to locate any reliable up-to-date data on the production of PBDEs. The production of brominated flame retardants is closely linked to the production of bromine. The USA Geological Survey has estimated the world production of bromine in 1970 to about 210,000 tons and 691,000 tons in 2008.[17] The four countries accounting for the majority of the world's bromine production in 2000 were the United States (39 %), Israel (38 %), the United Kingdom (9 %) and China (7 %). In 2008, the four leading countries were USA (40 %), Israel (24 %), China (20 %) and Jordan (12 %).

Globally, the consumption pattern of various commercial PBDE mixtures varies between different parts of the world. For example, PentaBDE has not been used or had a very minor use in Asia.[18] However, DecaBDE is by far the most commonly used PBDE globally and accounted for 81 % and 83 % of the global PBDE demand in 1999 and 2001.

The total annual production of technical Penta-, Octa- and DecaBDE in 1990 was estimated to be 4,000, 6,000 and 30,000 metric tons, respectively (Arias, 1992). The estimated total market demand in 2001 for the technical mixtures is given in Table 8.

Table 8: Total annual market demand by region in 2001 in metric tonnes (Palm et al., 2004).

Metric tonnes	PentaBDE	OctaBDE	DecaBDE	Total
America	7,100	1,500	24,500	33,100
Europe	150	610	7,600	8,360
Asia	150	1,500	23,000	24,650
Rest of the world	100	180	1,050	1,330
Total	7,500	3,790	56,150	67,440

For the European Union, the demand figures given in Table 8 are similar to those published by de Poortere (2000). A detailed study resulting in estimations of production, consumption and emission to air of commercial PentaBDEs during 1970 to 2000 was published by Prevedouros et al. in 2004. These estimations indicate that a total of 3,000-5,000 tons of PentaBDEs were produced in Europe during this period, with further 9,000-10,000 tons imported in finished articles.

[17] http://minerals.usgs.gov/ds/2005/140/bromine.pdf
[18] http://www.bsef.com/

According to figures from 1999[19] PBDEs accounted for about 33 % of the global BFR demand. This percentage is likely to have varied over the years, as the production, use and consumption pattern has varied, but details are not known.

4.2. Use

Previous PBDE demand has been reported for some European countries; given in tonnes per year for Germany: 3,000-5,000, Sweden: 1,400-2,000, UK: 2,000 and The Netherlands: 2,500-3,700 (WHO, 1994). In the EU risk assessment of DecaBDE (ECB, 2002) figures between 7,000 and 11,000 tonnes per year (total PBDE) were reported for the European Community in the years 1986-1989.

Official statistics on PBDE demand in Sweden is available from the Products Registry at the Swedish National Chemicals Agency, and varied between 15 and 124 tonnes per year in the years 1993-2001 (almost exclusively DecaBDE). Data can also be obtained for the Nordic countries from the joint Nordic consumption database SPIN,[20] for the years 2000-2001, and were 2.4 tonnes per year for Denmark (PentaBDE + DecaBDE) each of the years 2000 and 2001 and 1.9 tonnes per year for Finland in 2001 (only DecaBDE). These statistics cover the consumption as pure chemical or chemical product only and does not take use of PBDEs in imported goods into account.

It has not been possible to obtain detailed statistics on the present (2010) demand or import of DecaBDE for individual countries within Europe or for other countries.

According to the ECB risk assessment reports for the three groups of PBDE products these have been used as follows (ECB, 2001, 2003, 2004):

PentaBDE was mainly used as an additive in flexible polyurethane foam in upholstery and furniture (DoE, 1992 as cited by ECB, 2001). Other reported uses include addition to epoxy resins, phenolic resins, unsaturated polyesters and textiles (WHO, 1994).

Four major uses of polyurethane have been identified in the EU. These are:

- foam-based automotive applications,
- domestic furniture including mattresses,
- foam-based packaging,
- components as rigid polyurethane elastomer instrument casings.

Except from the use in polyurethane foam there could also have been minor uses of PentaBDE in textiles, electronic equipment, hydraulic fluids and rubbers.

The use of PentaBDE within the EU prior to the ban has been estimated to 300 tonnes per year and the corresponding amount in finished articles to 1,100 tonnes per year.

OctaBDE was primarily used in Europe in acrylonitrile-butadiene-styrene (ABS) polymers at 12-18 % by weight. Around 95 % of the total OctaBDE supplied in the EU was used in ABS. Other minor uses, accounting for the remaining 5 % use, included high impact polystyrene (HIPS), polybutylene terephthalate (PBT) and polyamide polymers. The flame retarded polymer products were typically used for the housings of office equipment and business machines. ABS is also commonly used in fresh and waste water pipes. It has not been possible to find information on whether ABS used in these applications did contain OctaBDE or not.

[19] http://www.bsef.com/
[20] www.spin2000.net/spin.html

DecaBDE. The use of DecaBDE within the EU was in the mid-1990s estimated to be 8,210 tonnes per year. In 2001, the world-wide demand for DecaBDE was reported to be 56,100 tonnes and the European market demand to be 7,600 tonnes (Table 8**)** whereof 20 % was used in textiles (drapery and furnishing fabric). The remaining 80 % was used in different plastics, in electronics and electrical supplies as printed circuit boards and other electronics in e.g. computers, TV-sets, laser printers, photocopiers, fax machines, junction boxes, cords and cables. According to ECB (2007) DecaBDE was in 2004 no longer produced in the EU but imported by at least three companies.

4.3. PBDEs in the environment

Several reports have emerged over the last 10 years on PBDEs in the environmental compartments, wildlife and humans. A selection of references are used below to describe PBDEs in air, soil, plants and how these compounds bioaccumulate. However, results from different studies need to be compared with caution due to different methodologies, different congeners analysed and different ways of expressing results, e.g. lower bound or upper bound approach.

4.3.1. Release into the environment

PBDEs can be released to the environment via many different routes and processes. During production, PBDEs can be released into the air, wastewater but also into soil and landfills. PBDEs can also be released during transport and handling as well as during the life cycle of consumer products treated with PBDEs (degradation, recycling, disposal). The release from articles and products occur mainly via air (particles and gaseous phase) and this is especially the case if the articles are heated and incinerated in accidental or other types of uncontrolled fires. It has been estimated that up to 43 tonnes of PentaBDE per year are released to the environment in Europe by volatilization from polyurethane foam used in a variety of consumer products (ECB, 2001). An average 10-year lifetime for products (finished articles) was also assumed, with an estimated 0.39 % of the PentaBDE burden being lost each year. Emissions to air of low (up to hexaBDEs) PBDE congeners are likely to exist in both the vapour and particulate phases and therefore be subject to long-range atmospheric transport. An additional source of PBDEs entering the environment is the use of municipal sewage treatment sludge as fertilizer.

4.3.2. Degradation in the environment

Degradation and transformation reactions in the environment, mainly debromination and hydroxylation, have been shown to occur in air, plants, animals, soil and sediments. For example, debromination of BDE-209 has been shown in birds in at least one experimental study by van den Steen et al. (2010). In this study accumulation, tissue-specific distribution and debromination of BDE-209 was investigated in European starling (*Sturnus vulgaris*) using silastic implants. BDE-209 accumulated in the blood to a mean peak concentration of 16-4.1 ng/mL on day 10. After this peak, there was a decline to 3.3-0.4 ng/mL blood at the end of the exposure period of 76 days. In the exposed group, the muscle concentrations by lipid weight were about two-fold those in liver. In addition to BDE-209, other PBDE congeners, particularly octa- and nonaBDEs, were also present in the muscle and liver, suggesting debromination of BDE-209. Debromination has also been reported to occur in wild birds. Gauthier et al. (2008) studied temporal trends of PBDE in samples of herring gull (*Larus argentatus*) eggs from the Great Lakes over the period 1982-2006. The concentrations of BDE-209 were 4.5 to 20 µg/kg w.w. in 2006. The source of the octa- and nonaBDE congeners (e.g., BDE-197 and -207) were found to be the result of the debromination of BDE-209, either metabolically by the birds or prior to uptake via their diet. Congeners deriving mainly from the PentaBDE and OctaPBDE formulations, in contrast, showed rapid increases in concentration up to 2000 but after this no trend could be demonstrated.

It should also be noted that debromination products from BDE-209 especially higher brominated diphenyl ethers have been demonstrated in house dust by Kohler et al. (2008). It is uncertain whether this debromination occurs at the particles or earlier.

4.3.3. Occurrence in the environment

4.3.3.1. Air and dust

Outdoor

There are several factors indicating long-range transboundary transport of PBDEs in the environment. They have a high persistency in air (Palm et al., 2002; Vulykh et al., 2004) and monitoring has detected a widespread occurrence in the European atmosphere (Ter Shure et al., 2004; Lee et al., 2004; Jaward et al., 2004; Harrad and Hunter, 2004; Harrad et al., 2004). The high persistency is based on the unfavourable physicochemical properties and slow reactivity (see Chapter 1.3.).

Schuster et al. (2010) studied trends of PBDEs in European background air sampled at eleven sites (southern England to northern Norway) during 2000 to 2008. Data showed a general decline in PBDE levels over time. A consistent decline was only observed at four sites and declines could only be calculated for BDE-47, -49, -99, -100, -153 and -154, for which half-lives ranged from 1.4 to 4.0 years. The absolute decline of the sum of PBDE levels between 2000-2002 and 2006-2008 ranged from 35 to 57 % and the concentration in air declined by 50 % every 2.2 ± 0.4 years.

Harrad et al. (2010) compiled data on the occurrence of PBDEs in outdoor air. Recorded levels of tri-hexaBDEs in the UK, Canada and Kuwait ranged from 0.49 to 32 pg/m^3 whereas BDE-209 was recorded from LOD up to 105 pg/m^3 in Ontario, Canada.

At a background coastal site on Crete, the average total PBDE concentration in air was 3.9 ± 2.1 pg/m^3 (Iacovidou et al., 2009). Jaward et al. (2004) sampled in 2002 a total of 71 passive air samples using semi permeable membrane devices for the PBDE congeners (BDE-28, -47, -49, -75, -99, -100, -153 and -154) at 71 remote as well as urban locations across 22 countries in Europe. PBDEs were detected in approximately 50 % of the samples, and the corresponding total PBDE air concentrations estimated from the passive sampler data ranged from 0.5 to 250 pg/m^3. The highest concentrations were found in the UK, which has a history of PBDE production and has also been a major user of PBDE formulations due to stringent fire regulations. Other high values were detected in urban centres as e.g. Athens, Bilthoven, Geneva, Milan, and Seville. Non-detectable/very low values occurred in remote/background sites, especially in Iceland, Ireland, Norway and Sweden, and the concentrations in Eastern Europe were also generally low.

During 2006-2007, outdoor air and precipitation samples were collected in the Pearl River Delta area of South China (Zhang et al., 2009). The concentrations of the sum of 15 PBDEs (BDE-17, -28, -47, -49, -66, -99, -100, -153, -154, -183, -196, -206, -207, -208 and -209) ranged from 77 to 372 pg/m^3 in air (particulate + vapour) and from 2.0 to 16 ng/L in rain from Guangzhou. BDE-209 was the predominant congener. The estimated annual dry and wet depositional rates were 0.91 and 0.45 mg/m^2 for BDE-209, and 0.99 and 0.39 mg/m^2 for the 15 PBDEs, indicating a dominant pathway for PBDE input to the soil and aquatic environments in this region. In an investigation by Chen et al. (2006a) the concentrations of the sum of eleven PBDEs (BDE-28, -47, -66, -100, -99, -85, -154, -153, -138, -183 and -209) in air from an industrialised area in the Guangzhou region ranged from 170 to 6,594 pg/m^3 (mean 3,673 pg/m^3) in the gas phase and from 230 to 11,464 pg/m^3 (mean 4,200 pg/m^3) in the particles phase. There are just a few recent samples from Europe. Quintana et al. (2006) reported levels of BDE-47, -99 and -100 in A Coruña (Spain) adsorbed to two fractions of particulate matter (PM)

$PM_{2.5}$ and PM_{10}[21] to 35 and 18 pg/m^3. Gans et al. (2007) reported 13-35 pg/m^3 in air sampled for 72 hours at twelve different locations during the first half of 2006 in Vienna (Austria) for 25 PBDE congeners (BDE-11, -17, -25, -28, -47, -49, -77, -85, -99, -100, -116, -118, -126, -138, -140, -153, -154, -155, -166, -181, -183, -196, -197, -203 and -209).

The most rapid route of transport for persistent organic contaminants to the Arctic is via the atmosphere. Doubling times of PBDEs in air at Alert, Artic Canada (calculated by dividing ln2 with the positive values of the linear regression slope of the Digital Filtration derived trend line) ranged from 3.5 years for BDE-209 to 28 years for BDE-153. These differences in doubling times are likely to be an effect of the phasing out of the Penta- and OctaBDE product in Europe and North America (Hung et al., 2009). The total concentration of PBDEs (sum of BDE-17, -28/33, -47, -66, -85, -99, -100, -138, -153, -154, -183, -190 and -209) at Alert thus showed a slowly increasing trend during 2002 to 2005 from 6.7 to 8.4 pg/m^3. The dominating congeners were BDE-47, -99 and -209.

Indoor

Harrad et al. (2010) compiled data on the occurrence of PBDEs in indoor air. The concentrations of tri-hexaBDEs in the UK, Canada and Kuwait ranged from 2.0 to 3,600 pg/m^3 and from the US, concentrations up to 15,000 pg/m^3 are reported. BDE-209 was determined from LOD (48) up to 651 pg/m^3 in Ontario, Canada.

Harrad et al. (2008) studied PBDEs in dust from 30 homes, 18 offices and 20 cars from the UK in 2006-2007. Average total concentrations of the sum of 13 PBDEs (BDE-28, -47, -49, -66, -99, -100, -153, -154, -183, -196, -197, -203 and -209) were 260,000, 31,000 and 340,000 ng/g, respectively. Concentrations of BDE-209 in three samples were the highest recorded at that time: 2,600,000 (car), 2,200,000 (home) and 1,400,000 (office) ng/g.

Sjödin et al. (2006) reported levels in household dust from Australia, Germany, the UK and the USA. The sum of seven PBDEs (BDE-47, -99, -100, -153, -154, -183 and -209) showed considerable differences between the countries. Germany showed the lowest levels (median 74, range 17-550 ng/g) followed by Australia (median 1,200, range 500-13,000 ng/g), the USA (median 4,200, range 520-29,000 ng/g) and the UK (median 10,000, range 950-54,000 ng/g). There were remarkable differences between USA and the other countries with respect to the content of the six non-decaBDE congeners. The dust from USA contained on average 2,000 ng/g of the six non-decaBDE congeners whereas the corresponding value for the other countries was around 200 ng/g. On the other hand, PBDEs in the dust from UK was found to be almost 100 % BDE-209.

In Queensland (Australia), Toms et al. (2009) studied PBDEs in homes and offices samples collected in 2005. In indoor air, total PBDE concentrations (sum of 26 congeners: BDE-17, -28, -33, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -166, -153, -154, -156, -183,-184, -191, -196, -197, -206, -207 and -209) ranged from 0.5 to 179 and from 15 to 487 pg/m^3 in homes and offices, respectively. In dust, PBDE concentrations ranged from 87 to 733 ng/g and from 583 to 3,070 ng/g in homes and offices, respectively. Congener profiles for both air and dust were dominated by BDE-209.

Fromme et al. (2009) reported that the concentrations of the sum of 16 different PBDEs including BDE-209, in indoor air and dust from homes in Bavaria (Germany) in 2005 ranged from 8.2 to 477 pg/m^3 and 36.6 to 1,580 ng/g, respectively. In both air and dust BDE-209 was the predominant congener. Similar results were recently presented by D'Hollander et al. (2010) in a study of PBDEs and other contaminants in dust collected in 43 homes and 10 offices in Flanders/Belgium. The concentration of the sum of nine PBDEs (BDE-47, -99, -100, -153, -154, -183, -196, -197 and -203) as well as BDE-209 in samples collected in the homes ranged from 4 to 1,214 ng/g (mean 104 ng/g) and < 5 to 5,295 ng/g (mean 590 ng/g), respectively. The corresponding concentrations in samples

[21] $PM_{2,5}$ and PM_{10}, stands for particles smaller than 2.5 and 10 micrometers in (aerodynamic) diameter respectively. PM2.5 are referred to as "fine fraction" particles and are clearly shown to pose the greatest health risks.

collected in the offices were 59 to 10,880 ng/g (mean 1,256 ng/g) and 69 to 11,574 ng/g (mean 1,513 ng/g), respectively.

Harrad and Abdallah (2011) studied the occurrence of individual PBDEs (BDE-47, -85 -99, -100, -153, -154, -183, -196, -197, -202, -203, -206, -207, -208 and -209) in dust collected in 14 car cabins. The median concentrations of congeners BDE-47 to -203 ranged from 2.5 to 130 ng/g, whereas those of BDE-206 to -208 ranged from 3,700 to 4,800 ng/g. The median concentration of BDE-209 was found to be 190,000 ng/g. Compared to the median concentration found in US cars (Lagalante et al., 2009), samples from the UK cars were around one order of magnitude lower with respect to the concentrations of BDE-47, -99, -100, -153, -154 and -183. On the other hand, the median concentration of BDE-209 in dust from the UK cars was found to be twice as high as that from the US cars. Harrad and Abdallah (2011) also estimated the exposure to UK adults and toddlers and found that the contribution via inhalation and dust to the overall exposure to all PBDEs studied, except for BDE-209 was around 1 % or much lower in both adults and toddlers. The contribution from dust to the overall exposure to BDE-209 was however estimated to be around 32 % for adults and around 59 % for toddlers.

4.3.3.2. Soil and uptake by plants

The dominating source of BFRs in arable soil is via application of sludge from wastewater treatment plants (Law et al., 2006a; Eljarrat et al., 2008; US-EPA, 2009). Based on median concentrations of PBDEs in sewage sludge from the Czech Republic in 2006, Stiborová et al. (2009) calculated that around 30 kg of non-decaBDEs was annually brought to arable land within the Czech Republic. The corresponding figure for decaBDE was around 70 kg. A similar exercise for Germany by Knoth et al. (2007) showed that 150 kg of non-decaBDE and 350 kg of decaBDE was annually transferred to arable land in Germany.

The uptake of PBDEs in plants has been studied in a few reports only. Vrkoslavová et al., (2010) studied the absorption and translocation of PBDEs from sewage sludge by tobacco (*Nicotiana tabacum*) and nightshade (*Solanum nigrum*). They found that PBDEs could be translocated into the plants but to different extents depending on species and log K_{ow} of the PBDE congener. Tobacco showed higher bioconcentration factors (BCFs, calculated as the ratio of the total plant concentration of a congener (dry weight) and the concentration (dry weight) of the same congener in the sewage sludge) than nightshade. For BDE-47, a BCF of around 0.29 was calculated for tobacco, whereas the corresponding BCF for nightshade was 0.02. BDE-100, -99 and -209 showed lower BCFs. In tobacco the BCF for BDE-209 was found to be 0.05, whereas this congener could not be found at all in nightshade.

Jin et al. (2008) determined PBDEs in plants sampled in China in 2006. Based on the sum of eleven PBDEs (including BDE-209), concentrations in grass sampled at different distances from BFR manufacturing plants in Laizhou Bay in Shandong Province (PR China) and two edible plants species, was found to range from 70 to 5,900 ng/g with the highest concentrations in grass sampled close to the factory. The edible plants Saline seepweed (*Suaeda* sp.) and Haricot bean (*Phaseolus vulgaris*) had concentrations of 70 and 160 ng/g, respectively. BDE-209 concentrations in six plant species (alfalfa (*Medicago sativa*), maize (*Zea mays*), pumpkin (*Cucurbita* spp.), radish (*Raphanus sativus*), ryegrass (*Lolium perenne*) and summer squash (*Cucurbita pepo*)) were studied by Huang et al. (2010a). The plants were grown in soil containing 5,000 ng/g of BDE-209 but no other PBDEs. Uptake of BDE-209 was observed in the roots and shoots of all species, and the uptake was positively correlated with the concentration of lipids in the root. Pumpkin showed the highest concentrations in roots and radish the lowest. In shoots, the highest concentrations were seen in alfalfa and the lowest in ryegrass. Nineteen different di- to nonaBDEs were detected in both soil and plant samples. Also, five OH-PBDE congeners were detected in the plants, indicating that debromination and hydroxylation may occur also in the soil-plant system. In a study by Mueller et al. (2006) uptake by radish (*Raphanus sativus*) and summer squash or zucchini (*Cucurbita pepo*) grown in soil experimentally contaminated with DE-71,

75 ng/g expressed as PentaBDE, showed that both species could take up PBDEs in roots and shoots. The concentrations in radish and zucchini were found to be around 1 and 4 ng/g plant tissue, respectively.

Based on the limited number of studies cited above, it is likely that at least some plant species can accumulate PBDEs from soil in a dose-dependent manner. Thus, plants grown on land containing PBDEs could accumulate PBDEs from the substrate. But reported BCFs are invariably below 1 and usually in the range of 0.1-0.01. This does not exclude that concentrations of 100 ng/g or higher in edible plants have been reported in the study by Jin et al. (2008). The origin of these edible plants is however uncertain as they are only attributed to as "from local market" and therefore it cannot be excluded that they could be grown and harvested in areas close to point sources of PBDEs or be contaminated between harvest and sale on the market.

PBDEs have been found in sewage sludge in a number of studies. It could therefore be possible that sewage sludge used as fertiliser could be a source to PBDEs in crops. It has however not been possible to find specific studies on the importance of this route of contamination.

4.3.4. Bioaccumulation in wildlife

Several of the PBDE congeners present in commercial PBDE mixtures degrade slowly in the environment. PBDEs have been shown to bioaccumulate and biomagnify in wildlife. Stapleton et al. (2004) calculated oral biomagnification factors (BMFs) in carp (*Cyprinus carpio*) to be 0.356, 1.359 and 0.028 for BDE-28, -47 and -153 respectively. Law et al. (2006b) studied Walleye (*Stizostedion vitreum*), whitefish (*Coregonus clupeaformis*), emerald shiner (*Notropis atherinoides*), burbot (*Lota lota*), white sucker (*Catostomus commersoni*) and goldeye (*Hiodon alosoides*) and zooplankton in Lake Winnipeg. The highest BMFs were found for fish/zooplankton ranging between 0.2-7.2, 0.1-5.5 and 2.9-34 for BDE-47, -153 and -209, respectively. BMFs above 1.0 were also found for Walleye/white fish and Burbot/emerald shiner. Mean logBMFs of PBDE congeners in Lake Michigan lake trout (*Salvelinus namaycush*) as compared with the concentration of the same congener in the surrounding water were calculated by Streets et al. (2006) to be 7.3, 7.3, 6.7 and 7.5 for BDE-47, -66, -99 and -100, respectively.

These and other studies have also focused on the potential for bioaccumulation and biomagnification of PBDEs in food webs. The studies show an increase of concentrations in biota with increasing trophic level in pelagic and Arctic food webs. The calculated BCFs, bioaccumulation factors (BAFs) and BMFs for BDE-99 indicate a potential for bioaccumulation and biomagnification. Lithner et al. (2003) reported a BAF for Zebra mussels (*Dreissena polymorpha*) of 1.8 based on the ratio between the lipid weight concentrations in mussels and organic carbon based concentrations in the suspended particulate matter. As one example of studies on biomagnification, Muir et al. (2006) reported average BMFs and ranges for Polar bear/Ringed seal from five different locations. The results are summarised in Table 9.

Table 9: Average BMFs and ranges of five individual PBDE congeners for Polar bear/Ringed seal from five different locations. BMF calculated as the mean lipid weight concentration in Polar bears divided by mean concentrations in Ringed seal blubber.

PBDE congener	BMF	
	Average	Range
BDE-47	3.9	1.8 - 7.4
BDE-99	5.8	1.0 - 11
BDE-100	4.7	0.6 - 8.8
BDE-153	71	8.8 - 130
BDE-154	1.8	0.2 - 2.9

As can be seen in Table 9, BDE-153 shows a higher biomagnification factor compared to the other congeners studied. It should however be noted that the study also showed profound differences between the different sites, as illustrated by the wide ranges.

A large number of studies show concentrations of concern in top predators. Many of these are summarised in a report from the "Persistent Organic Pollutants Review Committee" under the Stockholm Convention (UNEP, 2006). In a study by Ueno et al. (2004) concentrations of PBDEs between 0.18 to 4.7 ng/g fat are reported in Skipjack tuna (*Katsuwonus pelamis*) and Law et al. (2003) report the concentration in Atlantic tomcod (*Microgadus tomcod*) of 77 ng/g fat. Herzke et al. (2005) report the concentration of PBDE in eggs from White-tailed eagle (*Haliaeetus albicilla*) sampled in Norway to be 6-184 ng/g fat. Even higher concentrations are reported by Lindberg et al. (2004) in eggs of Peregrine falcon (*Falco peregrinus*) from Sweden ranging from 110-9,200 ng/g fat for BDE-99. These high levels in top predators are usually regarded to be an indication for the potential of a compound to bioaccumulate/biomagnify in the food chain.

4.4. Combustion

The combustion of domestic products containing common BFRs such as PBDEs may lead to concurrent emissions of PBDEs and polybrominated dibenzo-*p*-dioxins and furans (PBDD/Fs). Large amounts of brominated and mixed chloro-bromodioxins and furans can be formed in accidental fires where brominated flame retardants are present (Söderström and Marklund, 1999; Lundstedt, 2009).

In addition to dioxins and furans, a wide variety of other organic pollutants are formed and emitted from combustion processes. These include brominated benzenes and phenols (Lönnermark and Blomqvist, 2005; Cormier et al., 2006; Gullett et al., 2007).

High emissions of PBDD/Fs have also been observed during open burning of TV-sets (Zelinski et al., 1993; Lundstedt, 2009). In the study by Lundstedt (2009), the total levels of PBDD/Fs in the soot were 10,000-100,000 times higher than the total levels of PCDD/Fs.

Thus, incineration of materials containing BFRs can, especially when carried out under uncontrolled conditions, lead to large emissions of a variety of hazardous substances. In the EU, the recycling and recovery quotas set by the WEEE directive, ranging from 50 to 75 % for recycling and from 70 to 80 % for recovery, can only be achieved when including combustible fractions such as plastics into the recovery or recycling systems.

Also in situations with temperatures well below those during incineration, as they may occur in production (e.g. extrusion and moulding) and recycling processes, PBDEs can have the potential to form PBDD/PBDFs. Levels of PBDD/PBDFs in polymers after such "thermal stress" have been

shown to reach up to 2 % of the PBDE content (Ebert and Bahadir, 2003; Weber and Kuch, 2003; Luijk et al., 1992; Tamade et al., 2002; Kajiwara et al., 2008; Hanari et al., 2006).

5. Occurrence and patterns of PBDEs in food

5.1. Current occurrence of PBDEs in food: call for data

Following a European Commission request, in 2005 the CONTAM Panel (EFSA-Q-2005-244)[22] identified eight PBDE congeners (BDE-28, -47, -99, -100, -153, -154, -183 and -209), HBCDDs and the PBB congener BB-153 as the most important ones to be monitored. Optionally TBBP-A and other phenols, decabromodiphenyl ethane, hexabromobenzene, bis(2,4,6-tribromophenoxy)ethane were also recommended to be monitored. From October 2006, EU-wide monitoring of these compounds was organised and the results of this exercise were made available to EFSA.

Additionally, a call for data on BFRs[23] from the Dietary and Chemical Monitoring Unit (DCM) (former Data Collection and Exposure Unit, DATEX) was issued by EFSA in December 2009, with different deadlines according to the chemicals to be collected. The closing date for data submissions on PBDEs and PBBs was end of February 2010.

EFSA collected and evaluated the results reported from the analysis of 3,971 food samples, as provided by 11 European countries which covered the period from 2001 and 2009.

SAS Enterprise software was used to extract information from the occurrence data submitted. Data providers were asked to check and confirm that the extracted information was correct and provide clarifications in case of unclear or missing detailed information.

5.1.1. Summary of data collected

The origin of the 3,971 samples reported from the 11 European countries is illustrated in Figure 4. Norway provided 28 % of the data followed by Germany (24 %) and Ireland (11 %).

The EU-wide monitoring of BFR compounds, including PBDEs, was organised from October 2006, but as specified in the call for data (DCM call for data on BFRs[22]), any data available from 2000 to 2009 could have been provided to EFSA. The distribution of results over the years of sampling is illustrated in Figure 5. Over 60 % of the samples were analysed in the latest years, specifically in the period from 2006 and 2008. The year 2009 was probably not a complete year of sampling, as the closing date of the call for data for PBDEs was set to February 2010.

[22] http://www.efsa.europa.eu/en/scdocs/scdoc/328.htm
[23] http://www.efsa.europa.eu/en/data/call/datex091215.htm

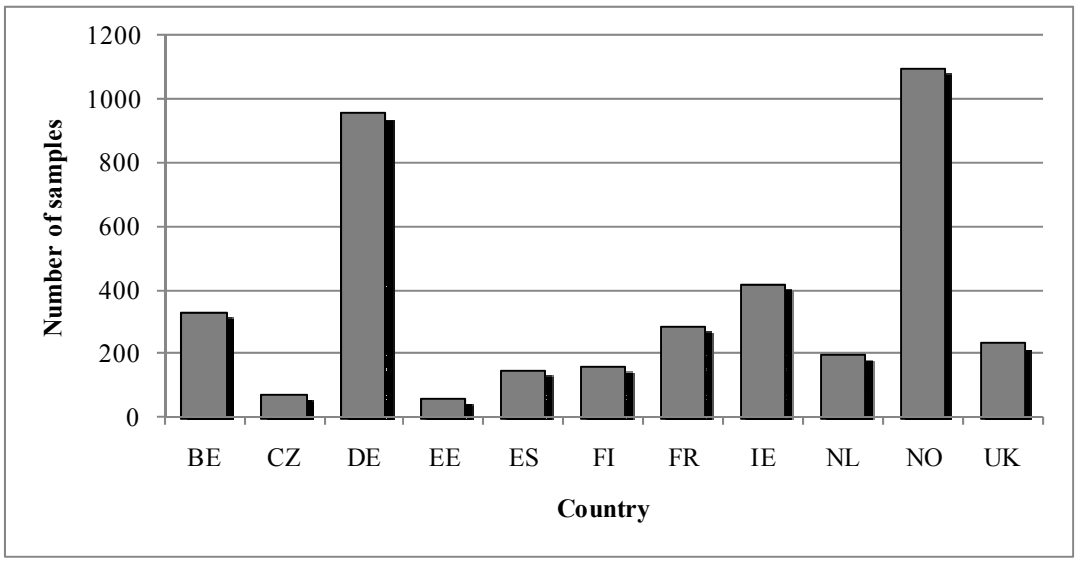

Figure 4: Distribution of samples across 11 European countries (BE: Belgium, CZ: Czech Republic, DE: Germany, EE: Estonia, ES: Spain, FI: Finland, FR: France, IE: Ireland, NL: The Netherlands, NO: Norway, UK: United Kingdom).

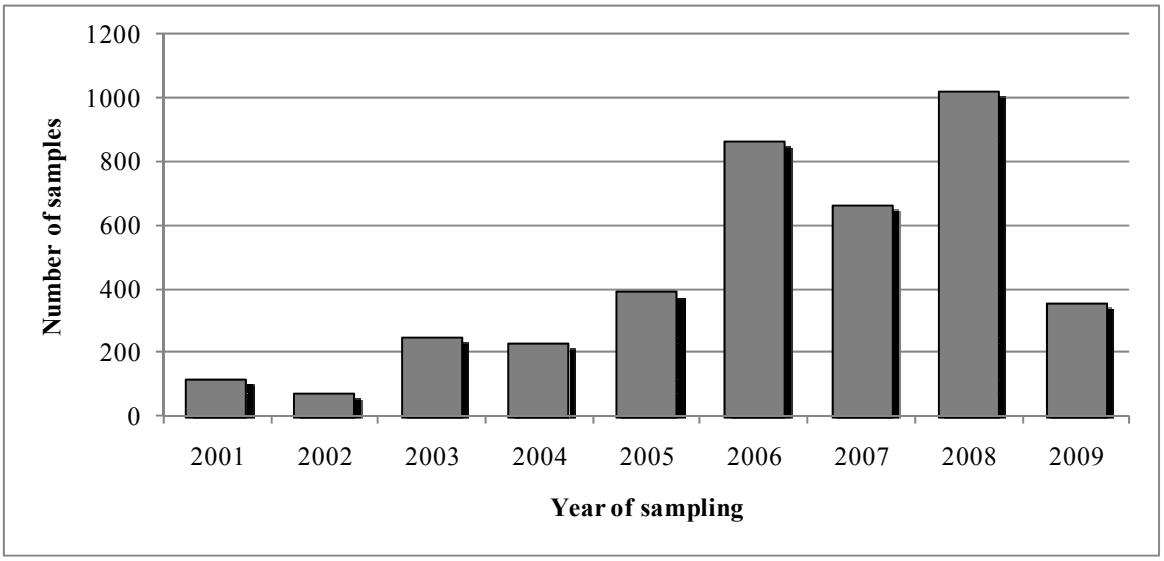

Figure 5: Distribution of samples over the years of sampling.

Analytical results identified during the data cleaning steps with incomplete or incorrect description of any of the required variables (e.g. parameter type, food classification, results value or results LOD-limit of quantification (LOQ)) of the Standard Sample Description[22] template, were returned to the respective data provider for further check, before excluding the records from the database.

Additionally, specific exclusions were performed concerning data from total diet studies (TDS) and from target surveys for a total of 80 samples. For the targeted surveys this was done because they could influence the overall occurrence values; for the TDS samples, because of not correct matching between the reported food descriptions of the TDS composite food with the food categories of the current FoodEx food classification system. Moreover, 47 results specifically for BDE-209 were excluded because of the uncertainty linked to the analytical method used. The data provider explained that those results were eventually influenced by background contamination and thus not suitable for exposure assessment purposes.

With final agreement of the respective data providers, a total of 36,087 analytical results covering 19 different PBDE congeners were included in the PBDE dataset for the calculation of the dietary intake of PBDEs.

5.1.2. Distribution of analytical results reported for PBDE congeners

A total of 3,971 samples were tested for different PBDE congeners. In certain cases in one food sample only the presence of some congeners was tested, in others a set of 19 different congeners was analysed simultaneously. From the results of those 3,971 food samples, 36,087 analytical results for individual congeners were collected and the distribution of the records reported for each single congener is illustrated in Figure 6.

Over 3,500 records were collected for BDE-47, -99, -100, -153 and -154. For BDE-28, -183 and -209 the number of analytical results reported was 3,217, 3,129 and 1,300, respectively. Additional data were collected for another 11 congeners, but with relatively low frequency.

Following the CONTAM Panel advice,[21] the monitoring exercise that was carried out from 2006 was mainly focused on the analysis of the PBDE congeners -28, -47, - 99, -100, -153, -154, -183 and -209. This is illustrated by the reported number of analytical results in Figure 6.

Based on the composition of the technical PBDE mixtures, occurrence in the environment and available data on toxicity, the CONTAM Panel decided to focus the dietary exposure assessment of the present opinion on the PBDE congeners BDE-28, -47, -99, -100, -153, -154, -183 and -209.

In all the initial 3,971 samples the presence of at least one of the 8 congeners considered was tested. In total 26,105 analytical results for the 8 congeners were considered for the analysis of the occurrence data in view of the dietary exposure assessment of PBDEs.

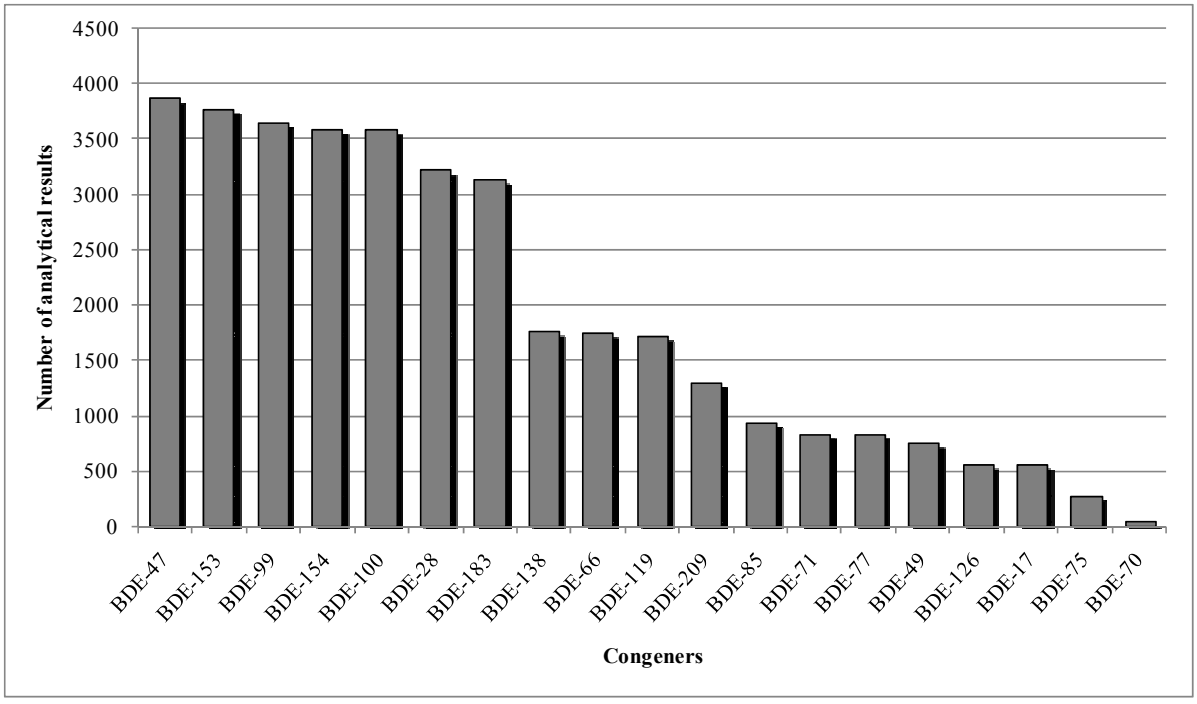

Figure 6: Distribution of analytical results across PBDE congeners.

5.1.3. Distribution of samples reported for food categories

Data providers were asked to codify all food descriptors according to the food classification system of EFSA Concise European Food Consumption Database (EFSA concise food categories).[24]

In order to improve the estimation of the dietary exposure assessment, the "Comprehensive European Food Consumption Database" was established in 2010 with a refined food classification named FoodEx.

FoodEx is a provisional food classification system developed by the DCM Unit in 2009 with the objective of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances. It contains 20 main food categories (first level),[25] which are further divided into subgroups comprising 140 items at the second level, 1,261 items at the third level and reaching about 1,800 end-points (food names or generic food names) at the fourth level. This classification system is based on a hierarchical coding for an easier cross-checking and it is structured as a child-parent relation. The distribution of the 3,971 samples across the different aggregated food categories is shown in Figure 7.

The category "Fish and other seafood (including amphibians, reptiles, snails and insects)" dominated the product coverage with 62 % of the total samples, followed by "Meat and meat products (including edible offal)" and "Animal and vegetable fats and oils", at 15 % and 7 % respectively, and "Milk and dairy products" and "Eggs and egg products" at 5 %.

For the food categories "Products for special nutritional use" and "Vegetables and vegetable products (including fungi)" respectively 76 and 52 samples were analysed for the presence of PBDEs. Less than 50 samples were reported for the remaining food categories.

Of the 20 food categories available in the first level of FoodEx, only 14 of them were covered in the current data collection. No analytical results for food products in the categories of "Legumes, nuts and oilseeds", "Sugar and confectionary", "Fruit and vegetable juices", "Non-alcoholic beverages (excepting milk based beverages)", "Alcoholic beverages", "Drinking water (water without any additives except carbon dioxide; includes water ice for consumption)" were submitted to EFSA.

[24] http://www.efsa.europa.eu/en/datex/datexfooddb.htm

[25] Grains and grain-based products, Vegetables and vegetable products (including fungi), Starchy roots and tubers, Legumes, nuts and oilseeds, Fruit and fruit products, Meat and meat products (including edible offal), Fish and other seafood (including amphibians, reptiles, snails and insects), Milk and dairy products, Eggs and egg products, Sugar and confectionary, Animal and vegetable fats and oils, Fruit and vegetable juices, Non-alcoholic beverages (excepting milk based beverages), Alcoholic beverages, Drinking water (water without any additives except carbon dioxide; includes water ice for consumption), Herbs, spices and condiments, Food for infants and small children, Products for special nutritional use, Composite food (including frozen products), Snacks, desserts, classification not possible.

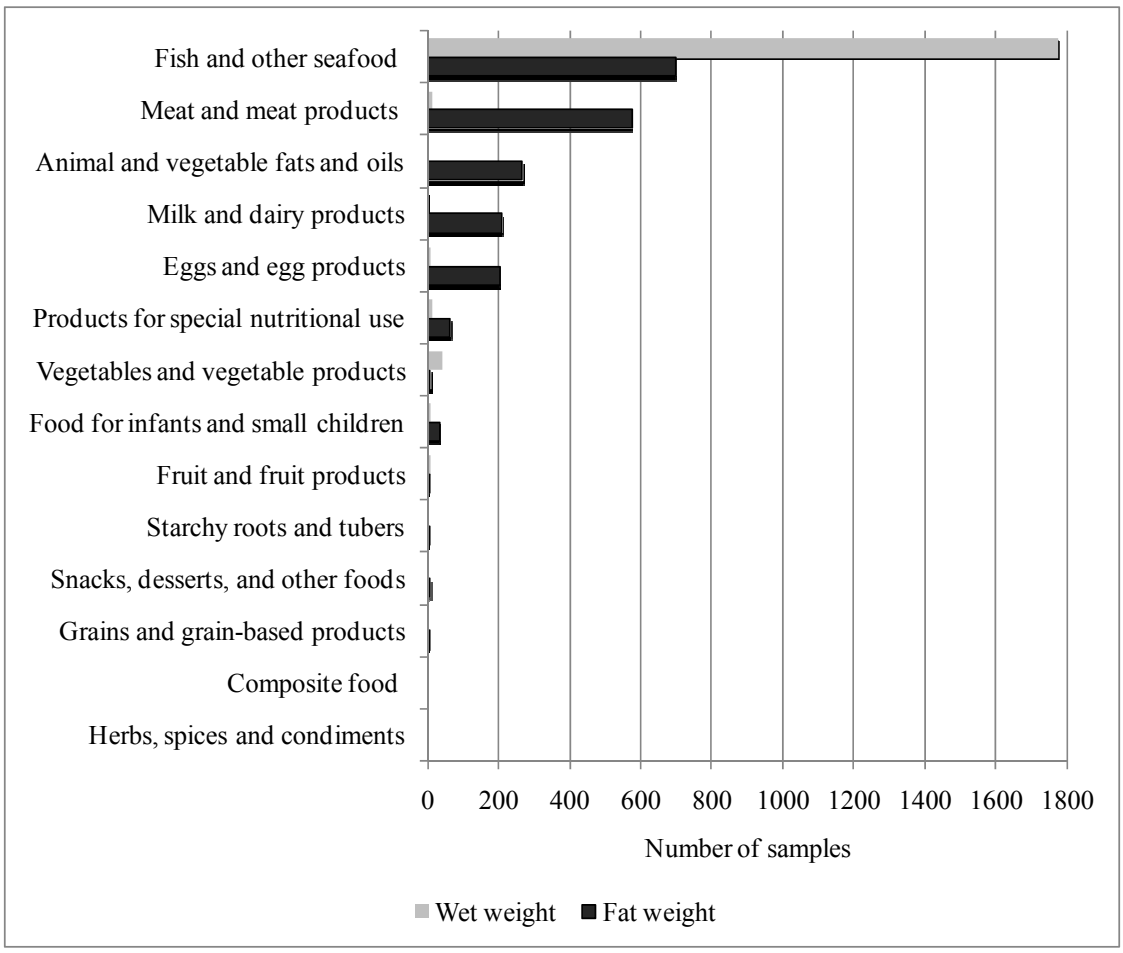

Figure 7: Distribution of samples in the FoodEx food categories (first level) and distribution of expression of results (wet weight, fat weight), across food categories.

The analysis of the samples from products of animal origin, excluding fish, was mainly carried out on the fat fraction, therefore the analytical results were reported on a fat basis in 84-98 % of the cases. In contrast, for "Fish and other seafood", less than 30 % of the samples the results were expressed on a fat basis.

For estimating the dietary exposure to PBDEs, all analytical concentrations expressed on fat weight need to be converted to whole weight basis (wet weight). For this reason the data providers were requested to report the fat content in the Standard Sample Description template for each analysed sample. For 79 samples (out of the total 3,971 samples) among the food categories (FoodEx first level) of "Meat and meat products", "Milk and dairy products", "Eggs and egg products", "Animal and vegetable fats and oils", "Food for infants and small children" the fat content was not provided. Table 10 shows the distribution of the missing information across the food categories of the fourth level of the FoodEx.

The missing information was replaced by the average fat content calculated on the samples for which the percentage of fat was given in the original data of the current database on BFRs[26] (Table 10). Only for 14 samples of "Whole egg, chicken", the average fat content calculated from the current database on BFRs were considered not representative of the average fat content for whole eggs and chicken and therefore not suitable for data conversions. In these cases the average fat content extrapolated from the

[26] As a consequence of the first deadline of the DCM call for data asking for analytical results on PBDEs and PBBs, the current EFSA database on BFRs include results reported from PBDEs and PBBs.

Comprehensive Food Consumption data base was applied. In Table 10, the average fat content calculated from both the database on BFRs[22] and the Comprehensive Food Consumption Database are reported.

Additionally, where the fat content in "liquid milk" (FoodEx third level) was reported higher than 20 % in the original samples, which was probably due to reporting errors, the average fat content calculated on "liquid milk" samples from the database on BFRs[22] was applied (3.61 %).

Table 10: Number of samples distributed across the FoodEx food categories at fourth level, where the fat content was not reported. The average fat content (%) calculated on the reported percentage of fat and the respective number of samples (in brackets) as present in the current database on BFRs[22] is provided. Additionally, the average fat content (%) extrapolated from the Comprehensive Food Consumption Database and the respective frequency of data reported (in brackets) is given.

FoodEx food categories (fourth level)	Number of samples of the PBDE database with missing fat content	Average fat content from the BFRs data set (%)	Average fat content from the Comprehensive database set (%)
Meat and meat products (including edible offal)			
Beef meat (*Bos* spp.)	30	9.4 (22)	9.4 (300)
Pork/piglet meat (*Sus scrofa*)	12	9.5 (32)	13.6 (408)
Mutton/lamb meat (*Ovis aries*)	6	16.7 (2)	15.8 (172)
Chicken meat (*Gallus domesticus*)	11	5.7 (81)	8.6 (272)
Milk and dairy products			
Cow milk, 3-4 % fat (whole milk)	1	3.6 (8)	3.6 (49)
Eggs and egg products			
Whole egg, chicken	14	13.9 (32)	10.5 (42)
Animal and vegetable fats and oils			
Fish oil	3	100 (0)	99.9 (1)
Vegetable oil	1	98.3 (13)	99.9 (28)
Food for infants and small children			
Ready-to-eat meal for children, meat/fish-based	1	2.6 (15)	3.4 (11)

5.1.4. Analytical methods used and limits of detection

The 26,105 original results for the congeners considered were reported in ng/g (45 %), in mg/kg (19 %), in pg/g (19 %) and in µg/kg (18 %). All the measurements have been converted to ng/g. The analytical methods used to perform the analyses of PBDEs are mainly physicochemical methods based on GC. The most commonly used method was GC-MS with 64 %, followed by GC-HRMS with 31 %, GC-MS/MS and GC-ECD with less than 1 %. For 3 % of the analytical results, no analytical method was specified, i.e. no instrumental details were provided (Figure 8).

According to the additional details reported for the results classified as GC-MS, only 9 % of the cases specified that the GC-MS was based on electron capture negative ionization (GC-ECNI, data not shown). Thus it can not be excluded that in the GC-MS category a considerable number of methods used HRMS detection.

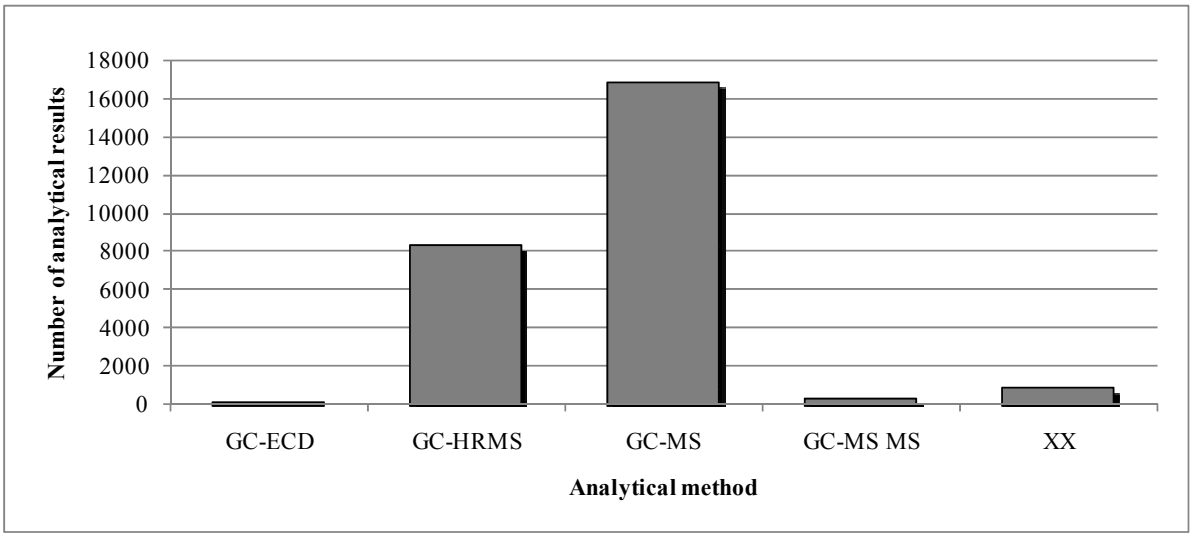

Figure 8: Distribution of analytical methods as reported (GC-ECD: 64 analytical results; GC-HRMS: 8,187 analytical results; GC-MS: 16,827 analytical results; GC-MS/MS: 224 analytical results; XX (analytical method not specified): 803 analytical results).

Figure 9 illustrates the distribution of the analytical methods as reported for the analysis of the eight congeners considered by the CONTAM Panel.

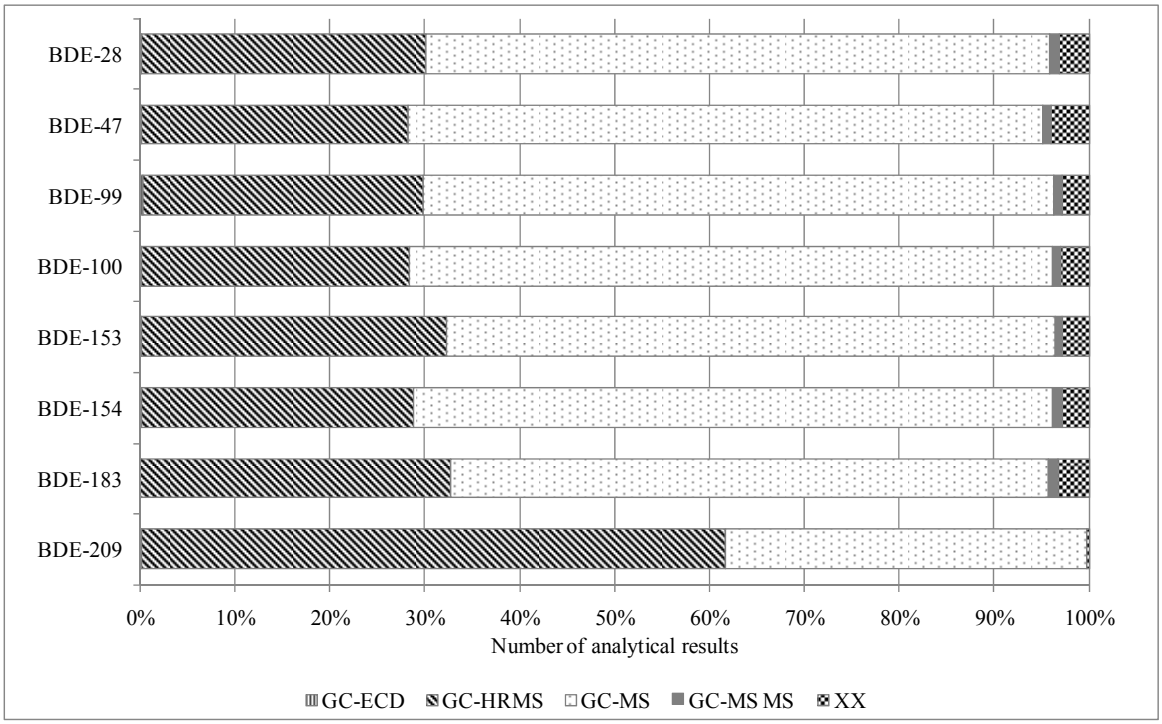

Figure 9: Distribution of the analytical methods reported for the determination of the respective congeners.

According to the specific requirements of the call for data (DCM call for data on BFRs[18]), the analytical results should have been reported accompanied with the percentage of recovery. Most of the data were correctly reported; therefore in order to harmonise the database, the correction for recovery was applied where needed. In some cases the analytical results were reported as not corrected for recovery. As the recovery rate was not provided, the results were used as had been reported.

The LOD and LOQ could vary with the congener analysed (Figure 10), the analytical method used, the food matrix and the reporting laboratory. In Figure 10, the box indicates 25th and 75th percentile with a line at the median, and the ends of the whiskers represent the 5th and 95th percentiles. In order to compare the values reported for LODs across congeners and across different food matrices, all the LODs values have been expressed on wet weight (w.w.).

The lowest LODs were reported for BDE-28 and -47 with medians of 0.0225 and 0.0280 ng/g w.w., respectively. The highest results were reported for BDE-209 with a median LOD of 0.5850 ng/g w.w. which reflects the difficulties in the determination of BDE-209 due to the demanding physical and chemical properties of this congener.

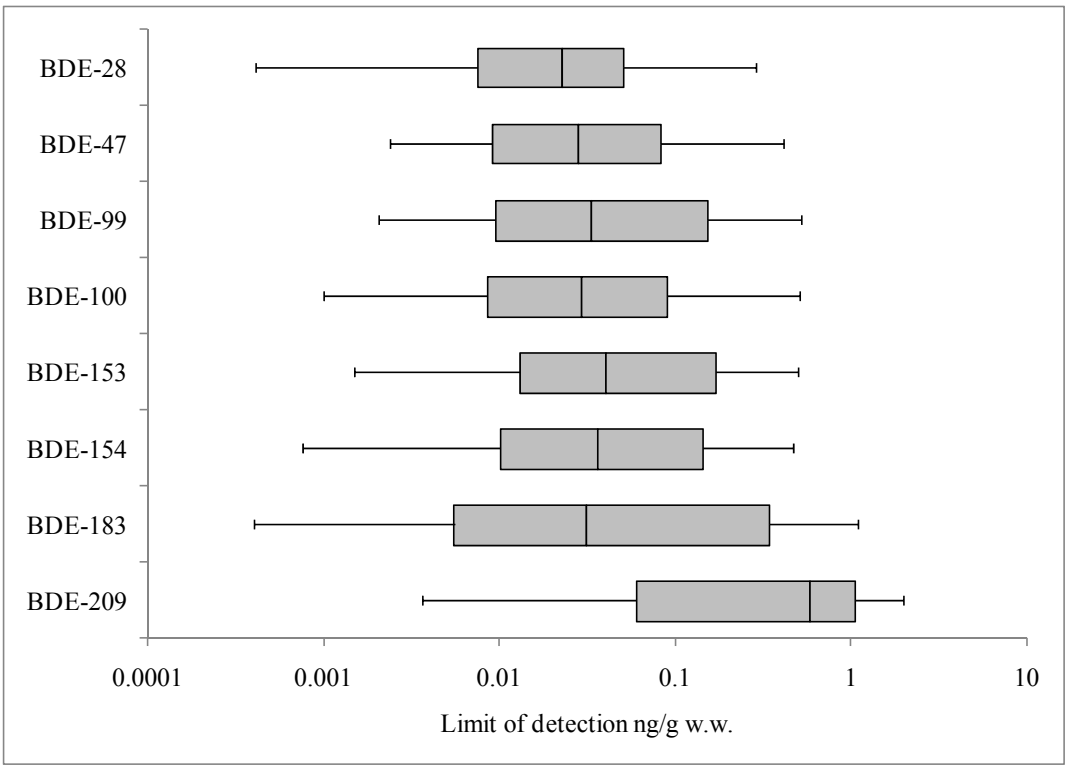

Figure 10: Distribution of the limits of detection (LOD) for the eight congeners considered.

The spread of the LODs reported across food categories should also take into account the variability of the different congener specific LODs within each food category. Particularly for BDE-209, the analytical method performance is different compared with that of the other seven congeners considered, as is shown in Figure 10.

For the median values of the set of seven congeners considered (excluding BDE-209) across food categories (FoodEx level 1), the lowest LODs were found for "Milk and dairy products" with a median of 0.0004 ng/g w.w. The highest LODs were reported for "Animal and vegetable fats and oils", with median of LODs of 0.0500 ng/g w.w. (conversion to wet weight was applied, where needed, to the original reported LOD).

Only in four food categories BDE-209 was not detected ("Meat and meat products": 2 records, "Fish and other seafood": 156 records, "Milk and dairy products": 34 records, "Animal and vegetable fats and oils": 25 records). Reported median LODs are 2 to 20 times higher than those reported for the other seven congeners.

5.1.5. Occurrence data by food category

The number of analytical records reporting quantified values was 56 % out of 26,105 observations across the eight congeners considered, ranging from 5 % for "Starchy roots and tubers" (out of 73 results) to 91 % for "Composite food (including frozen products)" (out of 23 results) (Figure 11).

Similarly, the number of quantified results was inspected for each of the eight congeners considered (Figure 12). The criteria for handling left-censored data which are described in a recently published EFSA report (EFSA, 2010) were applied as a screening tool to the PBDEs database, separately for each combination of PBDE congener and food group (first level of the FoodEx system). These criteria offer guidelines to apply statistical methods to left censored data when the sample size is greater than 50 observations (or there are more than 25 positive samples), and when the percentage of non detects is less than 80 %. In the event these criteria are not met, it is recommended to pool similar food categories to obtain a larger sample size, or to collect additional data.

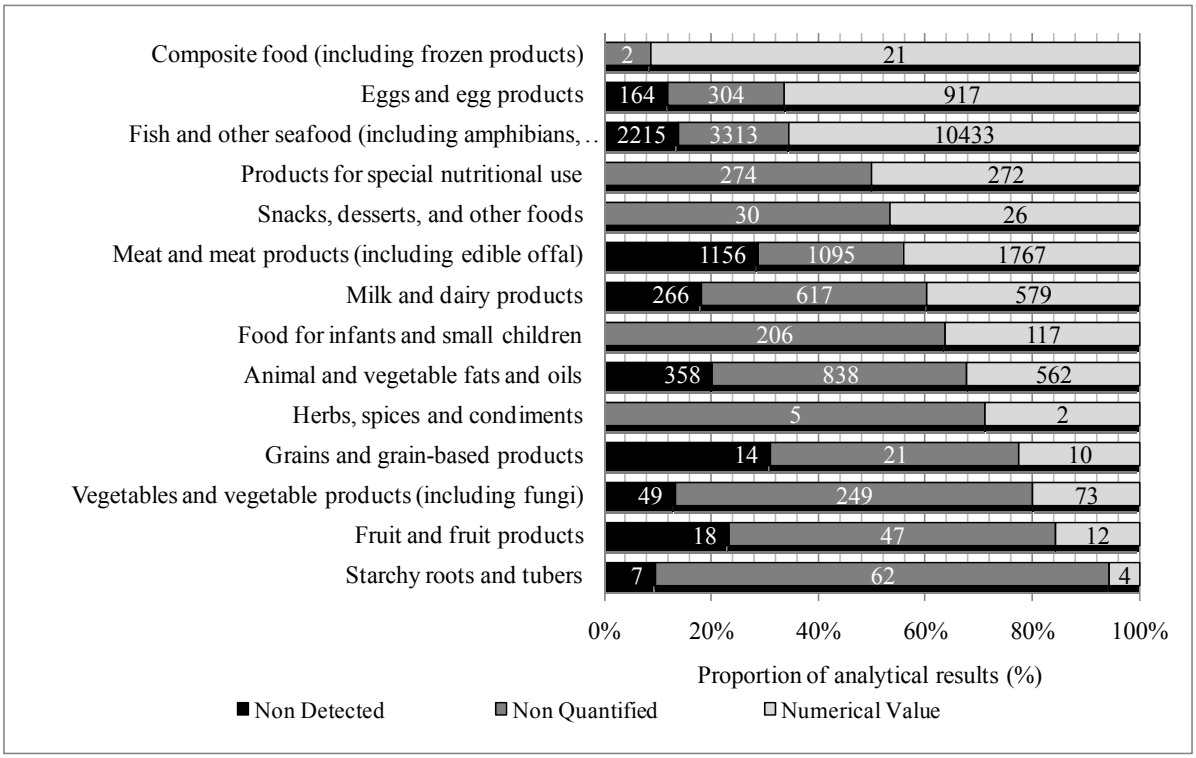

Figure 11: Proportion of non detected, non quantified and quantified analytical results across food categories in the first level (broad food categories) of the FoodEx classification system.

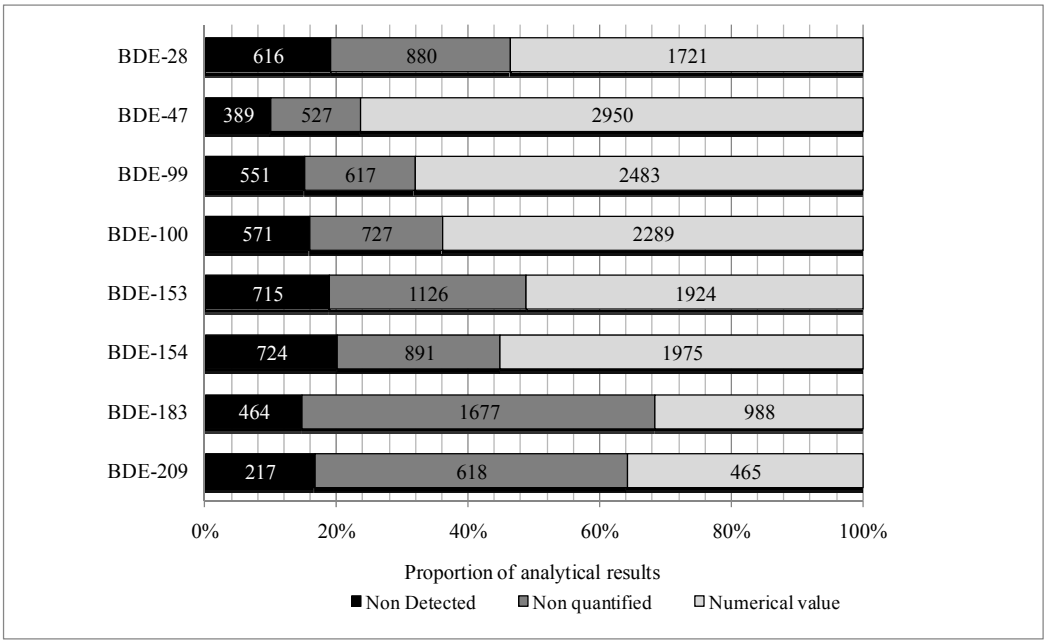

Figure 12: Proportion of non detected, non quantified and quantified analytical results across the eight congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209).

The results of this screening exercise showed that only the broad food categories of "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" met the statistical criteria set in the EFSA report (EFSA, 2010), for most of the congeners.

This finding is supported by literature data, which overall shows substantial evidence of PBDE contamination in food categories of animal origin (Tables A1, A2 and A3**,** in Appendix A), due to the lipophilic nature of those compounds. A previously published exposure assessment (FAO/WHO, 2006), showed that the main contributors to the PBDEs intake were food categories of animal origin similar to the one listed above.

In order to perform an exposure assessment based on relevant occurrence data, the CONTAM Panel decided to focus the exposure estimation for the eight PBDE congeners considered from a restricted list of food categories: "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". The screening exercise was not applied to the food category "Food for infants and small children", as separate intake estimates will be carried out for children.

As mentioned, the criteria described by the EFSA report (EFSA, 2010) were applied for screening purposes of the quality of the occurrence data. Although most of the food categories meet the criteria for most of the congeners and therefore are suitable for handling the left censored data with advanced statistical methods, not all of them have the same quality (based on percentage of observations or measured analytical results, and the percentage of censoring).

Therefore, the left-censored data in the PBDE database were handled in accordance with the guidelines of the WHO-Global Environment Monitoring System-Food Contamination Monitoring and Assessment Programme (GEMS/Food), according to which the lower and upper bounds (LB and UB) approach should be used when the quantified results are below 40 % (WHO, 2003). The LB is obtained by assigning a value of zero (minimum possible value) to all samples reported as lower than the LOD or lower than the LOQ. The UB is obtained by assigning the numerical value of the LOD to

values reported as <LOD, and LOQ to values reported as <LOQ (maximum possible value), depending on whether LOD or LOQ is reported by the laboratory.

All the food samples were classified according to the FoodEx classification system. The spread of the analytical results across the several FoodEx categories and the high percentage of not detected or not quantified analytical results prevented calculation of summary statistics at a very detailed level of the food classification system.

In order to report a description of the level of contamination for the eight congeners considered, Table 11 provides information on the mean occurrence for the food categories at the first level of the FoodEx. The mean fat content (%) calculated on the reported original samples is also reported.

PBDE-levels (mean concentration) are reported on a fat basis (ng/g fat) for the food categories of "Meat and meat products", "Animal and vegetable fats and oils", "Milk and dairy products", "Eggs and egg products", while for "Fish and other seafood", "Products for special nutritional use" and "Food for infants and small children" the concentration is reported on a wet weight basis (ng/g w.w.). In order to harmonise all the analytical results, conversion of the original data was applied, where needed, using the original fat content as reported for each individual sample when available or otherwise by applying the calculated fat content as listed in Table 10.

Since the analysis of the occurrence data is based on a restricted list of food categories, the data set of PBDEs includes only 3,933 samples (out of 3,971), of which 25,824 analytical results were reported for at least one of the eight PBDE congeners considered.

Eggs and egg products

In the food category "Eggs and egg products" (ng/g fat) 212 total samples were tested. The proportion of not detected and not quantified results is relatively low, around 30 % for all the congeners, with the exception of BDE-28 where it reaches 67 %. The highest mean concentration was registered for BDE-209 (122 samples) with 3.40 and 3.98 ng/g fat for LB and UB, respectively, while the lowest mean was calculated on samples tested for BDE-28 and BDE-183 (0.01 and 0.09 ng/g fat for LB and UB, and 0.04 and 0.07 ng/g fat for LB and UB, respectively).

Milk and dairy products

The food category "Milk and dairy products" (ng/g fat) was represented by 217 samples. Liquid milk (149 samples) and cheese (57 samples) were the two main sub-categories representing the dairy products. The reported fat content varied considerably from 3.5 to 26 % for liquid milk and cheese, respectively. All PBDE congeners had higher concentrations in cheese products, reaching on average more than double the values reported for liquid milk (data not shown). In the broad food category "Milk and dairy products" the highest mean concentration was measured for BDE-209 reaching 0.3 and 1.69 ng/g fat for LB and UB, respectively.

Table 11: Statistical description of concentrations of BDE-28, -47, -99, -100, -153, -154, -183 and -209, calculated on 25,824 analytical records (3,933 samples) across eight broad food categories of the FoodEx food classification system. PBDE levels (mean concentration) are reported on a fat (ng/g fat) or wet weight basis (ng/g w.w.) according to the different food categories. The mean fat content calculated from the original samples is also reported (%). n: number of results reported. The column ND indicates the percentage of results below the LOD or the LOQ.

		PBDE congeners																								
		BDE-28[a]			BDE-47			BDE-99			BDE-100			BDE-153[a]			BDE-154			BDE-183			BDE-209			Mean (%)
Food categories (FoodEx_Level 1)	**TYPE**	**n**	**MEAN**	**ND**	**n**	**MEAN**	**ND**	**n**	**MEAN**	**ND**	**n**	**MEAN**	**ND**	**n**	**MEAN**	**ND**	**n**	**MEAN**	**ND**	**n**	**MEAN**	**ND**	**n**	**MEAN**	**ND**	**fat in original sample**
Results expressed on a fat basis (ng/g fat)																										
Eggs and egg products	LB	167	0.01	67%	192	0.88	33%	179	3.12	22%	176	0.98	27%	216	0.67	20%	177	0.33	38%	156	0.04	35%	122	3.40	33%	13.5
	UB	167	0.09	67%	192	1.30	33%	179	3.20	22%	176	1.06	27%	216	0.74	20%	177	0.42	38%	156	0.07	35%	122	3.98	33%	13.5
Milk and dairy products	LB	163	0.00	79%	187	0.13	38%	186	0.09	39%	185	0.01	54%	206	0.02	48%	185	0.01	72%	187	0.01	82%	163	0.30	76%	10.9
	UB	163	0.06	79%	187	0.20	38%	186	0.17	39%	185	0.09	54%	206	0.13	48%	185	0.13	72%	187	0.14	82%	163	1.69	76%	10.9
Meat and meat products (including edible offal)	LB	546	0.00	79%	573	0.24	48%	569	0.18	45%	553	0.06	60%	638	0.03	51%	570	0.01	66%	341	0.03	48%	228	1.14	41%	8.38
	UB	546	0.30	79%	573	0.52	48%	569	0.44	45%	553	0.33	60%	638	0.28	51%	570	0.28	66%	341	0.08	48%	228	2.83	41%	8.38
Animal and vegetable fats and oils	LB	207	0.00	96%	235	0.07	45%	235	0.08	44%	235	0.01	69%	235	0.03	60%	235	0.01	73%	210	0.02	81%	166	0.21	87%	87.6
	UB	207	0.12	96%	235	0.18	45%	235	0.19	44%	235	0.13	69%	235	0.18	60%	235	0.16	73%	210	0.14	81%	166	1.50	87%	87.6
Results expressed on a wet weight basis (ng/g w.w.)																										
Fish and other seafood (including amphibians, reptiles, snails and insects)	LB	1986	0.06	27%	2472	1.30	12%	2275	0.13	26%	2231	0.33	24%	2264	0.03	48%	2264	0.03	48%	2030	0.01	70%	487	0.04	71%	9.58
	UB	1986	0.07	27%	2472	1.32	12%	2275	0.17	26%	2231	0.36	24%	2264	0.07	48%	2264	0.07	48%	2030	0.08	70%	487	0.40	71%	9.58
Products for special nutritional use	LB	70	0.06	54%	75	1.78	20%	75	0.31	31%	75	0.30	43%	75	0.05	53%	75	0.05	53%	75	0.00	93%	26	2.22	73%	74.8
	UB	70	0.09	54%	75	1.79	20%	75	0.34	31%	75	0.33	43%	75	0.12	53%	75	0.12	53%	75	0.07	93%	26	2.73	73%	74.8
Food for infants and small children	LB	36	0.00	75%	42	0.21	36%	42	0.08	43%	42	0.02	64%	41	0.00	80%	41	0.00	80%	42	0.00	93%	36	0.12	44%	4.42
	UB	36	0.00	75%	42	0.21	36%	42	0.08	43%	42	0.02	64%	41	0.01	80%	41	0.01	80%	42	0.00	93%	36	0.13	44%	4.42

(a): Replicates of analysis within one sample were reported in some cases. For this reason, the total number of individual samples does not always correspond with the total analytical results reported in this table.

Meat and meat products (including edible offal)

In the food category "Meat and meat products (including edible offal, ng/g fat)" a total of 588 samples were analysed. The proportion of not detected or not quantified results varies from 41 % for BDE-209, to 79 % for BDE-28. The levels of BDE-209 are also the highest (1.14 and 2.83 ng/g fat for LB and UB, respectively). The concentration (mean UB) of the other PBDE congeners ranges from 0.08 ng/g fat for BDE-183 to 0.52 ng/g fat for BDE-47. Looking at a more detailed food classification (third level of the FoodEx), 20 meat samples analysed in 2003 from rabbit, goose and duck were reported to contain levels of BDE-28, -47, -99, -100, -153 and -154 ten times higher than the average of other meat products and therefore raising the levels of the respective congeners in the broad food categories.

Animal and vegetable fats and oils

The food categories "Animal and vegetable fats and oils" (ng/g fat) consists of 277 samples. The products of "Animal fat" cover most of the samples analysed (218 samples) followed by "Vegetable oil" (46 samples), less than 5 samples were tested for the food groups of "Margarine and similar products", "Fish oil" and "Vegetable fat". The mean UB concentration measured for all the congeners varies from 0.12 to 1.50 ng/g fat. The highest concentration was measured for BDE-209.

Fish and other seafood (including amphibians, reptiles, snails and insects)

Most of the PBDE data collected belong to the food category of "Fish and other seafood (including amphibians, reptiles, snails and insects" (ng/g w.w.) with 2,473 samples analysed. The proportion of not detected or not quantified results is relatively low, varying from 12 % for BDE-47, to 71 % for BDE-209. The highest mean LB and UB levels were reported for BDE-47 with 1.30 and 1.32 ng/g w.w., respectively, followed by BDE-100 with 0.33 and 0.36 ng/g w.w., respectively. The corresponding mean LB and UB levels for BDE-209 were determined as 0.04 and 0.40 ng/g w.w., respectively.

For comparison, Figure 13 describes in detail the UB levels of BDE-47 and -209 across the fish species reported in the current database. Eel and herring were the two fish species that resulted in the highest levels for both BDE-47 and -209.

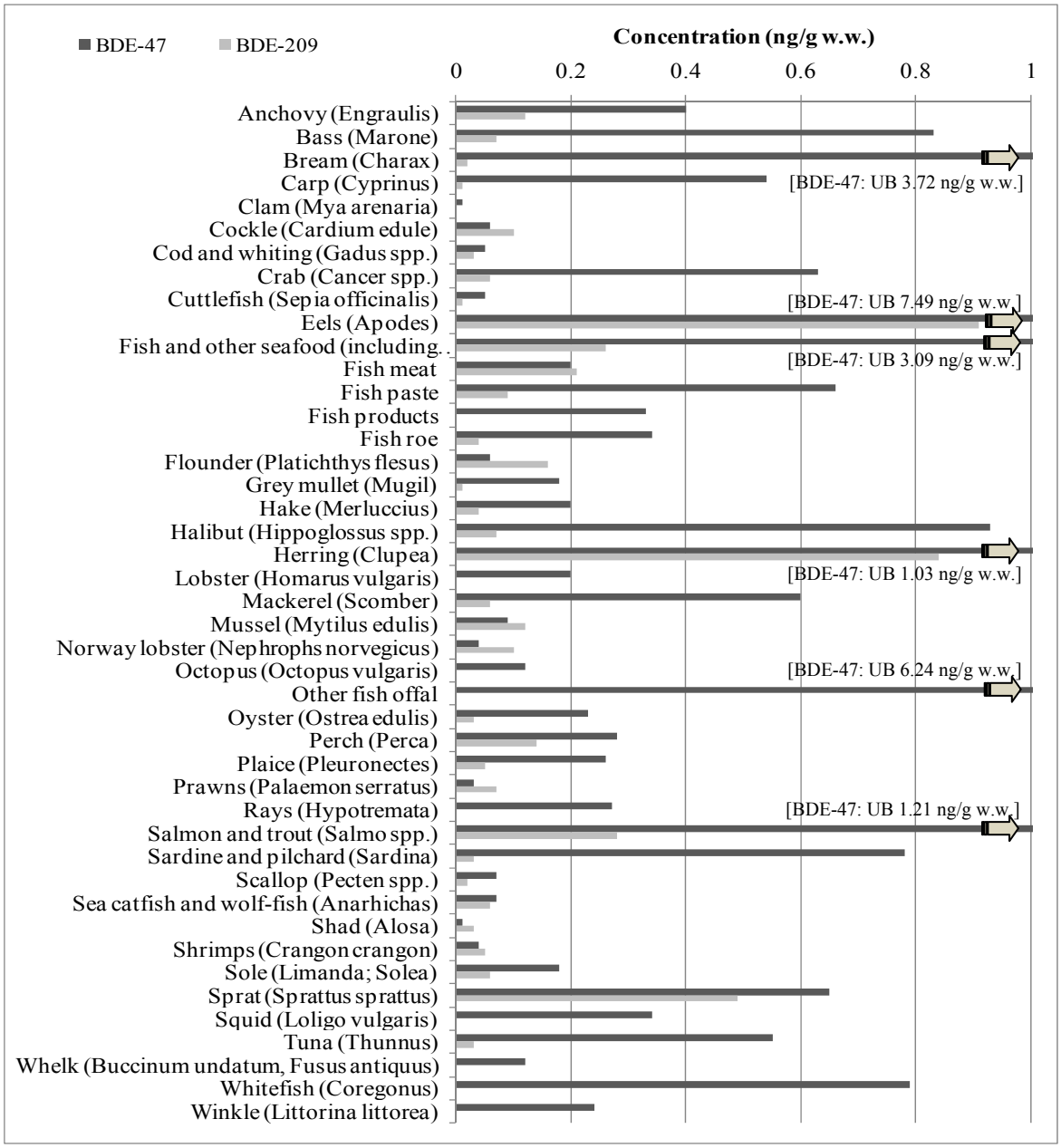

Figure 13: Mean upper bound levels (ng/g w.w.) for BDE-47 and -209 across the reported fish species. The arrows on a figure indicate that the respective level exceeds the scale of the concentration. In brackets the actual values are reported.

Table 12 shows the average fat content (%) calculated on the reported fat percentage in the original fish samples. A detailed analysis of the occurrence data reported by fish species (food category "Fish meat"), highlights the relationship between the fat content of fish and the contamination level of certain PBDEs. Depending on the fat content reported, three ranges of fat content were defined (more than 8 %, between 2 and 8 % and lower than 2 %). The mean occurrence (ng/g w.w.) of the analysed PBDE congeners was estimated for each group of samples falling into the three different ranges of fat content (Table 13). The results indicate a relationship between the PBDE levels and the fat content of the different fish species.

In almost all cases, an increasing fat content corresponds with increasing PBDE contamination levels. Especially in the case of BDE-47 and -100 in fish with a fat content higher than 8 %, contamination levels are almost double than those of fish with a fat content between 2 and 8 % and more than 10 times higher in the case of fish species with a fat content below 2 %. BDE-209 shows a different

behaviour with LB and UB concentrations being slightly lower for the group of fish with 8 % fat content compared to the group with 2 to 8 % fat content. A 10 fold difference in occurrence values is reported only for fish with less then 2 % fat content. However, the considerable differences between mean LB and UB concentrations for BDE-209 should be taken into account when interpreting this finding.

Table 12: Average fat content (%) calculated on the reported fat percentage in the original samples of the current database on PBDEs. Data reported refer to the samples classified according to the fish species available at the third level of the FoodEx system (from "Fish meat").

Fish species (FoodEx third level)	Fat content (%)
Eels	19.8
Mackerel	11.1
Sprat	10.3
Anchovy	10.2
Sardine and pilchard	10.1
Salmon and trout	8.4
Halibut	8.2
Herring	7.2
Bream	6.0
Tuna	5.5
Whitefish	4.6
Grey mullet	4.3
Carp	3.8
Sea catfish and wolf-fish	3.3
Flounder	3.1
Fish meat	3.1
Bass	2.8
Plaice	2.4
Perch	2.2
Rays	1.2
Sole	0.93
Cod and whiting	0.81
Hake	0.79

Table 13: Mean concentrations of the eight PBDE congeners considered analysed in the FoodEx food category "Fish Meat" across three groups of fish species defined according to the respective fat content. Lower (LB) and upper bound (UB) mean values shown are expressed on a wet weight basis.

	Mean occurrence values (ng/g w.w.)					
PBDE congeners	**≥8 % fat**		**8 % < fat > 2 %**		**≤ 2 % fat**	
	LB	UB	LB	UB	LB	UB
BDE-28	0.05	0.09	0.04	0.04	< 0.01	0.01
BDE-47	1.96	2.06	0.95	0.97	0.13	0.14
BDE-99	0.19	0.29	0.18	0.23	0.03	0.03
BDE-100	0.70	0.80	0.22	0.27	0.02	0.03
BDE-153	0.08	0.18	0.02	0.06	< 0.01	0.01
BDE-154	0.12	0.23	0.09	0.12	0.01	0.01
BDE-183	0.05	0.22	0.01	0.09	< 0.01	0.01
BDE-209	0.04	0.68	0.05	0.50	0.03	0.06

Products for special nutritional use

Of the food categories "Products for special nutritional use" (ng/g w.w.) 76 samples were analysed and they mainly belong to the group of the "Supplements containing special fatty acids like omega-3 or essential fatty acids" (54 samples). The highest mean values were measured for BDE-47 (1.78 and 1.79 ng/g w.w. for LB and UB mean) and BDE-209 (2.22 and 2.73 ng/g w.w. for LB and UB mean), with proportions of not detected or not quantified of 20 and 73 %, respectively.

Food for infants and small children

"Food for infants and small children" (ng/g w.w.) comprises 42 samples of which 29 were described as "Ready-to-eat meal for infants and young children", eight as "infant formulae" and "follow on formulae", two as "Cereal based food for infants and young children" and the remaining ones as "Food for infants and small children (non specified)". The proportion of not detected and not quantified results varies from 36 % for BDE-47 to 93 % for BDE-183. The levels of BDE-47 and -209 are the highest among the different congeners analysed with UB means of 0.21 and 0.13 ng/g w.w., respectively. It is important to notice that the occurrence mean values for BDE-99 in the category of "Food for infants and small children" are influenced by a unique sample which is almost 40 times higher than the average in the category. Therefore the LB and UB mean concentration for this food category could be overestimated.

Vegetables and vegetable products (including fungi)

In the "Vegetables and vegetable products (including fungi)" (ng/g w.w.) category in total 52 samples were analysed and low occurrence values were reported for all the congeners. Due to the low number of samples and the high proportion of non detects, these results are not listed in Table 11. The highest concentration were measured in BDE-209 with a mean UB concentration tested on 44 samples of 0.15 ng/g w.w. Looking at the second level of the FoodEx, the ten highest concentrations were measured in the category of leaf and root vegetables, ranging from 4 to 67 ng/g w.w. (data not shown), confirming the data reported in a published Japanese study (Ohta et al., 2002).

5.1.6. Study of the occurrence data in a specific sub-set of samples

The current PBDE database consists of 25,824 analytical results reported by the testing of 3,933 food samples for the levels of at least one of the eight congeners considered (BDE-28,- 47,- 99, -100, -153, -154, -183 and -209).

A specific study was carried out on a restricted set of samples. The sub-set consisted of those food samples in which the levels of seven selected congeners (BDE-28, -47, -99, -100, -153, -154 and -183) were simultaneously analysed. In 2,630 food samples, analytical results were reported for the seven congeners simultaneously, therefore resulting in 18,410 observations. To study the relationships between the different PBDE congeners, the relative contribution of the seven individual compounds (BDE-28, -47, -99, -100, -153, -154 and -183) to the concentration of the respective sum were calculated per food category for LB and UB mean values (Figures 14 and 15).

In order to allow a comprehensive comparison of the occurrence values of PBDE congeners in 3,933 or 2,630 samples across food categories (eight broad food categories of the FoodEx food classification system), the statistical descriptors were estimated and reported in Table B5 (Appendix B). The overall contamination of PBDEs across food categories was also estimated for the sub-set of samples (2,630 samples) as the sum of the seven congeners analysed simultaneously.

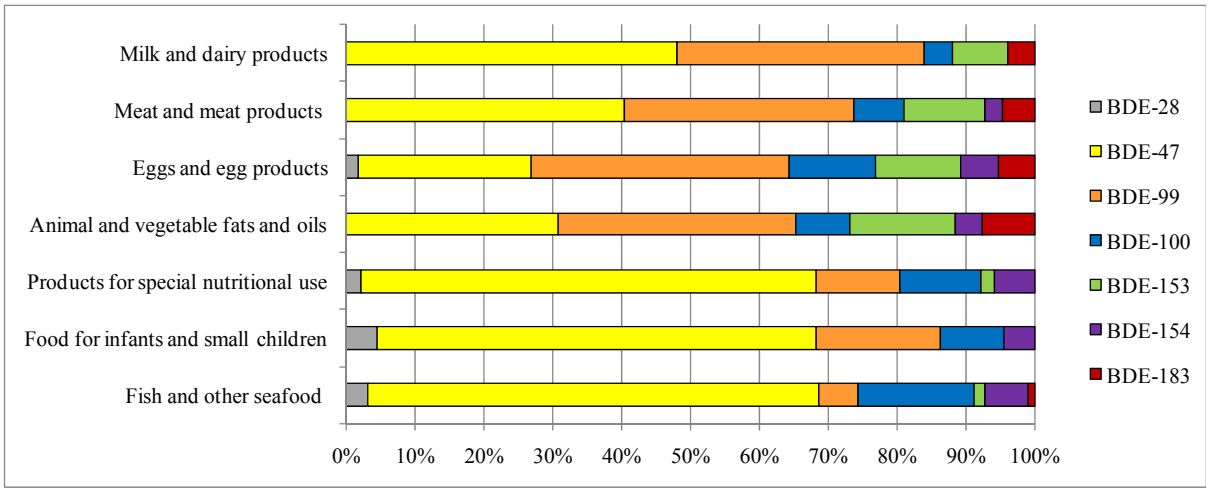

Figure 14: Mean lower bound (LB) relative contribution of the seven selected congeners (BDE-28, -47, -99, -100, -153, -154 and -183) across the eight selected FoodEx food categories (first level), for 2,630 samples.

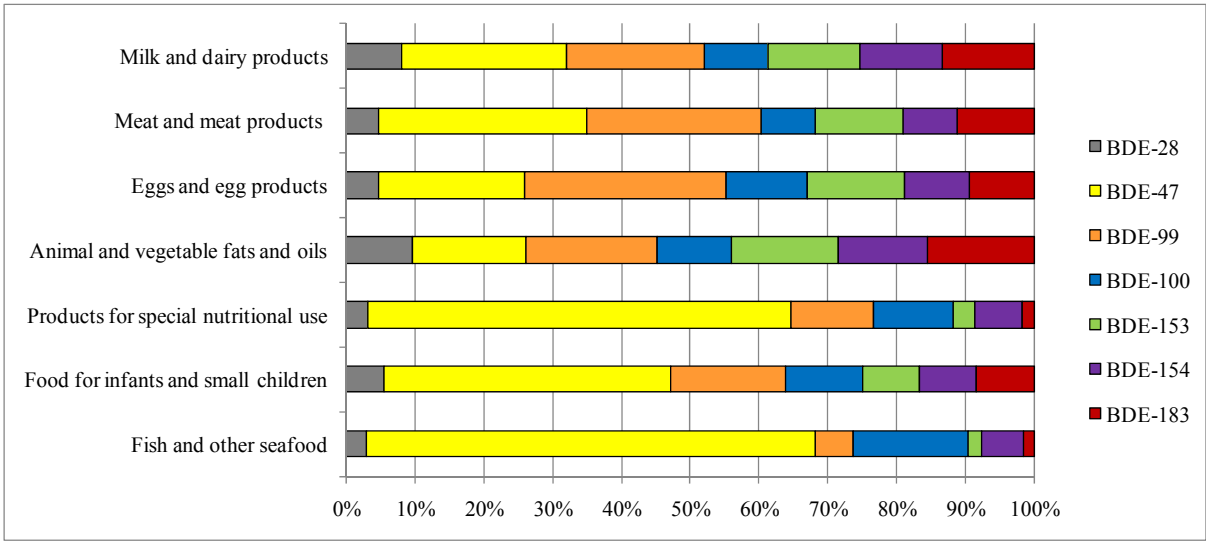

Figure 15: Mean upper bound (UB) relative contribution of the seven selected congeners (BDE-28, -47, -99, -100, -153, -154 and -183) across the eight selected FoodEx food categories (first level), for 2,630 samples.

Due to the high proportion of not detected or not quantified results, variability between mean LB and UB for many congeners was observed.

As reported in the literature (e.g. DVFA, 2003; van Leeuwen et al., 2008) the congener primarily contributing to the concentration of PBDEs in fish and seafood is BDE-47. The same refers to the food category "products for special nutritional use" mainly represented by "Supplements containing special fatty acids like omega-3 or essential fatty acids" (described as "cod liver based products").

As PBDEs are chemically stable lipophilic substances and assuming a similar occurrence distribution as for dioxins, for reasons of comparison, an additional food classification system was applied to the current reported samples. In Table B1 (Appendix B) the table of the occurrence values of the seven selected congeners and the respective sum is reported following the food categories defined by Commission Regulation (EC) No. 1881/2006, Annex Section 5, on setting maximum levels for certain

contaminants in foodstuffs. The food categories of "Other products" (ng/g w.w.) and "Infant and baby food" (ng/g w.w.) were added to include all those products addressed respectively to adult and to children that could not be classified according to the food categories defined in the Commission Regulation.

Additionally, for illustrative purposes, in Table B2, B3 and B4 (Appendix B) the highest percentiles (90^{th}, 95^{th}, 99^{th} percentiles) of occurrence are reported for the seven selected congeners individually and as a sum as well as for BDE-209, across the food categories as defined by the above legislation on dioxins, furans and PCBs.

5.1.7. Trends and occurrence data

Figure 16 shows the temporal trend for PBDEs in muscle from herring of the Northern Baltic Proper between 1999 and 2008. Each dot represents the annual geometric mean of 12 individual analyses. The trend lines are smoothers based on a simple 3-point running mean smoother fitted to the annual geometric mean values. While BDE-47, -99 and -100 show significant linear downward trends ($p<0.02$, 0.01 and 0.02, respectively), no significant linear trend was found for BDE-153 and -154.

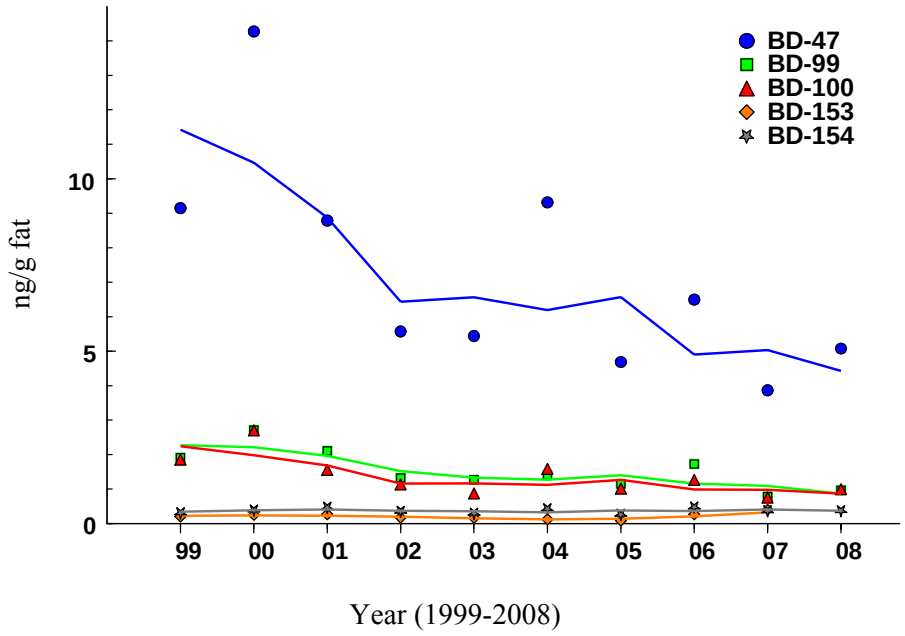

Figure 16: Temporal trends for PBDEs (ng/g fat) in herring muscle, Northern Baltic Proper during 1999-2008. Data compiled by A. Bignert based on Bignert et al. (2010). Each dot represents the annual geometric mean of 12 individual analyses for each year. The trend lines are smoothers based on 3-point running mean smoother fitted to the annual geometric mean values.

Table 14 shows the concentrations of seven PBDE congeners (without BDE-209) in 187 cod liver samples collected and analysed between 2006 and 2008 in the Norwegian Sea and Barents Sea. In the Norwegian Sea, the concentration for all congeners in samples from 2008 are considerably lower than in samples from 2006. This is especially true for the predominant congener BDE-47 where the mean levels in samples from 2008 are more than 50 % lower compared to samples from 2006.

Table 14: Lower (LB) and upper bound (UB) mean occurrence (ng/g w.w.) of seven PBDEs (BDE-28, -47, -99, -100, -153, -154 and -183) in cod liver between 2006-2008 in two different fishing areas (Barents Sea and Norwegian Sea) around Norway.

BARENTS SEA	***year of sampling***								
	2006			**2007**			**2008**		
n samples	27			25			48		
PBDE congeners	ND (%)	LB	UB	ND (%)	LB	UB	ND (%)	LB	UB
BDE-28	0	0.15	0.15	0	0.32	0.32	0	0.22	0.22
BDE-47	0	3.11	3.11	0	4.73	4.73	0	2.56	2.56
BDE-99	0	0.06	0.06	0	0.11	0.11	0	0.06	0.06
BDE-100	0	0.36	0.36	0	0.6	0.6	0	0.36	0.36
BDE-153	63	0.03	0.04	92	0	0.01	52	0.01	0.01
BDE-154	0	0.17	0.17	0	0.35	0.35	0	0.24	0.24
BDE-183	85	0	0.01	100	0	0.01	85	0	0.01

NORWEGIAN SEA	***year of sampling***					
	2006			**2008**		
n samples	25			48		
PBDE congeners	ND (%)	LB	UB	ND (%)	LB	UB
BDE-28	0	0.64	0.64	0	0.24	0.24
BDE-47	0	12.27	12.27	0	3.29	3.29
BDE-99	0	0.22	0.22	0	0.08	0.08
BDE-100	0	1.43	1.43	0	0.45	0.45
BDE-153	0	0.04	0.04	56	0.01	0.01
BDE-154	0	0.68	0.68	0	0.25	0.25
BDE-183	20	0.07	0.08	79	0	0.01

5.1.8. Summary of occurrence

Table 15 summarises the occurrence values for each of the eight congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) that are used for the exposure assessment. The occurrence values reported are calculated on 25,824 analytical records (3,933 samples) across eight broad food categories of the FoodEx food classification system. All PBDE levels (mean concentration) are reported on wet weight basis (ng/g w.w.). Where needed, conversion from fat weight to wet weight basis was applied as described in Chapter 5.3.3.

Table 15: Occurrence means for the eight congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) across eight broad food categories of the FoodEx food classification system that are used for the exposure assessment. The occurrence values reported are calculated on 25,824 analytical records (3,933 samples). Lower (LB) and upper bound (UB) mean values shown are expressed on a wet weight basis. Due to this conversion three figures are shown behind the decimal point.

Food categories (FoodEx_Level 1)		Mean occurrence values (ng/g w.w.)							
	TYPE	BDE -28	BDE -47	BDE -99	BDE -100	BDE -153	BDE -154	BDE -183	BDE -209
Eggs and egg products	LB	0.000	0.080	0.271	0.081	0.060	0.030	0.007	0.329
	UB	0.011	0.116	0.280	0.089	0.067	0.038	0.012	0.386
Milk and dairy products	LB	0.000	0.010	0.009	0.001	0.001	0.000	0.000	0.021
	UB	0.010	0.026	0.024	0.017	0.028	0.030	0.030	0.111
Meat and meat products (including edible offal)	LB	0.000	0.009	0.008	0.003	0.002	0.001	0.002	0.035
	UB	0.024	0.032	0.031	0.025	0.022	0.023	0.005	0.092
Animal and vegetable fats and oils	LB	0.002	0.060	0.063	0.011	0.026	0.006	0.014	0.175
	UB	0.105	0.158	0.161	0.116	0.157	0.142	0.131	1.318
Fish and other seafood (including amphibians, reptiles, snails and insects)	LB	0.056	1.299	0.132	0.326	0.029	0.113	0.014	0.044
	UB	0.069	1.324	0.170	0.364	0.066	0.149	0.075	0.401
Products for special nutritional use	LB	0.064	1.776	0.308	0.295	0.051	0.172	0.001	2.222
	UB	0.087	1.789	0.342	0.329	0.116	0.223	0.074	2.735
Food for infants and small children	LB	0.001	0.207	0.076	0.021	0.002	0.005	0.002	0.115
	UB	0.002	0.208	0.078	0.023	0.006	0.007	0.005	0.127
Vegetables and vegetable products (including fungi)	LB	0.000	0.001	0.000	0.000	0.001	0.000	0.000	0.125
	UB	0.004	0.004	0.004	0.002	0.002	0.002	0.002	0.153

5.2. Previously reported literature data on PBDEs occurrence

5.2.1. Occurrence in food

5.2.1.1. Fish

PBDEs are found in fish and seafood worldwide as they accumulate in both wild-caught species and farmed species. There is an extensive amount of data reported in the literature on levels in fish worldwide, and therefore only a selection was included in the table focusing on wild caught fish and seafood from Europe as it was assumed that this would best reflect the fish and seafood related dietary exposure of European citizens (Table A1, Appendix A). Data were included to cover Europe to a large degree (geographically), and to cover fish and seafood from various water bodies such as lakes and rivers, European seas like the Baltic Sea, Mediterranean Sea and North Sea, and the Atlantic Ocean. Some farmed fish is imported from outside Europe (e.g. salmon from Chile, tilapia from Ecuador and pangasius from Vietnam) (van Leeuwen et al., 2009) and therefore, data on these imported species are also included. Data on the commonly reported BDE-28, -47, -99, -100, -153, -154, -183 and -209 were included, although in several studies, a larger set of congeners was reported.

Fatty fish generally contained higher levels than lean fish (Leblanc et al., 2006). Herring and eel showed levels of up to 379 ng/g wet weight (w.w.) (DVFA, 2003; van Leeuwen and de Boer, 2008). Eel is well-known for its high contaminant levels, especially when caught in main rivers in industrialised areas. High levels were also observed in brown trout fillets from Lake Mjøsa, which is a highly contaminated lake in Norway. The sum of BDE-28, -47, -49, -66, -99, -100, -119, -153 and -154 amounted to 407±210 ng/g w.w. (Mariussen et al., 2008). Lean marine species such as cod, hake and sole contained often lower PBDE levels, especially when originating from the Atlantic Ocean (Domingo et al., 2008; Voorspoels et al., 2007). Mussels and shrimp also contained low PBDE levels (generally below 1 ng/g w.w., except for shrimp from the North Sea and blue mussels from France).

Among the farmed species, farmed salmon contained higher levels (up to 4.1 ng/g w.w.) than e.g. shrimp, tilapia and pangasius (up to 0.16 ng/g w.w.).

5.2.1.2. Food samples other than fish

Data on PBDE occurrence in food samples other than fish in European countries were explored through the literature. The number of studies found was small compared to those found for fish and seafood. Table A2 and A3 (Appendix A) summarise the results of studies conducted in the period 2003-2009 in meat and meat products, eggs, milk and dairy products and oils and fats, including fish or vegetable oil supplements. The food samples most frequently analyzed were eggs, meat (bovine and pork meat) and dairy products (milk and butter). Concentrations in elk and reindeer meat were reported in two studies (Kiviranta et al., 2006; Suutari et al., 2011), and Kotz et al. (2006) reported concentrations in kale.

PBDE concentrations were often expressed in ng/g fat and rarely in pg/g w.w. The majority of the studies reported both the median and the range of PBDEs concentration in the samples. For a number of studies the congener specific concentrations were not available, but the sum of a number of PBDEs. The following eight PBDE congeners BDE-28, -47, -99, -100, -153, -154, -183 and -209 were found to be the ones analysed in most of the studies.

Results from different studies need to be compared with caution due to different methodologies, different congeners analysed and different ways of expressing results, e.g. LB or UB approach. Taking this into account, BDE-47 and -99 were the most abundant congeners in those meat samples for which congener specific concentrations were available (median BDE-47: 0.00873-0.0227 ng/g w.w.; median BDE-99: 0.0093-0.025 ng/g w.w.). In lamb liver, a similar pattern was observed, with median concentrations of 0.142 ng/g fat and 0.120 ng/g fat for BDE-47 and -99, respectively (Table A2). BDE-209, when analysed and reported, showed concentrations between 0.00794-0.0116 ng/g fat.

In eggs, dairy products and oils, BDE-47 followed by BDE-99 were the most abundant congeners. Covaci et al. (2009) studied the seasonal variability of PBDEs in home-produced eggs showing in general higher values in autumn (median BDE-47: 0.28 ng/g fat, median BDE-99: 0.33 ng/g fat) than in spring (median BDE-47 and BDE-99: <0.15 ng/g fat) (Table A3). Milk showed maximum values of 0.0347 and 0.0198 ng/g fat for BDE-47 and BDE-99, respectively. Butter, cheese and cream samples showed a similar pattern, with maximum values of 0.0509 and 0.0223 ng/g fat for BDE-47 and BDE-99, respectively.

In fish or vegetable oils/supplements, the congener profile was dominated by BDE-47, -99 and -100. Jacobs et al. (2004) analysed dietary supplements rich in omega-3 fatty acids such as cod liver oil, whole body fish oil, vegetable and fish oil combinations and pure vegetable oils. The PBDE levels in cod liver oil were the highest and ranged from 14.6 to 34.2 ng/g fat. The other fish and fish/vegetable oils showed lower levels than the cod liver oil (0.8-2.7 ng/g fat for fish oil, and-1.9 ng/g fat for fish/vegetable oils). No PBDEs were detected in the pure vegetable oils (Table A3).

Nineteen composite food group samples collected from the 2003 and 2004 total diet studies in the UK (FSA, 2006) were analysed for seventeen PBDE congeners (BDE-17, -28, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -153, -154, -183 and -209). Meat products showed the highest concentrations, with BDE-209 as the predominant congener (3.64 ng/g w.w.). Except for canned vegetables and fish, BDE-209 was also the most abundant congener followed by BDE-47, -99 and -153 in the remaining composite food samples.

5.2.2. Occurrence in human milk

In 1999, Meironyté et al. reported on a time-related trend study on eight PBDEs in pooled Swedish human milk samples collected and archived between 1972 and 1997 (Meironyté et al., 1999). The

results indicated that the PBDE concentrations in Swedish human milk almost doubled every four years between 1972 and 1997. This finding initiated numerous studies worldwide on the contamination of human milk with PBDEs and the parameters that influence their levels. Table 16 summarises results from studies on PBDE levels in human milk from different European countries. Except for a few results all data represent mean values given as ng/g fat. The table indicates that the number of congeners analysed differs from study to study. While all studies reported on the occurrence of BDE-47, -99, -100 and -153, fewer studies covered BDE-28, -154 and -183, and only seven studies reported BDE-209 concentrations in human milk samples from European countries. Some papers reported additional congeners.

The average concentrations of the predominant PBDE congeners in human milk are rather comparable across various European countries. BDE-47 was the most predominant congener with mean concentrations across countries of 0.14-3.0 ng/g fat. The mean concentration of BDE-99 across European countries was <0.03-1.1 ng/g fat, and of BDE-153 it was 0.10-2.4 ng/g fat. However, the individual contamination may differ considerably as indicated by the wide concentration ranges for several PBDEs from various countries.

BDE-209 was analysed in seven studies with mean concentrations between 0.21 and 2.8 ng/g fat.

Compared to human milk samples from the USA and Canada (Hites, 2004; Frederiksen et al., 2009a), the current mean contamination of human milk from various European countries is at least one order of magnitude lower. Moreover, the samples from the USA and Canada often show somewhat different congener profiles which might be an indication that the exposure pathways differ from those in Europe.

Parameters that influence the PBDE levels in human milk

Vieth et al. (2005) investigated the impact of consumption habits and the duration of breast feeding on the levels in human milk. They showed that the PBDE levels in human milk decrease with the number of breast-fed babies. However, a reduction in the PBDE level was not observed after a 3-month breast-feeding period, possibly because the time period was too short. Age, body-mass-index, computer and television display screen exposure and also smoking status of the mother were not found to be influencing factors. Significant lower PBDE concentrations were found in the milk of mothers eating vegetarian diets compared to women who also consume animal products (Vieth et al., 2005). In contrast, a statistically significant association between the PBDE levels and the frequency of eating food of animal origin was not found by Raab et al. (2008).

PBDE levels in human milk over time

Meironyté et al. (1999) were the first to show an increasing trend of PBDE concentrations in human milk between 1972 and 1997. Pooled samples from 1972, 1976, 1980, 1984/1985, 1990, 1994, 1996 and 1997 contained concentrations for the sum of the eight PBDE congeners BDE-28, -47, -66, -85, -99, -100, -153 and -154 of 0.07, 0.35, 0.48, 0.73, 1.21, 2.17, 3.11 and 4.02 ng/g fat. Thus, the concentration of PBDEs in Swedish human milk almost doubled every 4 years. The major contributor was BDE-47 with respective concentrations of 0.06, 0.18, 0.28, 0.49, 0.81, 1.48, 2.08 and 2.28 ng/g fat. Obviously the peak of contamination was at the end of the 1990s as 15 individual Swedish human milk samples collected in 2000-2001 contained median concentrations of 2.14 ng/g fat and 1.15 ng/g fat for the sum of the eight PBDE congeners and BDE-47, respectively (Guvenius et al., 2003). According to data from the Swedish monitoring program, the sum of the eight PBDE congeners showed mean levels of 2.7, 2.0 and 2.5 ng/g fat from the years 2003, 2004 and 2007, respectively. A comparable trend was found by Fängström et al. (2008) who analysed pooled human milk samples from Sweden between 1980 and 2004. The levels for BDE-47 as the predominant congener continuously increased from 0.14 to 2.24 ng/g fat between 1980 and 1995 and then decreased to 0.92 ng/g fat in 2004. For BDE-153 the concentrations increased between 1980 and 2001 from 0.05 ng/g fat to 1.35 ng/g fat and then decreased to 0.90 ng/g fat in 2004 (Fängström et al., 2008). The

levels of BDE-47 in individual Swedish human milk samples from 2007 (n=10, Stockholm) were 0.32-2.1 ng/g fat, 2008 (n=10, Gothenburg) 0.35-2.8 ng/g fat, and 2009/2010 (n=19, Gothenburg) 0.45-2.0 ng/g fat, with median levels of 0.72, 0.56 and 0.71 ng/g fat, respectively (Bergman et al., 2010). The median 2007, 2008 and 2009/10 concentrations for BDE-99 and BDE-153 were 0.24, 0.11, 0.13 and 0.55, 0.50, 0.50 ng/g fat, respectively. While the median concentration of BDE-209 was found to be 1.1 ng/g fat in 2007, this congener was only detected in 6 out of the 29 individual human milk samples collected in 2008-2009/10 and then in the range of 0.12-6.48 ng/g fat (Bergman et al., 2010).

Fürst (2006) analysed a pooled sample of 300 individual human milk samples collected in 1992 and 79 individual human milk samples collected in 2002 from the same area in Western Germany. Compared to the level in 1992 the mean concentrations in the samples collected in 2002 almost doubled. However, with no results in between it is not possible to elicit a time trend from these two studies. Occurrence data of PBDEs in German human milk collected in 2005 indicate that also the contamination in Germany is decreasing (Raab et al., 2008). Moreover, a slight shift in the congener profiles can be seen. While in the early human milk samples BDE-47 was the predominant congener, in the current human samples from Germany most often BDE-153 is the major contributor.

Thomsen et al. (2010a) studied the elimination rates of PBDEs and other POPs in nine Norwegian primiparous mothers and one mother breast feeding her second child by collecting breast milk samples (n=70) monthly from about two weeks up to twelve months after birth. When comparing the concentrations in the first sample collected after birth with the samples taken about six months later, the tri- to hexabrominated PBDEs had decreased in eight and increased in two of the ten sample sets. Large variation was observed for BDE-209, and the concentrations were below LOQ in several samples.

Table 16: Mean occurrence (min-max) of PBDE congeners (ng/g fat) in human milk samples from various European countries.

Country, Year	Age	N	PBDE congener								Reference
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209	
CZ, 2003	17-39	103	0.15 (<0.02-0.16)	0.86 (0.16-8.13)	0.28 (<0.02-2.21)	0.17 (<0.02-1.54)	0.19 (<0.03-1.14)	0.11 (<0.02-0.22)	0.28 (<0.05-0.61)	nr	Kazda et al., 2004
DE, 1992	nr	300[(b)]	0.13	0.76	0.24	0.17	0.45	0.03	0.07	n.r.	Fürst, 2006
DE, 2001-2004	18-44	89[(c)]	0.04 (nr-0.17)	0.91 (n.r.-6.8)	0.38 (nr-6.4)	0.26 nr-2.2)	0.59 (nr-1.9)	0.03 (nr-0.35)	0.08 (nr-0.63)	0.21 (nr-4.5)	Vieth et al., 2005
DE, 2002	nr	79	0.13 (0.03-1.44)	1.63 (0.28-14.7)	0.75 (0.09-4.79)	0.32 (0.06-2.11)	0.74 (0.07-2.76)	0.04 (0.01-0.25)	0.07 (0.01-0.35)	nr	Fürst, 2006
DE, 2005	22-46	42 [(c)]	nr	0.67 (0.15-3.02)	0.26 (0.04-1.6)	0.17 (0.04-0.74)	0.64 (0.13-1.68)	nr	0.15 (0.06-0.41)	nr	Raab et al., 2008
DE, 2006-2008	nr	1,730 [(d)]	nr	0.33 (0.03-15.49)	0.10 (0.03-3.65)	0.09 (0.03-1.96)	0.52 (0.03-6.10)	nr	nr	nr	Hoopmann et al., 2009
DK, 1997-2001	23-43	36	0.10 (0.03-0.29)	1.05 (0.45-3.63)	0.44 (0.07-1.58)	0.26 (0.10-0.81)	1.00 (0.31-3.35)	0.04 (0.01-0.13)	0.05 (<LOQ-0.58)	nr	Main et al., 2007
DK (Faroe Islands), 1999	nr	9	nr	1.90 (0.90-4.5)	0.84 (0.33-1.8)	1.00 (0.30-2.8)	2.40 (1.5-3.8)	nr	nr	1.00 (<0.14-3.2)	Fängström et al., 2005a
ES, 2003-2004[(d)] (Getafe District)	nr	30	<0.01 (<LOQ)	0.22 (<0.003-1.2)	0.38 (0.15-0.72)	0.46 (0.15-1.0)	0.10 (<0.02-1.2)	<0.01 (<LOQ)	0.28 (<0.01-6.5)	2.80 (<0.16-33)	Gómara et al., 2007
ES, 2003-2004[(d)] (Vallecas District)	nr	22	0.01 (<0.01-0.01)	0.37 (0.03-3.6)	0.51 (0.30-3.3)	0.58 (0.18-1.9)	0.13 (<0.03-3.2)	0.02 <0.005-2.0)	0.30 (0.12-3.9)	2.9[(g)] (<0.16-52)	Gómara et al., 2007
FI, 1997-2001	20-39	32	0.12 (0.03-2.44)	1.24 (0.40-15.2)	0.39 (0.13-5.94)	0.30 (0.12-1.42)	0.67 (0.22-2.97)	0.04 (0.02-0.18)	nr	nr	Main et al., 2007
FR, 2004-2006	20-46	77[(a)]	0.18 (0.04-1.62)	2.16[(f)] (0.34-12)	1.10 (0.13-5.26)	0.41 (0.05-3.91)	1.02 (0.29-10.5)	0.10 (0.009-0.69)	0.17 (0.03-1.88)	1.88 (0.39-6.8)	Antignac et al., 2009; 2010.
IT, 1998-2001	21-40	39[(e)]	0.07 (nr)	1.26 (nr)	0.55 (nr)	0.28 (nr)	0.48 (nr)	0.04 (nr)	0.11 (nr)	nr	Ingelido et al., 2007
NO, 2000-2002	20-37	10	0.12 (<LOD-0.40)	1.74 (0.42-6.12)	0.49 (0.16-1.42)	0.38 (0.15-0.79)	0.77 (0.43-1.85)	0.07 (<LOD-0.25)	nr	0.22 (0.05-0.72)	Polder et al., 2008
NO, 2003-05	16-42	393	0.18 (<LOQ-6.8)	1.70 (0.15-56)	0.49 (0.16-1.42)	0.40 (<LOQ-6.4)	0.56 (<LOQ-5.0)	0.06 (<LOQ-1.2)	0.09 (<LOQ-0.61)	0.61[(z)] (<LOQ-5.8)	Thomsen et al., 2010b
PL, 2004	22-38	22	0.07 (<LOQ-0.33)	1.07 (0.31-5.62)	0.47 (<LOQ-1.43)	0.15 (<LOQ-0.55)	0.53 (0.15-1.12)-	nr	0.08 (<LOQ-0.32)	nr	Jaraczewska et al., 2006

Table 16: Continued.

Country, Year	Age	N	PBDE congener								Reference
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209	
Russia, 2003-2004[h]	19-31	10	nr	0.14 (nr)	<0.03 (nr)	0.04 (nr)	0.32 (nr)	nr	nr	nr	Tsydenova et al., 2007
SE, 1996-1999	20-35	93	nr	2.35 (0.20-16.1)	0.62 (0.11-4.47)	0.38 (0.05-5.14)	0.60 (0.20-4.32)	0.07 (0.03-0.27)	nr	nr	Lind et al., 2003
SE, 2003	nr	5	nr	1.50 (0.8-2.4)	0.50 (0.2-0.8)	0.60 (0.3-1.1)	1.70 (1.1-2.4)	0.50 (0.3-1.0)	nr	0.40 (0.3-0.4)	López et al., 2004
SE, 2000-2004[d] (Uppsala)	21-37	84	nr	1.4 (0.55-12.0)	0.20 (<0.1-5.2)	0.30 (<0.1-2.1)	0.70 (0.2-4.6)	nr	nr	nr	Glynn et al., 2011
SE, 2001[d] (Gothenburg)	19-40	36	nr	1.3 (0.60-8.9)	0.20 (<0.1-0.70)	0.20 (<0.1-0.60)	0.50 (0.2-1.0)	nr	nr	nr	Glynn et al., 2011
SE, 2003[d] (Lund)	25-39	36	nr	1.2 (0.33-9.3)	0.30 (<0.1-1.4)	0.30 (<0.08-1.1)	0.60 (0.2-1.9)	nr	nr	nr	Glynn et al., 2011
SE, 2003-2004[d] (Lycksele)	19-35	39	nr	1.8 (0.7-73)	0.50 (0.2-17)	0.40 (0.09-18)	0.60 (<1.2-8.0)	nr	nr		Glynn et al., 2011
UK, 2001-2003[i]	24-34	54	0.30 (ND-2.1)	3.00 (0.1-37)	0.90 (ND-0.13)	0.60 (ND-7.0)	1.40 (ND-4.9)	0.50 (ND-2.5)	nr	nr	Kalantzi et al., 2004

nr: not reported.
(a): 3-6 days pp.
(b): Pool (no range available).
(c): 1-2-weeks pp.
(d): Median values.
(e): Recalculated by Frederiksen et al. (2009a).
(f): The original paper gives a mean value of 0.167, which according to the authors is a typo and should read 2.16 (see Antignac et al., 2010).
(g): BDE-209 determined in a subset of 46 samples.
(h): Only primipara.
(i): geometric mean.

5.3. Effects of food processing

There are limited data available on the effects of processing on PBDE levels in foods. Cooking-induced changes in levels of PBDEs and other components in various foodstuffs like various fish and meat samples as well as potatoes and rice were investigated by Perelló et al. (2009). Foods included fish (sardine, hake, and tuna), meat (veal, steak loin of pork, breast and thigh of chicken, and steak and rib of lamb), string bean, potato, rice, and olive oil. The authors observed some variations in the concentrations of PBDEs before and after cooking. However, these effects depended not only on the type of cooking process (like fried, grilled, roasted or boiled), but mainly on the specific food item. The observed effects resulted in slightly lower or higher concentrations. The results of the study showed that in general cooking processes have limited influence on the PBDE concentrations in food.

In another study by Schecter et al. (2006) it was shown that broiling, with fat dripping from the food (ground beef, ground lamb, catfish, trout, and salmon) reduces the amount of PBDEs in these foods. The authors demonstrated in the pilot study for some food items a decline in PBDE levels of more than 50 % (based on wet weight calculations).

Due to the expected similar behaviour of PBDEs and PBBs, observations on the PBB content of contaminated food during various processing procedures could, with some precaution, also be taken for PBDEs. Following the PBB incident in Michigan/USA in the early 1970s, Zabik et al. (1978, 1980, 1999) studied the effects of processing and cooking on PBB residues in contaminated milk, the retention and distribution of PBBs in raw and cooked beef by different processing procedures and compared cooked values with those in the raw product. The following observations were made regarding PBBs: (i) spray drying removed one-quarter of the PBBs from whole milk and one-half of skim milk, (ii) pressure cooking chicken pieces resulted in a 39-57 % PBBs loss and (iii) cooking beef resulted in a one-quarter to one-half loss of PBBs with the high heat of broiling resulting in the higher losses.

The above data indicate that exposure estimations via food should take levels in the processed food rather than in the uncooked product into consideration.

Very recently an effect possibly in connection with food processing has been reported (Schecter et al., 2011). The analysis of butter samples, collected in 2010 in the United States, showed unexpectedly high concentrations of BDE-209 in one out of 10 butter samples (37.6 ng/g w.w.). As demonstrated by the authors, a migration effect from contaminated wrapping material (highly contaminated with technical DecaBDE) was most likely responsible for a level of 42 ng/g w.w. (original butter) for the sum of 23 PBDEs, among them the eight PBDEs considered. With the exception of elevated deca-, nona- and octaBDEs, the butter samples did not show unexpected high PBDE values. This indicates that a secondary contamination of food by packaging material or other sources between production site, point of sale and household can not be excluded.

In general, PBDEs are chemically stable lipophilic substances. Reduction of their content in processed foods is mainly caused by loss of fat, rather than degradation. On the other hand, contact with PBDE containing packaging material may result in elevated contamination of the respective food.

6. Food consumption

6.1. EFSA's Comprehensive European Food Consumption Database

In most of the latest EFSA opinions concerning contaminants, the EFSA Concise European Food Consumption database was used in order to assess exposure. The Concise database was operational since 2008 and contained information from individual dietary surveys from the majority of EU

Member States. However, it was intended to be used as a screening tool for exposure assessment as well as a first step towards generating a more comprehensive database.

As a next step, EFSA established in 2010 the "Comprehensive European Food Consumption Database". This is built on existing information for adults and children at a detailed level. Through a procurement project (DPPA/EFSA/DATEX/2008) 22 different Member States 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" (EFSA, 2011) and the summary tables in Appendix C (Table C1**).** All food consumption data were codified according to the FoodEx classification system which has been developed by the DCM Unit in 2009.

However, like the Concise European Food Consumption database, the "Comprehensive European Food Consumption Database" still includes methodological differences making these data not fully suitable for country-to-country comparisons.

Overall, the food consumption data gathered at EFSA in the Comprehensive European food consumption database are the most complete and detailed data currently available in the EU. Thanks to the detailed structure of the food classification (FoodEx) the "Comprehensive European Food Consumption Database" will allow the estimation of the intake from more detailed food categories than using the Concise Database.

For calculating PBDE exposure, food consumption and body weight data at the individual level were accessed in the "Comprehensive European Food Consumption Database".

6.2. Food consumption data for specific age and consumers group

Infants and young children are often more highly exposed to chemicals than adults when considering the food intake in relation to their body weight.

Estimating the potential PBDE exposure for infants from human milk and infant formula requires information about the quantity of liquid consumed per day and the duration over which such consumption occurs. According to the Institute of Medicine of the U.S. National Academies of Sciences (IOM), average human milk consumption is about 750-800 g per day (range, 450-1,200 g per day) for the first 4-5 months of life. Infant birth weight and nursing frequency have been shown to influence consumption (IOM, 1991). The WHO related human milk consumption to body weight rather than age with an estimated 125 mL/kg or 763 mL for a 3 month old child weighing 6.1 kg (Onyango et al., 2002). According to the German DONALD study, mean consumption of infant formula for a three month old child weighing on average 6.1 kg, was 780 mL per day with a 95th percentile consumption of 1,060 mL per day (Kersting et al., 1998). A common mean of 800 mL per day will be used in this opinion for consumption of human milk and infant formula when calculating exposure, with a high of 1,200 mL per day.

Within the Comprehensive European Food Consumption Database, detailed food consumption data for children are also included. In particular, results from consumption surveys from 13 different Member States for children gathered by means of the EFSA Article 36 project "Individual food consumption data and exposure assessment studies for children" (acronym EXPOCHI) (Huybrechts et al., in press) were incorporated in the database. All food consumption data were collected from infants to children of 18 years old and grouped according to the following ranges of age: 0 to 1 year old, 1 to 3 years old, 3 to 6 years old, 6 to 10 years old and from 10 to 18 years old.[27] Consumption records were codified

[27]Age classes are defined as follows: 0 to 1 year old refers to infants up to and including 11 months; 1 to 3 years old refers to toddlers from 12 up to and including 35 months of age; 3 to 6 years old refers to children from 36 months up to and

according to the FoodEx classification system which has been developed by the DCM Unit in 2009. The consumption data for children from the Comprehensive European Food Consumption Database (including the EXPOCHI data) are used in this opinion for the estimation of dietary PBDE intake of children according to the different age groups.

Due to the comparatively elevated PBDE levels of fish and seafood products, a specific diet characterised by high fish consumption might lead to higher dietary intake for this population, people who might consume fish every day (with particular focus on "Fish meat" only, regardless of the fish species; FoodEx level 2) like fishermen or fish sellers might be at even higher risk. In order to estimate the dietary intake of PBDEs for this specific scenario, a daily consumption of 2.6 g/kg b.w. fish meat eaten by the European population was retrieved from the Comprehensive European Food Consumption Database (see food consumption statistics according to the FoodEx food classification system for the total population and for consumers of respective food categories only[23]). This value was identified as the 95th percentile for consumers only, by selecting those dietary surveys with more than one day dietary record, and including more than 60 participants.

Another group of people that might have an elevated PBDE intake are consumers of food supplements, especially if these consist of fish oil capsules or fish liver oil. Since the consumption recommended on the package varies according to the different brands (e.g. one tea spoon or one table spoon), the CONTAM Panel assumed a maximum daily consumption of 15 mL of fish oil for the exposure estimate to cover a worst case scenario.

7. Human exposure assessment

7.1. Current estimates of mean and high dietary exposure to PBDEs for adults

For this opinion the mean and the 95th percentile dietary PBDE exposures (ng/kg b.w. per day) were calculated separately for each country for the whole population using consumption data recorded at the individual level from the Comprehensive European Food Consumption Database. Due to the methodological differences between the consumption surveys included in the Comprehensive European Food Consumption Database across countries, chronic dietary PBDEs exposure was estimated separately by country and consumption survey, and reported likewise.

The CONTAM Panel focused the exposure estimation on eight PBDE congeners and on eight selected broad food categories of the FoodEx food classification system ("Eggs and egg products", "Milk and dairy products", "Meat and meat products (including edible offal)", "Animal and vegetable fats and oils", "Fish and other seafood (including amphibians, reptiles, snails and insects)", "Products for special nutritional use", "Food for infants and small children)". LB and UB occurrence means used for the calculation of the exposure assessment are reported in Table 15.

Additionally, following the recently published guidance on the use of Comprehensive European Food Consumption Database for exposure assessment (EFSA, 2011), dietary surveys with only one record day per subject were not considered for the calculation of PBDEs chronic dietary exposure, as they are not adequate to assess repeated exposure. Moreover, in accordance to the specifications of the EFSA Guidance (EFSA, 2011), 95th percentiles estimates for dietary surveys/age classes with less than 60 observations were not considered statistically robust therefore not suitable for risk characterisation.

Table 17 and 18 show the dietary intake of respectively average and 95th percentile consumers of the eight congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209), with mean

including 71 months of age; 6 to 10 years old refers to children from 6 years up to and including 9 years and 11 months; and the last group includes individuals from 10 years up to and including 18 years old.

occurrence values estimated from 25,824 analytical records (3,933 samples). Summary statistics provided in Table 17 and 18 have been estimated taking into account the above mentioned recommendations.

The highest mean dietary exposure across the European dietary surveys was estimated for BDE-209 ranging from 0.35 to 2.82 ng/kg b.w. per day for the minimum LB and the maximum UB, respectively, with a median of 0.61 and 1.69 ng/kg b.w. per day for LB and UB, respectively. The dietary intake of BDE-209 is followed by BDE-47 and BDE-100, with minimum LB and maximum UB means across European surveys of 0.29 and 1.91 ng/kg b.w. per day and 0.07 and 0.70 ng/kg b.w. per day, respectively. The lowest dietary exposure for the eight congeners considered was calculated for BDE-28 and -183 with minimum LB and the maximum UB dietary intakes of 0.01 and 0.28 ng/kg b.w. per day and 0.01 and 0.36 ng/kg b.w. per day, respectively.

The same PBDE congener pattern is reflected in the dietary intake of high consumers (95^{th} percentiles). The minimum LB and the maximum UB dietary intake of BDE-209 across the European dietary surveys are 0.70 and 4.58 ng/kg b.w. per day respectively, followed by BDE-47 (1.10 and 4.51 ng/kg b.w. per day, for minimum LB and maximum UB) and BDE-100 (0.29 and 1.40 ng/kg b.w. per day for minimum LB and maximum UB).

The variation observed in exposure between countries and surveys is influenced by different consumption patterns only, since the PBDE congener concentrations in the eight broad food categories of the FoodEx food classification system were calculated at European level.

Table 17: Total dietary exposure (ng/kg b.w. per day) to the eight PBDE congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) for average adult (mean) consumers across a number of subjects (N) in European dietary surveys. The dietary intake was estimated using the lower (LB) and upper (UB) bound PBDE concentrations from 25,824 analytical records (3,933 samples) across eight broad food categories of the FoodEx food classification system.

European Country	N	Average dietary exposure to eight PBDE congeners (ng/kg b.w. per day)															
		BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		BDE-209	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
BE/1	1,356	0.03	0.15	0.70	0.83	0.18	0.32	0.17	0.31	0.04	0.22	0.07	0.25	0.02	0.18	0.67	1.68
CZ/1	1,666	0.01	0.17	0.40	0.57	0.18	0.34	0.11	0.28	0.05	0.24	0.04	0.25	0.02	0.18	0.55	1.68
DK	2,821	0.02	0.17	0.44	0.63	0.18	0.37	0.12	0.30	0.04	0.29	0.04	0.31	0.02	0.25	0.62	1.86
FR	2,276	0.03	0.16	0.71	0.87	0.20	0.35	0.19	0.34	0.05	0.24	0.07	0.27	0.02	0.19	0.61	1.69
DE/4	10,419	0.01	0.11	0.38	0.49	0.11	0.23	0.10	0.21	0.03	0.17	0.03	0.19	0.01	0.14	0.42	1.21
HU	1,074	0.01	0.19	0.29	0.49	0.21	0.41	0.09	0.29	0.05	0.30	0.03	0.30	0.02	0.23	0.69	2.04
IE	952	0.02	0.17	0.50	0.68	0.17	0.35	0.13	0.31	0.04	0.27	0.05	0.30	0.02	0.23	0.60	1.82
IT	2,314	0.04	0.19	1.02	1.20	0.26	0.43	0.27	0.45	0.06	0.28	0.10	0.33	0.02	0.23	0.81	2.20
LV	1,382	0.01	0.10	0.38	0.48	0.11	0.21	0.10	0.20	0.03	0.15	0.04	0.17	0.01	0.11	0.35	0.96
NL/2	750	0.01	0.15	0.33	0.50	0.13	0.30	0.07	0.24	0.03	0.26	0.03	0.28	0.01	0.23	0.54	1.63
ES/1	982	0.07	0.28	1.65	1.91	0.38	0.65	0.43	0.70	0.09	0.42	0.15	0.51	0.03	0.36	0.94	2.82
ES/2	418	0.06	0.24	1.47	1.69	0.34	0.56	0.37	0.60	0.08	0.37	0.14	0.44	0.03	0.31	1.00	2.63
ES/3	61	0.04	0.22	0.97	1.20	0.20	0.43	0.24	0.47	0.05	0.35	0.08	0.41	0.02	0.31	0.48	1.97
SE/1	1,081	0.02	0.13	0.58	0.72	0.17	0.31	0.15	0.30	0.04	0.24	0.05	0.27	0.01	0.22	0.37	1.34
UK	1,724	0.03	0.13	0.68	0.81	0.19	0.32	0.17	0.30	0.04	0.22	0.06	0.25	0.01	0.18	0.62	1.50
Minimum		**0.01**	**0.10**	**0.29**	**0.48**	**0.11**	**0.21**	**0.07**	**0.20**	**0.03**	**0.15**	**0.03**	**0.17**	**0.01**	**0.11**	**0.35**	**0.96**
Median		**0.02**	**0.17**	**0.58**	**0.72**	**0.18**	**0.35**	**0.15**	**0.30**	**0.04**	**0.26**	**0.05**	**0.28**	**0.02**	**0.23**	**0.61**	**1.69**
Maximum		**0.07**	**0.28**	**1.65**	**1.91**	**0.38**	**0.65**	**0.43**	**0.70**	**0.09**	**0.42**	**0.15**	**0.51**	**0.03**	**0.36**	**1.00**	**2.82**

b.w.: body weight; BE: Belgium; CZ: Czech Republic; DK: Denmark; FR: France; DE: Germany; HU: Hungary; IE: Ireland; IT: Italy; LV: Latvia; NL: The Netherlands; ES: Spain; SE: Sweden; UK: United Kingdom.

(a): Original acronyms of the dietary surveys and the number of subjects are given in Table C1 in Annex C; (b): the number of figures after the decimal point is the same for all congeners and for all food categories and does not reflect precision.

Table 18: Total dietary exposure (ng/kg b.w. per day) to the eight PBDE congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) for 95th adult consumers (P95) across a number of subjects (N) in European dietary surveys. The dietary intake was estimated using the lower (LB) and upper (UB) bound PBDE concentrations from 25,824 analytical records (3,933 samples) across eight broad food categories of the FoodEx food classification system.

European Country	N	95th percentiles dietary exposure to eight PBDE congeners (ng/kg b.w. per day)															
		BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		BDE-209	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
BE/1	1,356	0.11	0.31	2.65	2.82	0.48	0.72	0.64	0.87	0.11	0.49	0.23	0.58	0.04	0.40	1.34	3.37
CZ/1	1,666	0.08	0.30	2.01	2.22	0.43	0.67	0.52	0.74	0.11	0.44	0.18	0.49	0.04	0.36	1.02	3.02
DK	2,821	0.04	0.29	1.10	1.35	0.35	0.67	0.29	0.56	0.08	0.54	0.10	0.58	0.03	0.50	1.11	3.21
FR	2,276	0.07	0.27	1.77	1.97	0.38	0.62	0.46	0.68	0.09	0.42	0.16	0.49	0.03	0.37	1.06	2.87
DE/4	10,419	0.08	0.23	1.90	2.04	0.32	0.51	0.48	0.64	0.07	0.36	0.17	0.42	0.03	0.33	0.82	2.32
HU	1,074	0.05	0.31	1.31	1.53	0.44	0.73	0.34	0.60	0.11	0.51	0.12	0.53	0.03	0.42	1.17	3.31
IE	952	0.06	0.29	1.44	1.63	0.33	0.60	0.36	0.61	0.08	0.48	0.13	0.52	0.03	0.42	1.04	3.02
IT	2,314	0.13	0.33	3.07	3.28	0.55	0.80	0.78	1.04	0.13	0.47	0.27	0.59	0.05	0.41	1.40	3.53
LV	1,382	0.08	0.22	1.80	1.94	0.34	0.50	0.45	0.62	0.08	0.32	0.16	0.39	0.03	0.28	0.80	2.04
NL/2	750	0.06	0.27	1.54	1.72	0.30	0.58	0.39	0.58	0.07	0.50	0.13	0.54	0.03	0.46	0.87	2.83
ES/1	982	0.17	0.45	4.06	4.31	0.67	1.07	1.02	1.36	0.16	0.67	0.36	0.85	0.06	0.61	1.56	4.58
ES/2	418	0.17	0.42	4.13	4.51	0.69	1.03	1.02	1.40	0.15	0.64	0.37	0.83	0.06	0.59	1.70	4.38
ES/3	61	0.11	0.38	2.68	3.06	0.36	0.74	0.65	0.97	0.08	0.64	0.23	0.66	0.04	0.55	0.84	3.27
SE/1	1,081	0.06	0.24	1.45	1.65	0.34	0.57	0.36	0.60	0.08	0.45	0.13	0.53	0.03	0.44	0.70	2.46
UK	1,724	0.07	0.22	1.77	1.97	0.39	0.57	0.43	0.61	0.08	0.36	0.17	0.44	0.03	0.33	1.07	2.52
Minimum		**0.04**	**0.22**	**1.10**	**1.35**	**0.30**	**0.50**	**0.29**	**0.56**	**0.07**	**0.32**	**0.10**	**0.39**	**0.03**	**0.28**	**0.70**	**2.04**
Median		**0.08**	**0.29**	**1.80**	**1.97**	**0.38**	**0.67**	**0.46**	**0.64**	**0.08**	**0.48**	**0.17**	**0.53**	**0.03**	**0.42**	**1.06**	**3.02**
Maximum		**0.17**	**0.45**	**4.13**	**4.51**	**0.69**	**1.07**	**1.02**	**1.40**	**0.16**	**0.67**	**0.37**	**0.85**	**0.06**	**0.61**	**1.70**	**4.58**

b.w.: body weight; BE: Belgium; CZ: Czech Republic; DK: Denmark; FR: France; DE: Germany; HU: Hungary; IE: Ireland; IT: Italy; LV: Latvia; NL: The Netherlands; ES: Spain; SE: Sweden; UK: United Kingdom.

(a): Original acronyms of the dietary surveys and the number of subjects are given in Table C1 in Annex C; (b): P95 estimates for dietary surveys/age classes with less than 60 observations may not be statistically robust (EFSA, 2011) and therefore they should not be considered in the risk characterisation; (c): the number of figures after the decimal point is the same for all congeners and for all food categories and does not reflect precision.

7.2. Relative contributions of different food groups to the PBDE exposure

The contribution of each of the eight selected broad food categories of the FoodEx food classification system to the estimated individual PBDE intakes has been evaluated. LB and UB occurrence mean values for each of the eight selected food categories for all of the individual congeners were combined with consumption data from each European country. LB and UB contribution of each food category to the total dietary intake of each congener was therefore estimated across European countries. In order to provide an overview of the range of relative contribution of each food category to the overall PBDE dietary intake, the minimum LB intake and the maximum UB intake for each food category was considered across European countries. For easy reading, Table 19 describes the range of UB relative contributions (minimum and maximum UB contribution, expressed in percentage) of each food category to the overall diet across the European countries.

Dietary intake reflects the pattern of consumption figures as well as occurrence values. In particular, as a different number of samples were reported by congeners and by food category, any comparison among congeners in Table 19 should be avoided.

Up to 40.7 % of the maximum UB dietary intake of BDE-28 is covered by meat and meat products, followed by animal and vegetable fats and oils and milk and dairy products.

The highest contribution to the dietary exposure of BDE-47 is due to the consumption of fish and other seafood, with up to 78.5 % of coverage (maximum UB across European countries and surveys). Animal and vegetable fats and oils and milk and dairy products follow with only 20.8 and 26.2 % of maximum UB contribution, respectively.

In the case of BDE-99, the main food category contributing is milk and dairy products (41.3 %, maximum UB across European countries and surveys) followed by meat and meat products and fish and seafood with 25.8 and 29.7 % contribution, respectively (maximum UB across surveys).

Fish and seafood are the main contributors to the intake of BDE-100 (59.1 %, maximum UB across countries) followed by milk and dairy products and animal and vegetable fats and oils.

The exposure to BDE-153 is mainly due to the consumption of milk and dairy products with up to 57.6 % (maximum UB across European countries and surveys) of the total dietary intake, followed by animal and vegetable fats and oils and meat and meat products.

For BDE-154, the main food category that contributes to the intake is again milk and dairy products (54.5 % maximum UB across countries), followed by fish and other seafood and animal fats and oils with almost the same relative contribution to the dietary exposure (around 33 % of the maximum UB across countries).

The highest exposure to BDE-183 is due to the consumption of milk and dairy products, for which the maximum UB intake can reach up to 68.6 % across countries. Animal and vegetable fats and oils and fish and other seafood follow with a relative contribution of 40.5 % and 23.5 %, respectively (maximum UB across European countries and surveys).

Although the number of samples reporting on levels BDE-209 in the different food categories is limited, the food categories that contribute most to the exposure to BDE-209 are animal and vegetable fats and oils and milk and dairy products with a relative contribution of 43.5 % and 41.7 %, respectively (maximum UB across European countries and surveys).

Table 19: Range of relative contribution (%) to the overall PBDE dietary intake of the eight selected broad food categories of the FoodEx food classification system. The range provides minimum and maximum upper bound (UB) contributions (Min (%) and Max (%)) of each food categories to the overall diet across the European dietary surveys. Percentages values refer to the intake of each congener (BDE-28, -47, -99, -100, -153, -154, -183 and 209) estimated from UB mean values occurrence and individual food consumption. The number of samples from which the occurrence mean values for each food category/congener were derived is reported (n).

Food categories (FoodEx Level 1)	Food categories relative contributions (%) to overall dietary exposure and number samples analysed per each congener (n)	PBDE congeners[(a)]							
		BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209
		UB	UB	UB	UB	UB	UB	UB	UB
Animal and vegetable fats and oils	n	*207*	*235*	*235*	*235*	*235*	*235*	*210*	*166*
	Min (%)	17.6	4.3	11.1	8.4	15.9	12.5	14.3	19.3
	Max (%)	36.1	20.8	26.2	26.1	36.0	31.3	40.5	43.5
Eggs and egg products	n	*167*	*192*	*179*	*176*	*216*	*177*	*156*	*122*
	Min (%)	0.5	1.6	6.5	2.6	1.8	1.0	0.4	1.7
	Max (%)	2.1	8.7	25.5	11.6	8.3	4.8	2.0	7.0
Fish and other seafood (including amphibians, reptiles, snails and insects)	n	*1986*	*2472*	*2275*	*2231*	*2264*	*2264*	*2030*	*487*
	Min (%)	4.4	32.2	5.1	15.5	2.7	6.1	4.0	2.4
	Max (%)	27.8	78.5	29.7	59.1	17.7	33.0	23.5	16.1
Meat and meat products (including edible offal)	n	*546*	*573*	*569*	*553*	*638*	*570*	*341*	*228*
	Min (%)	20.4	3.9	11.5	8.8	10.6	9.6	2.5	6.9
	Max (%)	40.7	16.7	25.8	22.9	26.4	24.1	7.6	16.7
Milk and dairy products	n	*163*	*187*	*186*	*185*	*206*	*185*	*187*	*163*
	Min (%)	13.5	5.9	15.6	10.8	26.7	25.3	36.2	14.1
	Max (%)	36.1	26.2	41.3	36.1	57.6	54.5	68.6	41.7
Products for special nutritional use	n	*70*	*75*	*75*	*75*	*75*	*75*	*75*	*26*
	Min (%)	0.1	0.7	0.2	0.3	0.1	0.2	0.1	0.4
	Max (%)	5.2	19.0	9.5	9.5	4.7	7.8	3.7	14.4
Vegetables and vegetable products (including fungi)	n	*36*	*42*	*42*	*42*	*41*	*41*	*42*	*36*
	Min (%)	2.3	0.4	1.0	0.5	0.7	0.5	0.8	9.0
	Max (%)	7.9	1.8	2.9	1.6	2.6	1.9	3.0	24.1

LB: lower bound; UB: upper bound.
(a): Since a different number of samples (n) were reported by congeners and by food category, any comparison between congeners should be avoided.

7.3. Dietary exposure of specific sub-groups of the population

7.3.1. Infants (less than 1 year old)

Breast-fed infants

For the exposure assessment of infants below six months of age, a value of three months was selected, equivalent to a weight of about 6.1 kg, with an estimated average daily consumption of about 800 mL (Table 20**)** and a high consumption of 1,200 mL of human milk (Table 21). For the occurrence data see Chapter 5.2.2.

For breast-fed infants with average human milk consumption, the mean daily exposure of BDE-47, -99 and -153 across countries ranges from 0.64-13.77, <0.14-5.05 and 0.46-11.02 ng/kg b.w. For BDE-209, the exposure scenario based on average human milk consumption results in a range of 0.96-13.31 ng/kg b.w. per day.

For infants with a high human milk consumption the respective mean daily exposure to BDE-47, -99 and -153 across countries ranges from 0.96-20.64, <0.14-7.57 and 0.69-16.51 ng/kg b.w., respectively. For BDE-209 the exposure scenario based on high human milk consumption amounts to 1.44-19.95 ng/kg b.w. per day across countries.

Table 20: Exposure scenario based on **average human milk consumption** (ng/kg b.w. per day) for infants below 6 months (assumption: 800 mL per day, 3.5 % fat and 6.1 kg b.w.). Exposure calculated from the occurrence data reported in studies carried out in different European countries and reported in the literature (see Chapter 5.2.2.).

Coutry, Year	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209	References
CZ, 2003	0.69	3.95	1.29	0.78	0.87	0.50	1.29	-	Kazda et al., 2004
DE, 1992	0.60	3.49	1.10	0.78	2.07	0.14	0.32	-	Fürst, 2006
DE, 2001-04	0.18	4.18	1.74	1.19	2.71	0.14	0.37	0.96	Vieth et al., 2005
DE, 2002	0.60	7.48	3.44	1.47	3.40	0.18	0.32	-	Fürst, 2006
DE, 2005	-	3.08	1.19	0.78	2.94	-	0.69	-	Raab et al., 2008
DE, 2006-08	-	1.51	0.46	0.41	2.39	-	-	-	Hoopmann et al., 2009
DK, 1997-2001	0.46	4.82	2.02	1.19	4.59	0.18	0.23	-	Main et al., 2007
DK (Faroe Islands), 1999	-	8.72	3.86	4.59	11.02	-	-	4.59	Fängström et al., 2005a
ES, 2003-04 (Getafe District)	<0.05	1.01	1.74	2.11	0.46	<0.05	1.29	12.85	Gómara et al., 2007
ES, 2003-04 (Vallecas District)	0.05	1.70	2.34	2.66	0.60	0.09	1.38	13.31	Gómara et al., 2007
FI, 1997-2001	0.55	5.69	1.79	1.38	3.08	0.18	-	-	Main et al., 2007
FR, 2004-2006	0.83	9.91	5.05	1.88	4.68	0.46	0.78	8.63	Antignac et al., 2009; 2010
IT, 1998-2001	0.32	5.78	2.52	1.29	2.20	0.18	0.50	-	Ingelido et al., 2007
NO, 2000-2002	0.55	7.99	2.25	1.74	3.53	0.32	-	1.01	Polder et al., 2008
NO, 2003-2005	0.83	7.80	2.25	1.84	2.57	0.28	0.41	2.80	Thomsen et al., 2010b
PL, 2004	0.32	4.91	2.16	0.69	2.43	0.37	-	-	Jaraczewska et al., 2006

Table 20: Continued.

Coutry, Year	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209	References
Russia, 2003-2004	-	0.64	<0.14	0.18	1.47	-	-	-	Tsydenova et al., 2007
SE, 1996-1999	-	10.79	2.85	1.74	2.75	0.32	-	-	Lind et al., 2003
SE, 2003	-	6.89	2.30	2.75	7.80	2.30	-	1.84	López et al., 2004
SE, 2000-2004 (Uppsala)	-	6.42	0.92	1.38	3.21	-	-	-	Glynn et al., 2011
SE, 2001 (Gothenburg)	-	5.97	0.92	0.92	2.30	-	-	-	Glynn et al., 2011
SE, 2003 (Lund)	-	5.51	1.38	1.38	2.75	-	-	-	Glynn et al., 2011
SE, 2003-2004 (Lycksele)		8.26	2.30	1.84	1.84	-	-	-	Glynn et al., 2011
UK, 2001-2003	1.38	13.77	4.13	2.75	6.43	2.30	-	-	Kalantzi et al., 2004

CZ: Czech Republic; DE: Germany; DK: Denmark; ES: Spain; FI: Finland; FR: France; IT: Italy; NO: Norway; PL: Poland; RU: Russia; SE: Sweden; UK: United Kingdom.

Table 21: Exposure scenario based on **high human milk consumption** (ng/kg b.w. per day) for infants below 6 months (assumption: 1,200 mL per day, 3.5 % fat and 6.1 kg b.w.). Exposure calculated from the occurrence data reported in studies carried out in different European countries and reported in the literature.

Country, Year	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209	References
CZ, 2003	1.03	5.92	1.93	1.17	1.31	0.76	1.93	-	Kazda et al., 2004
DE, 1992	0.89	5.23	1.65	1.17	3.10	0.21	0.48	-	Fürst, 2006
DE, 2001-2004	0.28	6.26	2.61	1.79	4.06	0.21	0.55	1.44	Vieth et al., 2005
DE, 2002	0.89	11.21	5.16	2.20	5.09	0.28	0.48	-	Fürst, 2006
DE, 2005	-	4.61	1.79	1.17	4.40	-	1.03	-	Raab et al., 2008
DE, 2006-2008	-	2.27	0.69	0.62	3.58	-	-	-	Hoopmann et al., 2009
DK, 1997-2001	0.69	7.22	3.03	1.79	6.88	0.28	0.34	-	Main et al., 2007
DK (Faroe Islands), 1999	-	13.07	5.78	6.88	16.51	-	-	6.88	Fängström et al., 2005a
ES, 2003-2004 (Getafe Dsitrict)	<0.07	1.51	2.61	3.16	0.69	<0.07	1.93	19.26	Gómara et al., 2007
ES, 2003-04 (Vallecas District)	0.07	2.55	3.51	3.99	0.89	0.14	2.06	19.95	Gómara et al., 2007
FI, 1997-2001	0.83	8.53	2.68	2.06	4.61	0.28	-	-	Main et al., 2007
FR, 2004-2006	1.24	14.86	7.57	2.82	7.02	0.69	1.17	12.93	Antignac et al., 2009; 2010
IT, 1998-2001	0.48	8.67	3.78	1.93	3.30	0.28	0.76	-	Ingelido et al., 2007
NO, 2000-2002	0.83	11.97	3.37	2.61	5.30	0.48	-	1.51	Polder et al., 2008
NO, 2003-2005	1.24	11.70	3.37	2.75	3.85	0.41	0.62	4.20	Thomsen et al., 2010b
PL, 2004	0.48	7.36	3.23	1.03	3.65	0.55	-	-	Jaraczewska et al., 2006
Russia, 2003-2004	-	0.96	<0.14	0.28	2.20	-	-	-	Tsydenova et al., 2007
SE, 1996-1999	-	16.17	4.27	2.61	4.13	0.48	-	-	Lind et al., 2003
SE, 2003	-	10.32	3.44	4.13	11.70	3.44	-	2.75	López et al., 2004

Table 21: Continued.

Country, Year	BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	BDE-209	References
SE, 2000-2004 (Uppsala)	-	9.63	1.38	2.06	4.82	-	-	-	Glynn et al., 2011
SE, 2001 (Gothenburg)	-	8.94	1.38	1.38	3.44	-	-	-	Glynn et al., 2011
SE, 2003 (Lund)	-	8.26	2.06	2.06	4.13	-	-	-	Glynn et al., 2011
SE, 2003-2004 (Lycksele)		12.38	3.44	2.75	4.13	-	-	-	Glynn et al., 2011
UK, 2001-2003	2.06	20.64	6.19	4.13	9.63	3.44	-	-	Kalantzi et al., 2004

CZ: Czech Republic; DE: Germany; DK: Denmark; ES: Spain; FI: Finland; FR: France; IT: Italy; NO: Norway; PL: Poland; RU: Russia; SE: Sweden; UK: United Kingdom.

Total dietary intake for infants

The dietary exposure to the eight PBDE congeners considered for infants from 0 to 1 year old was estimated by using LB and UB occurrence values as reported in Table 15 and the available consumption data from the Comprehensive European Food Consumption Database (including EXPOCHI data). With regard to the mean occurrence values, only 42 samples were specifically reported for the category "Food for infants and young children" and with respect to the consumption data only two consumption surveys are available reporting dietary habits for children younger than 1 year (861 individuals from Bulgaria and 16 individuals from Italy), therefore the exposure estimate should be considered as not being representative for the European infant population. In Table 22 the LB and UB intake (ng/kg b.w. per day) estimated from the two consumption surveys (from Bulgaria and from Italy) for infants below 1 year old are reported.

Taking into account the above mentioned limitations, the highest exposure for average infant consumers is to BDE-47 and -209 with intakes ranging respectively from 3.63 to 18.05 ng/kg b.w. per day and 2.81 to 12.88 ng/kg b.w. per day (across the two consumption surveys).

Table 22: LB and UB intake (ng/kg b.w. per day) estimated from two consumption surveys (from Bulgaria and from Italy) available in Europe, for infants below 1 year old.

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for average consumers				
	Consumption surveys			
	Bulgarian		**Italian**	
	LB	**UB**	**LB**	**UB**
BDE-28	0.02	0.31	0.07	0.38
BDE-47	3.63	4.02	17.70	18.05
BDE-99	1.54	1.92	6.54	6.93
BDE-100	0.41	0.82	1.84	2.25
BDE-153	0.10	0.71	0.24	0.88
BDE-154	0.10	0.76	0.41	1.07
BDE-183	0.05	0.69	0.17	0.83
BDE-209	2.81	5.32	10.16	12.88
Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for high consumers (95th percentile)				
	LB	UB	LB	UB
BDE-28	0.03	0.89	0.20	0.74
BDE-47	10.41	10.65	69.02	69.41
BDE-99	3.92	4.37	25.44	26.01
BDE-100	1.11	1.95	6.96	7.57
BDE-153	0.26	2.15	0.79	1.84
BDE-154	0.26	2.30	1.50	2.46
BDE-183	0.11	2.27	0.61	1.82
BDE-209	6.33	11.86	38.44	42.23

Among the eight selected FoodEx food categories considered for the exposure estimates, the food categories mainly contributing to the PBDE intake in both surveys are "Food for infants and small children", "Animal and vegetable fats and oils" and "Milk and dairy products".

Due to the fact that not all of the eight congeners considered were simultaneously analysed in the set of data used for calculating the LB and UB levels, only a generic estimation from the Bulgarian dietary survey of the contribution of each food category to the overall congener's intake could be applied (data not reported). Only the Bulgarian dietary survey was used for this estimation because in

this survey consumption data were available from a larger number of individuals. In the case of BDE-28, -153, -154 and -183 the major contributor is the food category "Milk and dairy products", covering around 50 and 80 % of the total exposure of the individual congeners. Dietary intake of BDE-47 and -99 is mainly through consumption of "Food for infants and small children" (from 65 to 83 % of coverage). Exposure to BDE-100 and -209 is due to the consumption of both "Milk and dairy products" and "Food for infants and small children" contributing both for around 36 to 45 % of the diet.

7.3.2. Children (1-18 years old)

Individual food consumption data from 13 different Member States for children were combined with the mean PBDE concentration data (LB and UB from Table 15) for the estimation of the PBDE intake across different age groups (1 to 3 years old, 3 to 6 years old, 6 to 10 years old and from 10 to 18 years old). Not all Member States provided consumption information for all age groups or in certain cases more than one consumption survey was provided by the same country. Details on the consumption surveys used for the PBDEs exposure assessment estimation are reported in Table C1, Appendix C.

Summary statistics, number of surveys and the number of individuals included in the exposure assessment depending on the age group are given in Table 23. Details on the exposure assessments across all European surveys can be found in Tables D1, D2, D3 and D4 in Appendix D.

As a trend, the daily intake of PBDEs diminishes with increasing age as the food intake per kg body weight decreases. Children from 1-3 years old have the highest exposure to all PBDE congeners. In particular, the median average intake of BDE-47 and -99, calculated across different dietary surveys, is 5 to 7 times higher than for adults, with minimum LB and maximum UB for BDE-47 of 1.04 and 6.40 ng/kg b.w. per day and for BDE-99 of 0.58 and 2.99 ng/kg b.w. per day.

It is important to notice that the category "Food for infants and small children" contributed up to 72 % to the total dietary exposure to BDE-99 of children from 1-3 years old. As indicated in Chapter 5.1.5 the average concentration of BDE-99 in this food group could be overestimated, and consequently this could also be the case for the exposure to BDE-99 of this age group.

The median across surveys of the average intake of BDE-209 is the third highest estimate for children between 1 and 3 years old, with values almost 4 times higher than for adults, with minimum LB and maximum UB of 1.55 and 9.69 ng/kg b.w. per day. The median across surveys of average exposure of the remaing congeners is between 2 and 3 times higher than the respective estimates for adults.

The highest PBDE intake for children with high consumption (95^{th} percentiles) is estimated for BDE-47 and -209, with minimum LB and maximum UB across dietary surveys of 2.90 and 17.63 ng/kg b.w. per day, respectively.

Table 23: Summary statistics of the total dietary exposure (ng/kg b.w. per day) to eight PBDE congeners for **children** with **average and high consumption** (95th percentile). The dietary intake was estimated using the lower (LB) and upper bound (UB) PBDE concentrations estimated from 3,933 samples. Minimum (MIN), median (MEDIAN) and maximum (MAX) values are reported as estimated across consumption surveys (N surveys) in European countries. The total number of individuals participating in the surveys in each age group is also reported (N subjects).

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children with average consumption																			
				BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		BDE-209	
Age class	N surveys	N Subjects		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
1 -3	9	1,600	MIN	0.02	0.38	1.04	1.68	0.58	1.22	0.19	0.85	0.09	0.84	0.07	0.91	0.03	0.80	1.55	5.72
			MEDIAN	0.03	0.51	3.50	4.02	1.18	1.93	0.47	0.97	0.13	1.09	0.13	1.14	0.05	1.07	2.61	6.02
			MAX	0.15	0.87	5.57	6.40	2.15	2.99	1.10	1.86	0.21	1.62	0.37	1.81	0.09	1.56	4.38	9.69
3 - 6	15	4,466	MIN	0.02	0.30	0.82	1.30	0.39	0.75	0.17	0.58	0.07	0.62	0.06	0.65	0.02	0.57	0.86	3.20
			MEDIAN	0.04	0.49	1.17	1.78	0.54	1.12	0.29	0.90	0.12	0.87	0.10	0.96	0.05	0.85	1.38	5.36
			MAX	0.11	0.67	3.01	3.61	0.87	1.56	0.77	1.37	0.19	1.42	0.27	1.52	0.07	1.37	2.24	7.41
6 -10	16	3,958	MIN	0.01	0.17	0.38	0.57	0.17	0.36	0.10	0.29	0.04	0.29	0.04	0.31	0.02	0.24	0.54	1.68
			MEDIAN	0.03	0.35	0.85	1.27	0.34	0.78	0.22	0.61	0.07	0.66	0.08	0.74	0.03	0.59	0.99	3.82
			MAX	0.09	0.54	2.20	2.61	0.59	1.24	0.58	1.00	0.14	1.12	0.20	1.20	0.05	1.07	1.55	5.91
10-18	18	6,559	MIN	0.01	0.11	0.21	0.33	0.09	0.21	0.05	0.17	0.02	0.18	0.02	0.19	0.01	0.15	0.34	1.12
			MEDIAN	0.02	0.20	0.64	0.85	0.24	0.46	0.16	0.38	0.05	0.36	0.06	0.38	0.02	0.31	0.71	2.17
			MAX	0.06	0.30	1.42	1.68	0.36	0.66	0.37	0.63	0.09	0.49	0.13	0.54	0.03	0.42	1.00	3.17
Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children with high consumption (95th percentiles)																			
Age class	**N surveys**	**N Subjects**		**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
1 -3	9	1,600	MIN	0.10	0.65	4.44	5.09	1.36	2.24	0.76	1.69	0.20	1.53	0.26	1.65	0.07	1.53	2.90	9.76
			MEDIAN	0.13	0.79	10.03	10.38	3.80	4.14	1.21	1.86	0.26	1.75	0.35	1.90	0.11	1.78	6.20	10.54
			MAX	0.18	1.40	14.69	15.57	5.31	6.16	1.80	3.09	0.36	3.18	0.50	3.45	0.16	3.24	9.55	17.63
3 - 6	15	4,466	MIN	0.08	0.43	2.92	3.41	0.85	1.47	0.64	1.09	0.15	1.06	0.22	1.08	0.05	1.05	1.69	5.79
			MEDIAN	0.15	0.75	4.26	4.86	1.15	1.90	0.93	1.69	0.22	1.53	0.33	1.73	0.07	1.43	2.47	8.33
			MAX	0.32	1.08	7.89	8.63	1.96	3.11	1.96	2.82	0.37	2.30	0.69	2.49	0.14	2.33	4.10	11.89
6 -10	16	3,958	MIN	0.08	0.37	1.96	2.22	0.51	0.76	0.49	0.78	0.11	0.57	0.17	0.64	0.04	0.52	1.32	3.87
			MEDIAN	0.11	0.61	2.80	3.27	0.79	1.45	0.71	1.29	0.18	1.11	0.25	1.25	0.05	1.08	1.84	6.59
			MAX	0.27	1.03	6.46	6.98	1.10	1.84	1.61	2.20	0.27	1.70	0.56	1.85	0.13	1.66	2.79	11.90
10-18	18	6,559	MIN	0.05	0.23	1.24	1.41	0.26	0.51	0.31	0.49	0.06	0.40	0.11	0.43	0.03	0.37	0.74	2.44
			MEDIAN	0.11	0.41	2.56	2.78	0.54	0.97	0.64	0.91	0.13	0.69	0.23	0.82	0.04	0.62	1.37	4.25
			MAX	0.18	0.52	4.21	4.60	0.78	1.28	1.07	1.49	0.19	0.90	0.37	1.01	0.07	0.86	1.80	5.92

7.3.3. People following specific diets

7.3.3.1. High and frequent fish consumers

High consumption of fish is considered as a special diet with specific concern for PBDE exposure.

Among the high fish consumers, people who might consume fish every day (with particular focus on "Fish meat" consumption), like e.g. fishermen or fish sellers, might even have a higher exposure. In the case of these frequent and high consumers of fish meat, a daily fish consumption of 2.6 g/kg b.w. per day was retrieved from the Comprehensive European Food Consumption Database (as described in Chapter 6.2.) and combined with the PBDE occurrence mean values of fish meat, grouped according to the fat content (as described in Table 13) (Table 24).

Table 24: Additional exposure estimations (ng/kg b.w. per day) to eight PBDE congeners for high and frequent consumers of fish meat (FoodEx level 2) grouped according to the reported fat content in the original samples (≥8 % fat, 8 % < fat > 2 %, ≤ 2 % fat). The dietary intake was estimated using the lower (LB) and upper (UB) bound PBDE mean concentrations.

Additional dietary exposure to PBDEs for high and frequent fish consumers (ng/kg b.w. per day)						
PBDE congeners	**≥ 8 % fat**		**8 % < fat > 2 %**		**≤ 2 % fat**	
	LB	**UB**	**LB**	**UB**	**LB**	**UB**
BDE-28	0.13	0.23	0.09	0.11	0.01	0.02
BDE-47	5.10	5.36	2.47	2.51	0.34	0.35
BDE-99	0.49	0.75	0.47	0.59	0.07	0.08
BDE-100	1.81	2.07	0.57	0.71	0.06	0.07
BDE-153	0.21	0.47	0.06	0.16	0.01	0.03
BDE-154	0.32	0.59	0.22	0.32	0.02	0.03
BDE-183	0.13	0.58	0.02	0.22	0.01	0.03
BDE-209	0.11	1.77	0.13	1.29	0.09	0.16

b.w.: body weight.

7.3.3.2. Consumption of food supplements

Additional intake of PBDEs could also derive from high consumption of "Products for special nutritional use" (FoodEx level 1), and in particular "Supplements containing special fatty acids (e.g. omega-3, essential fatty acids)" (FoodEx level 3). These types of supplements are mainly based on fish oil derived from tissues of oily fish. Fish liver is also an important primary source for the preparation of supplements, and in particular cod liver, sold as liquid oil or capsules. Because the liver is the major filtering and detoxifying organ, PBDE concentrations can be higher in such products than in the more common fish oil produced from the processing of whole fish.

From 10 to 54 samples were reported as "Supplements containing special fatty acids (e.g. omega-3, essential fatty acids)". In Table 25 the LB and UB mean concentrations, the number of analytical results (N) and the respective proportion of non detects (ND (%)) for each of the eight PBDE congeners considered are reported. No specific information on the product form was provided (capsules or liquid). A maximum daily consumption of 15 mL fish oil for the exposure estimate to the listed congeners was assumed (see Chapter 6.2.). Exposure estimates reported in Table 25 are made assuming 60 kg as b.w.

The proportion of non detects for the congeners (except BDE-183 and -209) is below 39 % and it can be more accurately estimated that supplements containing special fatty acids provide an additional intake of BDE-47 up to 0.62 ng/kg b.w. per day (mean UB), followed by BDE-99 (0.12 ng/kg b.w. per day, mean UB), BDE-100 (0.11 ng/kg b.w. per day, mean UB), and finally BDE-154, -153 and -183

with an additional intake below 0.1 ng/kg b.w. per day (mean UB). Due to high proportion of non detects (more than 90 %) for BDE-183 and -209, the calculated intake mainly reflect the LODs and LOQs reported rather than the actual PBDEs levels.

Table 25: Additional exposure to the eight PBDEs considered (upper bound (UB) and lower bound (LB)) due to the consumption of "Supplements containing special fatty acids (e.g. omega-3, essential fatty acids)" to the base diet.

PBDE congener			Mean concentration (ng/g w.w.)		Additional intake in ng (assuming 15 mL oil consumption)		Additional intake assuming 60 kg b.w. (ng/kg b.w. per day)	
	N	ND	LB	UB	LB	UB	LB	UB
BDE-28	52	38 %	0.09	0.11	1.29	1.63	0.02	0.03
BDE-47	54	6 %	2.46	2.47	36.9	37.1	0.62	0.62
BDE-99	54	15 %	0.43	0.46	6.39	6.96	0.11	0.12
BDE-100	54	20 %	0.41	0.45	6.15	6.72	0.10	0.11
BDE-153	54	39 %	0.07	0.15	1.06	2.26	0.02	0.04
BDE-154	54	31 %	0.24	0.30	3.57	4.49	0.06	0.07
BDE-183	54	96 %	0.00	0.09	0.01	1.37	0.00	0.02
BDE-209	10	90 %	5.25	5.80	78.8	87.0	1.31	1.45

w.w: wet weight; ND: non detects; b.w.: body weight.

7.3.3.3. Vegetarians

PBDEs are persistent and lipophilic compounds with low water solubility that bioaccumulate in the food chain. Thus, consumption of food of animal origin represents the main route of human exposure to PBDEs. Since uptake of PBDEs by plants from soil is low, the contamination of food of plant origin is generally of minor importance. This is substantiated by the occurrence data on PBDEs in food samples of plant origin submitted by several European countries to EFSA which were almost completely below LOD/LOQ. Consequently, it can be assumed that the dietary PBDE exposure for vegetarians is even lower than that for people consuming a mixed diet.

7.4. Summary of dietary sources of human exposure to PBDEs

A summary of the dietary sources of PBDEs for different groups of the population is shown in Table 26.

As shown in Table 22 infants below one year old are, on a ng/kg b.w. per day basis, highly exposed via food to PBDEs, in particular to BDE-47, -99 and -209. However, the limited occurrence data available in the category "Food for infants and small children" were not considered adequate to represent products consumed by infants below one year of age (e.g. infant formula and follow-up formula). Considering also the restricted number of consumption data for infants (only two dietary surveys available), it was decided not to further consider this age group in the risk assessment.

For children from 1-3 years old the average and high (P95) intake of BDE-47, -99, -153 and -209 calculated across different dietary surveys is about 3-6 times higher than for adults. As indicated before the exposure to BDE-99 of this age group could be overestimated.

With regard to adult average consumers, the highest dietary exposure was reported for BDE-209 with range of exposure across European surveys between 0.35 and 2.82 ng/kg b.w. per day (minimum LB and maximum UB), followed by BDE-47 with 0.29 and 1.91 ng/kg b.w. per day (minimum LB and maximum UB), BDE-100 with 0.07 and 0.70 ng/kg b.w. per day (minimum LB and maximum UB),

and BDE-154 with 0.03 and 0.51 ng/kg b.w. per day (minimum LB and maximum UB). The congeners that resulted with lowest dietary intake are BDE-28 and BDE-183.

Individuals that might consume fish every day (2.6 g/kg b.w. per day) and consumers of supplements containing special fatty acids (e.g. omega-3, essential fatty acids; 15 ml per day) were considered as a specific population exposed to an additional intake of PBDEs. In Table 26 the total intake of the eight individual PBDE congeners is reported as the sum of the basic diet expressed as the minimum LB and maximum UB across the averages European dietary intakes (Table 17**)** and the additional intake due to fish (Table 24) or supplements, such as fish oil (Table 25).

A higher increase in PBDEs intake compared to the basic diet is due to consumption of fish with high fat content (≥ 8 %). Exposure to BDE-47 in this case can reach 7.27 ng/kg b.w. per day (maximum UB), followed by BDE-100 (2.77 ng/kg b.w. per day) and BDE-99 (1.40 ng/kg b.w. per day). In the case of BDE-209, the total intake can reach 4.59 ng/kg b.w. per day but due to the high proportion of non detects (79 %, data not reported), the estimation varies considerably between minimum LB and maximum UB (0.46 ng/kg b.w. per day, mean LB). The intake for the remaining PBDE congeners is less than 1.1 ng/kg b.w. per day.

The additional consumption of 15 mL of supplements containing special fatty acids has a higher impact in the exposure to BDE-47 and -209 where maximum UB of the basic diet (1.91 and 2.82 ng/kg b.w. per day for BDE-47 and BDE-209, respectively) can increase up to 2.53 and 4.27 ng/kg b.w. per day, respectively.

Table 26: Overview of daily PBDE exposure estimates for different population groups and different food categories.

Exposed population	Food category	Minimum LB and maximum UB exposures estimates across European dietary surveys (ng/kg b.w. per day) for average consumers															
		BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		BDE-209	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Infants	Human milk – average consumption of human milk[a]	(<0.05, 1.38)		(0.64, 13.77)		(<0.14, 5.05)		(0.18, 4.59)		(0.46, 11.02)		(<0.05, 2.30)		(0.23, 1.29)		(0.96, 13.31)	
Infants (less than 1 year)	Diet based on eight selected food categories[b][c]	0.02	0.38	3.63	18.1	1.54	6.93	0.41	2.25	0.1	0.88	0.1	1.07	0.05	0.83	2.81	12.9
Children 1-3 years old	Diet based on eight selected food categories[b]	0.02	0.87	1.04	6.40	0.58	2.99	0.19	1.86	0.09	1.62	0.07	1.81	0.03	1.56	1.55	9.69
Children 3-6 years old	Diet based on eight selected food categories[b]	0.02	0.67	0.82	3.61	0.39	1.56	0.17	1.37	0.07	1.42	0.06	1.52	0.02	1.37	0.86	7.41
Adult	Diet based on eight selected food categories[b]	0.01	0.28	0.29	1.91	0.11	0.65	0.07	0.70	0.03	0.42	0.03	0.51	0.01	0.36	0.35	2.82
		Minimum LB and maximum UB exposures estimates across European dietary surveys (ng/kg b.w. per day) for high consumers															
Infants	Human milk – high consumption of human milk[d]	(<0.07, 2.06)		(0.96, 20.64)		(<0.14, 7.57)		(0.28, 6.88)		(0.69, 16.51)		(<0.07, 3.44)		(0.34, 1.93)		(1.44, 19.95)	
Infants (less than 1 year)	Diet based on eight selected food categories[b][c]	0.03	0.89	10.4	69.4	3.92	26	1.11	7.57	0.26	2.15	0.26	2.46	0.11	2.27	6.33	42.2
Children 1-3 years old	Diet based on eight selected food categories[b]	0.1	1.40	4.44	15.6	1.36	6.16	0.76	3.09	0.20	3.18	0.26	3.45	0.07	3.24	2.90	17.6
Children 3-6 years old	Diet based on eight selected food categories[b]	0.08	1.08	2.92	8.63	0.85	3.11	0.64	2.82	0.15	2.30	0.22	2.49	0.05	2.33	1.69	11.9
Adult	Diet based on eight selected food categories[b]	0.04	0.45	1.1	4.51	0.30	1.07	0.29	1.40	0.07	0.67	0.1	0.85	0.03	0.61	0.7	4.58
Adult	High and frequent fish consumers[e]	0.14	0.51	5.39	7.27	0.60	1.40	1.88	2.77	0.24	0.89	0.35	1.10	0.14	0.94	0.46	4.59

b.w.: body weight; LB: lower bound; UB: upper bound.

Table 26: Continued.

Exposed population	Food category	Minimum LB and maximum UB exposures estimates across European dietary surveys (ng/kg b.w. per day) for high consumers															
		BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		BDE-209	
		LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
Adult	Consumers of supplements containing special fatty acids[(f)]	0.03	0.31	0.91	2.53	0.22	0.77	0.17	0.81	0.05	0.46	0.09	0.58	0.01	0.38	1.66	4.27

b.w.: body weight; LB: lower bound; UB: upper bound.
(a): Lowest and highest value of intake for average consumption of human milk (800 mL) among countries as reported in Table 20.
(b): 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, Food for infants and small children.
(c): Those estimates refer to two ranges of exposure (minimum and maximum) estimated from the only two available consumption surveys (Table 22).
(d): Lower and highest value of intake for high consumption of human milk (1,200 mL) among countries as reported in Table 21.
(e): Diet based on eight selected food categories[(a)] additional consumption of fish with more than 8 % fat content; assumed daily intake of 2.6 g/kg b.w. fish meat. Exposure estimates are derived by summing the basic diet expressed as minimum LB and maximum UB across European surveys for average adult consumers plus the additional PBDEs intake throughout fatty fish as reported in Table 24.
(f): Diet based on eight selected food categories[(a)] and additional consumption of supplements containing special fatty acids (e.g. omega-3, essential fatty acids); assumed daily intake of 15 mL (as maximum daily consumption of cod liver oil). Exposure estimates are derived by summing the basic diet expressed as minimum LB and maximum UB across European surveys for average adult consumers plus the additional PBDEs intake throughout food supplements as reported in Table 25**.**

7.5. Previously reported literature data on PBDEs exposure

7.5.1. Dietary intake of PBDEs

A number of studies have reported the dietary intake of PBDEs in several European countries (Table 27). Comparison between studies should be done carefully due to the different methodologies (sampling methods and food consumption data) used, food categories covered and varying number of PBDE congeners analysed.

In Belgium, Voorspoels et al. (2007) carried out a market-basket survey representative for the general Belgian population. Seven selected PBDEs and BDE-209 were analysed in fish and seafood, meat products, cheese, butter, eggs and fast food. The survey did not include milk, vegetable oils, fruit and vegetables. The total average dietary PBDE intake was estimated between 23 and 48 ng per day, for LB and UB intake, respectively. Fish was the major contributor to the intake (39 %), followed by meat products (30 %).

In Germany, Fromme et al. (2009) estimated the exposure of the adult German population using duplicate diet samples collected in 2005 daily over seven consecutive days. Values were reported for six PBDE congeners (BDE-47, -99, -100, -153, -154 and -183). The estimated daily intake for the sum of the six PBDEs was 69.6 and 176.9 ng per day for average and high scenario, respectively (or 1.19 and 2.50 ng/kg b.w. per day considering a body weight of 60 kg). BDE-183 followed by BDE-99 and -47 were the congeners contributing most to the intake.

In Spain, Gómara et al. (2006) estimated the dietary intake of PBDEs by analysing a total of 104 food samples randomly acquired from several local supermarkets all over Spain including fish and shellfish, meat and meat products, dairy products, eggs and oils. A total of 15 PBDE congeners were analysed, among them the eight PBDEs considered by the CONTAM Panel. The estimated UB total daily intake for the sum of the 15 PBDEs analysed was 38.5 ng per day.

Bocio et al. (2003) and Domingo et al. (2008) estimated the dietary exposure to PBDEs for the general population in Catalonia (Spain) by analysing food samples randomly acquired in local markets, supermarkets and grocery stores from a number of cities in this region in 2000 and in 2006, respectively. The estimated medium bound PBDE intake by the adult population in 2000 was 97.3 ng per day (or 1.4 ng/kg b.w. per day considering a b.w. of 70 kg), while in 2006 the estimated intake was 75.4 ng per day (or 1.1 ng/kg b.w. per day). The highest contribution to the intake corresponded to fish and shellfish, followed by oils and fats and meat and meat products, although in the 2006 study the contribution of cereals was similar to that of fats and oils.

In Finland, Kiviranta et al. (2004) carried out a market basket study on the dietary intake of PBDEs. A total of 228 different food items (3,988 individual samples) collected between 1997 and 1999 were pooled into 10 market baskets. Five PBDE congeners were analysed (BDE-47, -99, -100, -153 and -154). The average intake for the sum of the five PBDEs was 44 ng per day (or 0.58 ng/kg b.w. per day, considering 76 kg as the average b.w. of the population participating in the dietary survey). The congener contributing mainly to the intake was BDE-47, followed by BDE-99 and -100.

In France, ANSES (2010 - documentation provided to EFSA) carried out a TDS covering the years 2006-2010. Fifteen individual sub-samples were gathered in order to analyse one pooled sample, every sample being representative of consumption, purchases and purchase places of the French consumers. The occurrence data were combined with the French consumption survey carried out by AFSSA in 2006-2007 (INCA2). The seven selected PBDEs and BDE-209 were analysed. Mean adult exposure estimates for the sum of the seven PBDEs were 0.20 and 0.22 ng/kg b.w. per day for LB and UB, respectively. For children, mean exposure estimates were 0.31 and 0.34 ng/kg b.w. per day for LB and UB, respectively. The 95th exposure estimates were around 3 times higher than those reported for mean exposure both for adults and children. BDE-47 was the congener contributing mostly to the

exposure estimates (46 and 45 % for adults and children, respectively) followed by BDE-99 (21 and 22 %) and BDE-183 (10-15 and 11-17 %). For both adults and children, fish and other seafood and meat and meat products were the food category contributing mostly to the PBDE exposure. For BDE-209, mean and 95th adult exposure estimates were 3 times higher than the exposure to BDE-47 (mean exposure: 0.33-0.35 ng/kg b.w. per day for LB and UB, respectively) (95^{th} exposure: 0.67-0.72 ng/kg b.w. per day for LB and UB, respectively). Compared to the previous French exposure estimate (AFSSA, 2006), the current exposure estimate for adults for the seven selected PBDEs is between 5 and 10 times lower, while for children it is around 5 to 14 times lower.

In Ireland, Trudel et al. (2010) estimated the PBDE exposure from food by using two probabilistic and one semi-deterministic method. A total of nine PBDE congeners were analysed (the eight PBDE congeners considered and BDE-49). Almost all occurrence data were taken from regular monitoring programmes in Ireland. The food consumption data for the adult Irish population was taken from the North/South Food Consumption Survey published in 2001. For males the mean (median) external dose estimates for the sum of the nine PBDEs calculated with a probabilistic modelling taken as reference method were 0.62 (0.49) and 0.95 (0.83) ng/kg b.w. per day LB and UB, respectively. For females the values obtained were in the same range. BDE-47 and -99 were the congeners contributing most to the estimated intakes, contributing more than 50 % to the total intake. Fish, including fish oil, is the food group contributing most to the intake (50 % and 40 % for female and male adults, respectively), followed by milk and dairy products and meat.

In The Netherlands, Bakker et al. (2008) estimated the dietary intake of the Dutch population using the concentration of five PBDE congeners (BDE-47, -99, -100 and -153+154) in food consumed by the general population in 2003/2004 and consumption data of the third Dutch National Food Consumption Survey (1997/1998). The median dietary intake for the sum of the congeners analysed was 0.53 and 0.79 ng/kg b.w. per day for LB and medium bound, respectively. BDE-47 was the congener contributing most to the dietary intake (60-80 % of the total). The main food categories contributing most to the intake were dairy products (39 %) followed by fish (28 %) and meat (7 %).

Zeilmaker et al. (2008) estimated the dietary PBDE intake using 24-hour duplicate diets collected in 1978, 1984, 1994 and 2004 and results were reported for three PBDE congeners (BDE-47, -99 and -209, the latter only in the samples form 2004). For BDE-47, the median (mean) intake was 0.62 (0.57), 0.03 (0.08), 0.21 (0.14) and 0.54 (0.77) ng/kg b.w. per day for the years mentioned above, respectively. For BDE-99 the intake was 0.03 (0.12), 0.34 (0.30), 0.49 (0.61), 0.41 (0.50) ng/kg b.w. per day for the years mentioned above, respectively. For BDE-209, the intake was 0.26 (0.48) ng/kg b.w. per day for the year 2004.

In Norway, Knutsen et al. (2008) calculated the dietary intake of PBDEs in a group of Norwegians with a wide range of seafood consumption and in a reference subgroup with average seafood consumption using a food frequency questionare covering the total diet the previous year and PBDE concentration in foods on the Norwegian market. The mean (median, range) dietary exposure for all participants for the sum of seven selected PBDEs (BDE-28, -47, -99, -100, -153, -154 and -183) was 1.47 (1.11, 0.14-7.36) ng/kg b.w per day and for the reference group 1.08 (0.77, 0.14-3.63) ng/kg b.w per day (LB). Oily fish species and fish products were the dominating dietary source of PBDEs, followed by dairy products, lean fish and meat. BDE-47 was the main congener contributing to the intake followed by BDE-99. The estimated exposure to BDE-209 was 1.4 (0.5-4.62) ng/kg b.w. per day for all participants, which is in the same range as the exposure to the sum of the seven PBDEs. In this case dairy products were the food group contributing most to the dietary intake, followed by bread, cereals and fish.

Thomsen et al. (2008) calculated the total dietary intake for PBDEs in a group of high consumers of fish from a contaminated lake in Norway (Lake Mjøsa). The mean (median, range) intake for the sum of the seven selected PBDEs was 48 (30, 0.3-260) ng/kg b.w. per day. The contribution from fish from the contaminated lake to the total exposure accounted for 98.7 %. These intake values are much higher in comparison to those estimated for Norwegians eating food with background levels of contamination

(Knutsen et al., 2008). However, for BDE-209 the mean dietary intake was in the same range (1.1 ng/kg b.w. per day).

Dirtu and Covaci (2010) estimated the human exposure to PBDEs through consumption of food of animal origin in Eastern Romania. A total of 71 food samples including meat products, dairy products, vegetable oil and eggs were analysed for the eight PBDEs considered. Fish samples were not included in the food basket collected. The median (5^{th}-95^{th}) intake for the sum of seven selected PBDEs (without BDE-209) was 40 (35-60) ng per day for adults and 24 (21-36) ng per day for toddlers (6-24 months). BDE-209 was below the LOQ in all samples analysed.

In Sweden, Darnerud et al. (2006) assessed the dietary intake of PBDEs using a Swedish market basket study from 1999. Six food groups (including fish, meat, dairy products, eggs, fats/oils and pastries) comprising 52 food items were analysed for five PBDE congeners (BDE-47, -99, -100, -153 and -154). The estimated daily intake of the sum of the five PBDE congeners was 37.0, 50.9 and 64.9 ng per day for LB, MB and UB, respectively (or 0.50, 0.69 and 0.88 ng/kg b.w. per day considering a mean b.w. of 73.7 kg). Fish was the food group mostly contributing to the intake (47 %) followed by dairy products (17 %) and meat (14 %).

Harrad et al. (2004) carried out a preliminary assessment of the exposure to PBDEs via diet in the UK with duplicate diet samples collected in 1999-2000 comprising both omnivorous and vegan diets. A total of five PBDE congeners were analysed (BDE-47, -99, -100, -153 and -154). The median (mean, range) estimated UB daily intake was 117 (130, 59-235) ng per day based on omnivorous diets only.

The FSA (2006) estimated the dietary PBDE intake of UK consumers by analysing 19 composite food samples collected for the 2003 and 2004 total diet studies (TDS). A total of 17 PBDE congeners were analysed, including the eight PBDEs considered in this opinion. The UB estimated average adult intake from the whole diet was 5.9 ng/kg b.w. per day. Meat products followed by fish were the food groups contributing most to the intake.

Despite the fact that previously published studies on PBDE intake are based on different numbers of measured PBDE congeners and food items analysed, the food category contributing most to the dietary PBDE intake was fish and fish products (up to 50 % in some cases), followed by meat and meat products, fats and oils and dairy products. The main congener contributing to the intake was reported to be BDE-47 (up to 80 % in some cases) followed by BDE-99. The majority of the published intake values of the most prevalent congeners (Table 27) are in the same range as those currently estimated in this opinion for average adult consumers (0.29 (LB) to 1.91 (UB) ng/kg b.w. per day for BDE-47 and 0.11 (LB) to 0.65 (UB) ng/kg b.w. per day for BDE-99, Table 26).

In the four studies reporting on BDE-209, the intake was between 0.26 and 4.5 ng/kg b.w. per day, which is in good agreement with the estimate of this opinion for average adult consumers that is between 0.35 (LB) and 2.82 (UB) ng/kg b.w. per day.

Table 27: Dietary exposure to PBDEs reported in the literature for different European countries.

Country, Year	Units	Estimation	PBDE congener										Reference
			BDE -28	BDE -47	BDE -99	BDE -100	BDE -153	BDE -154	BDE -183	Sum 7 PBDEs	BDE -209	Sum PBDEs	
BE, 2005	ng per day	LB UB	nr	nr	nr	nr	nr	nr	nr	23 48	na	-	Voorspoels et al., 2007
DE, 2005	ng per day ng/kg b.w. per day	ns	na	9.63 0.161	15.28 0.255	3.88 0.065	3.07 0.051	3.03 0.051	30.32 0.505	-	na	69.61 1.19	Fromme et al., 2009
ES, 2003-2005	ng per day	UB	nr	nr	nr	nr	nr	nr	nr	-	nr	38.5[(a)]	Gómara et al., 2006
ES, 2000 (Catalonia)	ng per day ng/kg b.w. per day	MB	-	-	-	-	-	-	-	-	na	97.3[(b)] 1.4	Bocio et al., 2003
ES, 2006 (Catalonia)	ng per day ng/kg b.w. per day	MB	-	nr	nr	nr	nr	nr	nr	-	na	75.4 1.1	Domingo et al., 2008
FI, 1997-1999	ng per day[(c)] ng/kg b.w. per day	LB, UB	na	nr	nr	nr	nr	nr	na	-	na	44 0.58	Kiviranta et al., 2004
FR, 2006-2010	ng/kg b.w. per day	UB	0.005	0.092	0.042	0.019	0.015	0.012	0.030	0.216	0.350	0.565	ANSES, 2010
IRE, ns	ng/kg b.w. per day[(d)]	UB	0.022	0.25	0.15	0.058	0.05	0.03	0.039	-	0.29	0.95[(e)]	Trudel et al., 2010
NL, 2003-2004	ng/kg b.w. per day	MB	na	0.40	0.11	0.08	0.14		na	-	na	0.79[(f)]	Bakker et al., 2008

na: not analysed. nr: not reported. LB: lower bound (nd=0), MB: medium bound (nd=1/2 LOD), UB: upper bound (nd=LOD).

Table 27: Continued.

Country, Year	Units	Estimation	PBDE congener									Reference
			BDE -28	BDE -47	BDE -99	BDE -100	BDE -153	BDE -154	BDE -183	Sum 7 PBDEs	BDE -209	Sum PBDEs	
NL, 1978 1984 1994 2004	ng/kg b.w. per day[g]	ns	nr	0.62 0.03 0.21 0.54	0.03 0.34 0.49 0.41	nr	nr	nr	nr	-	na na na 0.26	-	Zeilmaker et al., 2008
NO, 2002-2006	ng per day[c][h] ng/kg b.w. per day	LB	3.0 0.04	52.4 0.69	12.2 0.16	8.4 0.11	2.3 0.03	3.0 0.04	0.8 0.01	82.1 1.08	105.6 1.39	-	Knutsen et al., 2008
NO, 2002-2006[i]	ng per day[j] ng/kg b.w. per day	LB	nr	nr	nr	nr	nr	nr	nr	3,888 48	na	-	Thomsen et al., 2008
RO, 2007 (Iasi)	ng per day[g]	MB	nr	nr	nr	nr	nr	nr	nr	40	nr	-	Dirtu and Covaci, 2010
SE, 1999	ng per day ng/kg b.w. per day[k]	MB	na.	26.5 0.36	nr	nr	nr	nr	nr	-	nr	50.9[l] 0.69	Darnerud et al., 2006
UK, 1999-2000	ng per day[g][l]	UB	na	46.4	42.6	8.2	11.7	11.7	na	-	nr	117	Harrad et al., 2004

Table 27: Continued.

Country, Year	Units	Estimation	PBDE congener									Reference
			BDE -28	BDE -47	BDE -99	BDE -100	BDE -153	BDE -154	BDE -183	Sum 7 PBDEs	BDE -209	Sum PBDEs	
UK, 2001-2004	ng/kg b.w. per day	UB	nr	0.5	0.5	0.08	0.1	nr	nr	-	4.5	5.91[(m)]	FSA, 2006

ns: not specified.
na: not analysed.
nd: not detected.
(a): Sum of 15 BDE congeners (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, -183, -184, -191, -196, -197 and -209).
(b): Results were reported for homologue groups, i.e. tetra-, penta-, hexa-, hepta- and octaBDE.
(c): Based on an average b.w. of 76 kg.
(d): Mean PBDEs external dose estimates (i.e. before uptake) for male adults applying a probabilistic modelling taken as reference method.
(e): Sum of nine PBDE congeners (BDE-28, -47, -49, -99, -100, -153, -154, -183 and -209).
(f): Sum of five congeners (BDE-47, -99, -100 and -153+154)
(g): Median values.
(h): Mean values for the reference group in the study.
(i): Population group with a high consumption of fish from a contaminated lake.
(j): Based on a mean b.w. of 81 kg.
(k): Based on a mean b.w. of 73.7 kg.
(l): Sum of five PBDE congeners (BDE-47, -99, -100, -153, and -154).
(m): Sum of seventeen PBDE congeners (BDE-17, -28, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -153, -154, -183 and -209).

7.6. Non dietary exposure

Non-dietary human exposure to PBDEs can occur via inhalation of gas-phase PBDEs and PBDEs on particles as well as oral intake of house dust. Such exposure can occur in homes as well as in work places. No reports could be identified which indicate that dermal exposure should be of any importance for the total human exposure.

In a study by Fromme et al. (2009) concentrations in indoor air and dust (cumulative tri- to decaBDE congeners readings) ranged from 8.2 to 477 pg/m³ (median: 37.8 pg/m³) and 36.6 to 1,580 ng/g (median: 386 ng/g), respectively. In the same study, the median and 95th percentile daily dietary intake of six tetra- to heptaBDE congeners, as calculated from the 7-day median values of each study subject, were 1.2 and 3.3 ng/kg b.w., respectively, or 67.8 and 208 ng/day, respectively.

BDE-209 is by far the most abundant PBDE congener in house dust although widely different levels are reported. In European house dust, the BDE-209 concentrations as compiled by Fromme et al. (2009) ranged from 63 to 10,000 ng/g in dust from Germany, Sweden and the UK. The concentrations of the sum of BDE-47, -99, -100, -153, -154 and -183 in the same samples were substantially lower and ranged from 26 to 170 ng/g dust. Interestingly, the concentrations of BDE-209 in North American and European house dust samples are reported to be quite comparable: 63-10,000 ng/g in European house dust vs. < 500 to 2,000 ng/g in North American house dust (Fromme et al., 2009). In contrast, the concentration of the sum of BDE-47, -99, -100, -153, -154 and -183 in North American house dust well exceeded European levels: 187-7,184 ng/g vs. 26-170 ng/g.

For BDE-209 the reported concentration in European house dust ranges from 63 to 10,000 ng/g dust. Assuming a daily intake of 50 mg dust and a body weight of 70 kg, the exposure for adults would result in a range of 0.045 to 7 ng/kg b.w. per day. For comparison, the median dietary intake for BDE-209 across countries was estimated to range between 0.62 and 1.79 ng/kg b.w. per day for LB and UB. Knutsen et al. (2008) reported a dietary BDE-209 intake of 1.4 ng/kg b.w. per day which is similar to the exposure estimated in this opinion.

It must be emphasised that children are likely to ingest higher amounts of dust than adults because of e.g. crawling and mouthing behaviour. The EPA assumed that while an adult ingests an average of 50 mg per day, a child ingests an average of 100 mg per day (based on soil ingestion rates) (US-EPA, 2008). Oomen et al. (2008) concluded the same value as a conservative but realistic estimate of dust ingestion for children in The Netherlands.

Performing a BDE-209 exposure estimation from dust (63-10,000 ng/g in European house dust) for children 1-3 years old (assuming a body weight of 12 kg) would thus result in a daily exposure of 0.53-83 ng/kg b.w which might be considerably higher than the corresponding calculated median dietary intake (LB and UB) of BDE-209 ranging between 2.59 and 6.4 ng/kg b.w.

Fromme et al. (2009) used a simplified toxicokinetic model to predict the body burden from the exposure doses in the study and found that these body burden predictions were in the same order of magnitude as the measured blood concentrations. Based on these measurements and exposure assumptions in the study group consisting of 27 female and 23 male healthy subjects, aged 14-60 years, dietary exposure was suggested to be the dominant intake pathway, responsible for 97 % (average intake) and 95 % (high intake) of the total intake of the sum of BDE-47, -99, -100, -153, -154 and -183 of an adult population all of whom resided in 34 homes in southern Bavaria (Table 28).

Table 28: The overall estimated adult average daily intake (pg/kg b.w. per day) of PBDEs in Germany from food, house dust and inhalation of indoor and outdoor air (after Fromme et al., 2009, Table 4).

	Daily intake (pg/kg b.w. per day)[a]			
Congener	**Indoor air**	**Outdoor air**	**House dust**	**Diet**
BDE-47	1.9	0.2	7.5	161
BDE-99	0.5	0.1	10.4	255
BDE-100	0.1	0.02	2.1	65
BDE-153	0.05	0.01	2.3	51
BDE-154	0.03	0.01	1.4	51
BDE-183	0.1	0.02	3.6	505
Sum PBDEs[b]	2.6	0.3	32.6	1,194
BDE-209	1.9	0.3	260	-

(a): Dietary intake was assessed by means of a duplicate diet study for an adult of 60 kg b.w. Dust and air intakes were obtained by combining German monitoring data with assumed daily intakes of 50 mg, inhalation of 13.3 m^3 of inhaled air and 90 % of the daily time spent indoor.
(b): Sum of BDE-47, -99, -100, -153, -154 and -183.

Based on concentrations found in home and office dust, D'Hollander et al. (2010) performed an estimation of human exposure through ingestion of dust by toddlers (12 kg b.w.) and adults (70 kg b.w.), using average adult and toddler ingestion of dust figures of 0.5 and 5.2 mg per hour, respectively. These figures were then combined with the average awake time spent indoors. Using high (95th percentile) intake estimates, average dust intake were calculated to be 215 and 20 mg per day for toddlers and adults, respectively. Based on these data the daily intake from dust of the sum of 9 PBDEs (BDE-28 excluded from the set of ten) and BDE-209 were calculated for toddlers, working and non-working adults. The results are summarised in Table 29. It can be noted the intake estimated is generally higher in toddlers compared to non-working adults whereas working adults fall in between these two categories.

Table 29: Estimated daily intake (ng) of PBDEs via house and office dust (D'Hollander et al., 2010). A: average concentration in dust. B: high (95th percentile) concentration in dust.

		Toddlers		**Non-working adults**		**Working adults**	
		Average dust intake	High dust intake	Average dust intake	High dust intake	Average dust intake	High dust intake
Sum of 9 PBDEs[a]	A	1.4	5.8	0.2	0.5	0.5	1.3
	B	13.5	57.0	2.0	5.2	17.1	47.8
BDE-209	A	16.0	67.3	2.2	6.1	2.5	7.0
	B	77.1	325.3	22.8	29.7	23.5	65.8

(a): Sum of BDE-47, -99, -100, -153, -154, -183, -196, -197 and -203.

The highest estimated daily intakes by toddlers of the sum of none PBDEs (57 ng) and BDE-209 (325 ng) expressed as exposure by dividing the intakes with the weight used by D'Hollander et al. (2010) (12 kg) resulted in 4.7 and 27 ng/kg b.w. per day, respectively.

In a recent study Harrad and Abdallah (2011) estimated the exposure to UK adults and toddlers from car dust. The contribution to overall exposure from all PBDEs studied was marginal, except for BDE-209. The exposure of BDE-209 from car dust was estimated to be 160 ng per day for adults and

390 ng per day for toddlers. Considering body weights at 70 and 10 kg, respectively, the contribution from car dust could be estimated to 2.3 and 39 ng/kg b.w. per day for adults and toddlers, respectively.

These exposure estimates indicate that house and car dust can be important routes of exposure especially for children to BDE-209.

Kohler et al. (2008) compared OctaBDE congener patterns in sediments from a Swiss lake with octaBDE congener patterns from known sources revealed that they were distinctively different from those in technical PBDE products but that they were similar to those in house dust and photodegradation products of DecaBDE, suggesting that BDE-209, via debromination, could be an important source to especially higher brominated PBDEs found in house dust. In a study by Tamade et al. (2002) dust in television sets were found to on average contain 4.1 µg/g of PBDDs/DFs with 4-8 bromines, and 230 µg/g of PBDEs. This indicates that not only de-bromination but also transformation of PBDE to PBDDs/DFs should be considered when estimating total human exposure to BFRs and related compounds.

8. Hazard identification and characterisation

8.1. Toxicokinetics

8.1.1. Absorption

Several experimental studies in rodents have addressed the absorption of PBDEs using individual ^{14}C-labelled congeners or administration of mixtures of PBDE congeners (see below). These studies indicate that while the uptake of BDE-209 after oral dosage occurred at a limited extent, the gastrointestinal absorption of lower brominated diphenyl ethers can be much higher. In addition to diet, indoor dust is a likely source of PBDE intake. Indirect evidence for the absorption of PBDEs by inhalation in animals was provided by toxicological studies in rats intermittently exposed to a dust aerosol for 13 weeks contaminated with an OctaBDE commercial product (cited in ATSDR, 2004). Whereas inhalation has been estimated to be negligible, ingestion of household dust can be a significant contributor to the daily PBDE intake (Lorber, 2008). Huwe et al. (2008) demonstrated that absorption of PBDEs dissolved in corn oil or adsorbed on dust did not differ.

BDE-47

Gastrointestinal absorption of BDE-47 in rodents can be estimated from a study carried out by Örn and Klasson-Wehler (1998) in rats and mice administered by gavage a single dose of 15 mg ^{14}C-BDE-47. Faeces and urine were collected daily until day 5, when the animals were sacrificed. The parent compound excreted in the faeces on day 1 was assumed to represent non-absorbed dose and corresponded to approximately 6 and 8 % of the administered dose in rats and mice, respectively, suggesting that over 90 % of the dose was absorbed. Toxicokinetic experiments carried out by Staskal and co-workers confirmed this value, showing that over 80 % of the dose was absorbed when different doses of ^{14}C-BDE-47 were orally administered to mice (Staskal et al., 2005, 2006a).

Sanders et al. (2006) investigated potential sex and species differences in the toxicokinetics of BDE-47, monitoring the fate of ^{14}C-BDE-47 (1 µmol/kg b.w.) given by gavage in corn oil. An estimate of the extent of absorption of BDE-47 in rats and mice was made by comparing tissue distribution and excretion data of ^{14}C-BDE-47. Rats absorbed about 75 % of the dose while mice absorbed about 85 %, suggesting that intestinal absorption may be lower in rats than in mice.

BDE-209

The early works regarding BDE-209 were conducted in rats fed this compound at high dietary concentrations (> 230 mg/kg feed) and suggested that BDE-209 was poorly absorbed from the gastrointestinal tract (NTP, 1986; ATSDR, 2004; Hardy et al., 2009). However, in a more recent study carried out in rats dosed by gavage with radiolabelled BDE-209 (2.8 mg/kg b.w.) Mörck et al. (2003) estimated that BDE-209 gastrointestinal absorption was about 10 %. Sandholm et al. (2003) performed a study of the bioavailability of BDE-209 in rats in which one subset of rats was dosed orally by gavage with radiolabelled BDE-209 (1.9 mg/kg b.w.) while a second subset was dosed intravenously. Blood plasma was monitored at regular intervals (at 1, 3, 6, 24, 48, 72, 96, 120 and 144 h) over the 6-day monitoring period. The oral bioavailability (defined as the fraction of administered parent compound reaching systemic circulation) was determined to be 26 %, with the maximum plasma concentration (264 pmol/mL) occurring 6 hours after dosing. Quantitative oral absorption data in humans were not located.

Other PBDE congeners and metabolites

Hakk and co-workers investigated the fate of radiolabelled BDE-99, -100 and -154 in rats after a single oral dose (between 2.2 and 7.2 mg/kg b.w., depending on the congener) of each of these compounds (Hakk et al., 2002, 2006, 2009). Gastrointestinal absorption was estimated to be 50, 73 and 77 % of the ingested dose, respectively. These values are consistent with those reported in rodents by others for BDE-99 (85 %) (Chen et al., 2006b) and BDE-153 (70 %) (Sanders et al., 2006).

No studies have yet been performed regarding uptake and absorption of PBDE metabolites, i.e. OH-PBDEs. This is logical since OH-PBDEs are formed *in vivo* from individual PBDE congeners. However, OH-PBDEs are also natural products from marine biota (see Chapter 8.1.3) and may accordingly be taken up via the food web. A major natural product, 6-OH-BDE-47, is also a BDE-47 metabolite and the compound is e.g. identified in human blood from the general Swedish population (Hovander et al., 2002). However, the origin of human levels of 6-OH-BDE-47 is not clear.

8.1.2. Distribution

The tissue distribution of a variety of lower and higher brominated diphenyl ethers has been studied in rats and mice. Substantial differences were observed between BDE-209 and other PBDE congeners.

BDE-47

In a study carried out by Örn and Klasson-Wehler (1998), adult male Sprague-Dawley rats or male C57B1 mice were given by gavage a single dose of approximately 15 mg/kg of ^{14}C-labeled BDE-47. Adipose tissue, liver, lung, kidney, brain, and plasma were analyzed for ^{14}C-BDE-47 and metabolites. After 5 days, 86 % of the administered dose was retained in rat tissues, apparently stored as the parent compound. Distribution of the radioalabel expressed on a lipid weight basis was as follows: adipose tissue > lung > kidney, liver > brain. ^{14}C levels in plasma were low. In mice, 47 % of the dose remained in the body after 5 days, mainly as the parent compound. On a lipid weight basis, concentrations of ^{14}C in mice were highest in adipose and liver tissues and were of similar magnitude, followed by kidney and lung. Only traces were found in brain. The data obtained by Staskal et al. (2005) in C57BL/6 mice administered a single oral dose (0.1, 1.0, 10 or 100 mg/kg) of ^{14}C-BDE-47 are in accordance with those of Örn and Klasson-Wehler (1998). Five days after dosing, the concentration in adipose tissue was highest, levels in skin, liver, muscle, and lung were intermediate and those in kidney, blood, and brain were low. The concentrations roughly reflected the tissue levels of lipid and support the hypothesis that BDE-47 accumulates in lipid-rich tissues. Concentrations in all tissues increased with dose. Additional studies performed in rodents with ^{14}C-BDE-47 confirmed that the majority of residues were contained in adipose tissue (Darnerud and Risberg, 2006; Sanders et al., 2006).

Sanders et al. (2006) examined the impact of repeat dosing on the disposition of BDE-47 in male rats. Doses of 0.1 µmol/kg (approximately 0.05 mg/kg) of ^{14}C-BDE-47 were administered for 1, 5, or 10 consecutive days. Accumulation of radioactivity showed a linear response with time and did not appear to reach saturation in adipose tissue, liver, brain, adrenal, skin, thymus and kidney over the course of the 10 daily doses. BDE-47-derived radioactivity appeared to be at or near steady state in the lung, muscle, and thyroid by the fifth dose.

Staskal et al. (2006a) investigated the disposition of BDE-47 in C57BL/6 mice at various developmental stages. Groups of six pups (three males and three females; one pup per litter) were orally administered 1 mg/kg ^{14}C-BDE-47 dissolved in corn oil on postnatal day (PND) 10. The pups were sacrificed at 3, 8, or 24 hours or 5 or 10 days after dosing. The tissue levels in the pups were compared with those in adult rats from the Staskal et al. (2005) study discussed above. Based on total body level of radiolabel, the retention of administered dose was significantly higher in pups than in adults at all time points.

Recently, Ta et al. (2011) orally exposed female C57BL/6J mice to daily doses of 0, 0.03, 0.1 or 1 mg/kg b.w. BDE-47, beginning 4 weeks prior to conception, continuing through gestation and lactation, and ending at weaning on PND21. After 4 weeks of exposure, levels of BDE-47 in blood, brain, liver and adipose tissue of dams reached 36.8±6.1, 162±23, 1,510±60 and 20,800±500 ng/g tissue, respectively, for the 1mg/kg group. Concentrations were not significantly different at parturition (after an exposure period of 8 weeks), except for brain for which the levels were approximately two fold higher than at 4 weeks. BDE-47 tissue levels in the dams decreased between parturition and weaning. BDE-47 levels in the offspring from the 1 mg/kg b.w. group decreased from 366±117 (PND1) to 202±158 (PND21) in the brain, and from 516±326 (PND7) to 249±93 (PND21) in blood.

BDE-209

In a study in which a single dose (2.8 mg/kg b.w.) of ^{14}C-BDE-209 was administered to male rats by gavage, the amount of radioactivity remaining in the body after 3 and 7 days was approximately 9 % of radioactivity ingested (Mörck and Klasson-Wehler, 2001; Mörck et al., 2003). The highest concentrations on a fresh weight basis were in adrenals, kidneys, heart, and liver after both 3 and 7 days. Based on lipid weight, plasma and liver had the highest concentrations and adipose tissue had the lowest concentrations at both time points. Viberg et al. (2003a) administered ^{14}C-BDE-209 by a single oral gavage to groups of neonatal mice on PND3, 10, or 19 and measured radioactivity in brain, heart, and liver 24 h and 7 days post-dosing. For animals treated on PND3, concentrations in brain increased 0.48 % of the dose (day 1) to 0.74 % of the dose (day 7), whereas for PND19 group, residues in brain accounted for 0.06 % of the dose at day 1 and remained the same level at day 7. In liver, the residues for PND3 animals decreased from 12.8 (day 1) to 4.8 % dose (day 7), whereas for PND19 animals the values were 5.8 and 0.31 % dose, respectively.

Riu et al. (2008) investigated the fate of ^{14}C-BDE-209 in pregnant rats. Animals were force-fed daily with 99.8 % pure ^{14}C-BDE-209 (2 mg/kg b.w. per day) at a late stage of gestation (days 16 to 19). Animals were sacrificed on day 20 of gestation, 24 h after the last treatment. More than 19 % of the administered dose was recovered in tissues and carcasses of the dams and the highest residual levels were found in adrenals (33 µg/g), ovaries (16 µg/g) and liver (11 µg/g). Only small amounts of BDE-209 residues were found to cross the blood-brain barrier, but about 0.5 % of the dose was found in foetuses (whole litter) demonstrating that BDE-209 residues are able to cross the placental barrier in rats. In all tissue extracts, most of the radioactivity was associated with unchanged BDE-209.

BDE-209 has been found to account for approximately 50 % of the total PBDE congeners present in 50 human placental samples collected in Denmark (Frederiksen et al., 2009b). Antignac et al. (2009) identified BDE-209 in 36 of the 72 cord blood samples collected in the southwest of France (LOD=0.7 ng/g fat), demonstrating the capability of this contaminant to cross the placenta.

Recently, Cai et al. (2011) evaluated the maternal transfer of BDE-209 to fetuses and pups in rats exposed during pregnancy and lactation periods. Starting at gestational day (GD) 7, animals were treated daily by gavage with 5µmol (corresponding to 4.8 mg) BDE-209 per kg b.w. for 18 days (including a postpartum period of 3 days). GC-MS analyses of whole fetal and pup rat at GD15, GD21 and PND4 indicate a time-dependent increase of BDE-209 concentrations (from approximately 20 µg/g fat at GD15 to 45 µg/g fat at PND4). In addition to BDE-209, which was the predominant compound in all investigated samples, substantial amounts of nonaBDEs (BDE-206, -207 and -208) as well as traces of octaBDEs were found in the blood of rat dams, in placenta and in foetuses and neonates.

Other PBDE congeners and metabolites

Studies performed in rats with PBDEs such as BDE-99, -100 and -153 resulted in a body distribution similar to BDE-47, with a preference for the lipid-rich tissues such as adipose tissue, and to a lesser extent gastrointestinal tract, skin, adrenals and liver (Hakk et al., 2002; 2006; 2009).

The distribution of radiolabelled BDE-85 and -99 was investigated in mice (Darnerud and Risberg, 2006). No significant difference in distribution between these two congeners was observed, the adipose tissue and the liver being the major tissues in which residues were retained. Milk transfer and tissue concentrations of BDE-85 and -99 were also determined during the neonatal period (12-15 days post partum). Following maternal exposure, the fetal uptake was limited, whereas during lactation an important fraction of the dose (about 20 % of the studied pentaBDEs) given to the dam was transferred to the offspring. Staskal et al. (2006b) compared the toxicokinetics of radiolabelled BDE-99, -100 and -153 in mice after intravenous injection of these congeners. All compounds distributed with similar patterns into lipophilic tissues. However, tissue concentrations 5 days following exposure were much higher for BDE-153 than for -100 and -99, respectively.

For higher brominated diphenyl ethers such as octa- and nona-substituted congeners, no specific data were identified.

Mixture studies indicated that, relative to each other, more BDE-47 was distributed to adipose tissue, more BDE-153 accumulated in the liver, and BDE-99 was metabolized to the greatest extent (Sanders et al., 2006). Reistad et al. (2006) investigated the distribution of PBDE congeners in rats after a single intraperitoneal injection (13.2 ± 0.7 mg/kg b.w.) of DE-71 in which BDE-99, -47 and -100 were the major congeners, representing 49 %, 32 % and 9.5 % of the total, respectively. Residues were monitored in liver and brain 72 h after treatment. Liver samples contained 4,010 µg/kg w.w. (sum of BDE-28, -47, -49, -99, -100, -138, -153, -154 and -183), whereas brain samples contained 559 µg/kg for the same sum of congeners. The hepatic levels for individual congeners were 2,212, 753 and 337 µg/kg for BDE-99, -47 and -100, respectively, whereas in the brain the corresponding concentrations were 252, 193 and 77 µg/kg, respectively.

In a recent study, Huwe et al. (2008) measured PBDE congeners in tissues of rats fed an oil solution prepared with technical PBDE mixtures for 21 days to simulate subchronic low-level exposures to PBDEs. They found that all major tri- to octaBDE congeners found in the fat had reached or were approaching a steady state concentration after 14 days of dosing. They also reported that the BCFs for adipose tissue were inversely related to the degree of bromination and ranged between 7 and 24 for tri- to hexaBDEs, 1-6 for hepta- to nonaBDEs, and <1 for decaBDE. All investigated congeners exhibited a BCF for the liver < 1. A notable difference in bioconcentrating potential between two hexa-brominated congeners, BDE-154 and -153 has been reported. In all dose groups, BCFs for BDE-153 were 3-4 times higher than for BDE-154 in adipose tissue and 6-9 times higher in liver. One reason for this may be the low metabolism of BDE-153 compared to BDE-154 (Staskal et al., 2006b).

The phenolic PBDE metabolites (OH-PBDEs) may, depending on their structures, bind to blood proteins to become retained in human blood (Athanasiadou et al., 2008; Qiu et al., 2009; Yu et al.,

2010). A few OH-PBDE congeners have been shown to bind to transthyretin, the thyroxine (T4) transporting protein (Malmberg, 2004).

8.1.3. Metabolism

Like PCBs, PBDEs can be transformed into hydroxylated (OH-) metabolites (Hakk and Letcher, 2003). In mice, BDE-47 can be transformed into different tri- or tetrabrominated hydroxylated metabolites (Örn and Klasson Wehler, 1998). BDE-99 and -100 have also been found to be metabolised to a number of different OH-PBDEs in the rat (Hakk et al., 2002, 2006). Exposure of rats to seven PBDEs commonly found in the environment has been shown to generate up to 16 OH-PBDEs (Malmberg et al., 2005).

Although metabolic studies have been performed on a limited number of PBDE congeners, available experimental data indicate that all types of PBDEs are biotransformed in rodents, including highly brominated congeners such BDE-209. The first step in metabolism of highly brominated diphenyl ethers is debromination of the molecule followed by an oxidative pathway resulting in the production of hydroxylated metabolites (OH-PBDEs).

OH-PBDEs may be named hydroxylated PBDEs or polybrominated phenoxyphenols which in part may imply the origin of the compounds, i.e. in the former case being metabolites of the industrial chemicals, the PBDEs, and in the latter case originating from biosynthesis by marine organisms (Capon et al., 1981; Carté and Faulkner, 1981; Hakk and Letcher, 2003; Malmberg et al., 2005; Marsh et al., 2006). A number of naturally occurring OH-PBDEs have been structurally identified with the common feature that the hydroxy group is attached to one of the *ortho*-positions in the PBDE structure (Marsh et al., 2004; Teuten et al., 2005; Wan et al., 2009; Löfstrand et al., 2010; Nordlof et al., 2010). A major natural product, the 6-OH-BDE-47, is shown in Figure 17, but several other OH-PBDEs are known as natural products. Further, also polybrominated phenoxyanisols, also named methoxylated PBDEs (MeO-PBDEs), have been identified as natural products (Anjaneyulu et al., 1996; Cameron et al., 2000; Teuten et al., 2005) but are not reported as metabolites of PBDEs. However, MeO-PBDEs may be demethylated to form OH-PBDEs (Wan et al., 2009). Hence the OH-PBDEs may originate form several sources. The MeO-PBDEs are lipophilic neutral compounds that can be absorbed and distributed in living organisms similarly as PBDEs. OH-PBDEs are less readily taken up from food since the OH-PBDEs are primarily localized to the blood compartment of vertebrates. OH-PBDEs in mussels may however be a source for humans even though there still is a lack of data in this context.

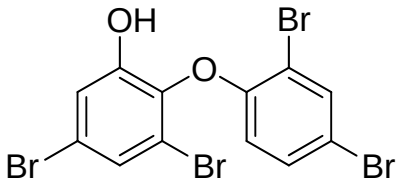

Figure 17: 6-OH-BDE-47, a metabolite of BDE-47 and a major natural product.

Numerous OH-PBDEs, as metabolites of PBDEs, have been structurally identified. Metabolites of BDE-47 (Örn and Klasson-Wehler, 1998; Marsh et al., 2006), BDE-99 (Hakk et al., 2002), BDE-100 (Hakk et al., 2006), BDE-154 (Hakk et al., 2009) and BDE-209 (Mörck et al., 2003; Sandholm et al., 2003), have been reported from the experimental studies referred to.

BDE-47

A general mammalian metabolic pathway of BDE-47 is shown in Figure 18, indicating major metabolites formed. Faeces from rats dosed orally with ^{14}C-BDE-47 have been analysed for hydroxylated metabolites (Marsh et al., 2006). Six hydroxylated tetraBDEs, as well as three hydroxylated triBDEs were structurally identified. They were 2'-hydroxy-2,4,4'-triBDE, 3'-hydroxy-2,4,4'-triBDE, 4'-hydroxy-2,2',4-triBDE, 6-hydroxy-2,2',4,4'-tetraBDE, 2'-hydroxy-2,3',4,4'-tetraBDE, 3-hydroxy-2,2',4,4'-tetraBDE, 5-hydroxy-2,2',4,4'-tetraBDE, 4'-hydroxy-2,2',4,5'-tetraBDE and 4-hydroxy-2,2',3,4'-tetraBDE. Analysis of biliary metabolites collected from rats receiving 1 µmol/kg (*ca* 0.5 mg/kg) ^{14}C-BDE-47 intravenously (Sanders et al., 2006), resulted in the identification of two glutathione conjugates, namely 5-(glutathion-S-yl)-2,2',4,4'-tetraBDE and 6-(glutathion-S-yl)-2,2',4,4'-tetraBDE. In the metabolic pathway proposed by the authors the glutathione conjugates were formed through an arene oxide intermediate. This is consistent with the presence of non extractable radioactivity in several organs of rodents treated with ^{14}C-BDE-47 (Örn and Klasson-Wehler, 1998) suggesting the formation of reactive intermediates. In addition, a glucuronide and a sulfate conjugate of 2,4-dibromophenol were detected in the urine of BDE-47-treated rats (Sanders et al., 2006).

Recently, Lupton et al. (2009) showed that BDE-47 was metabolized by human liver microsomes with relatively large interindividual differences. Two metabolites were identified: a dihydroxylated BDE-47 and 2,4-dibromophenol.

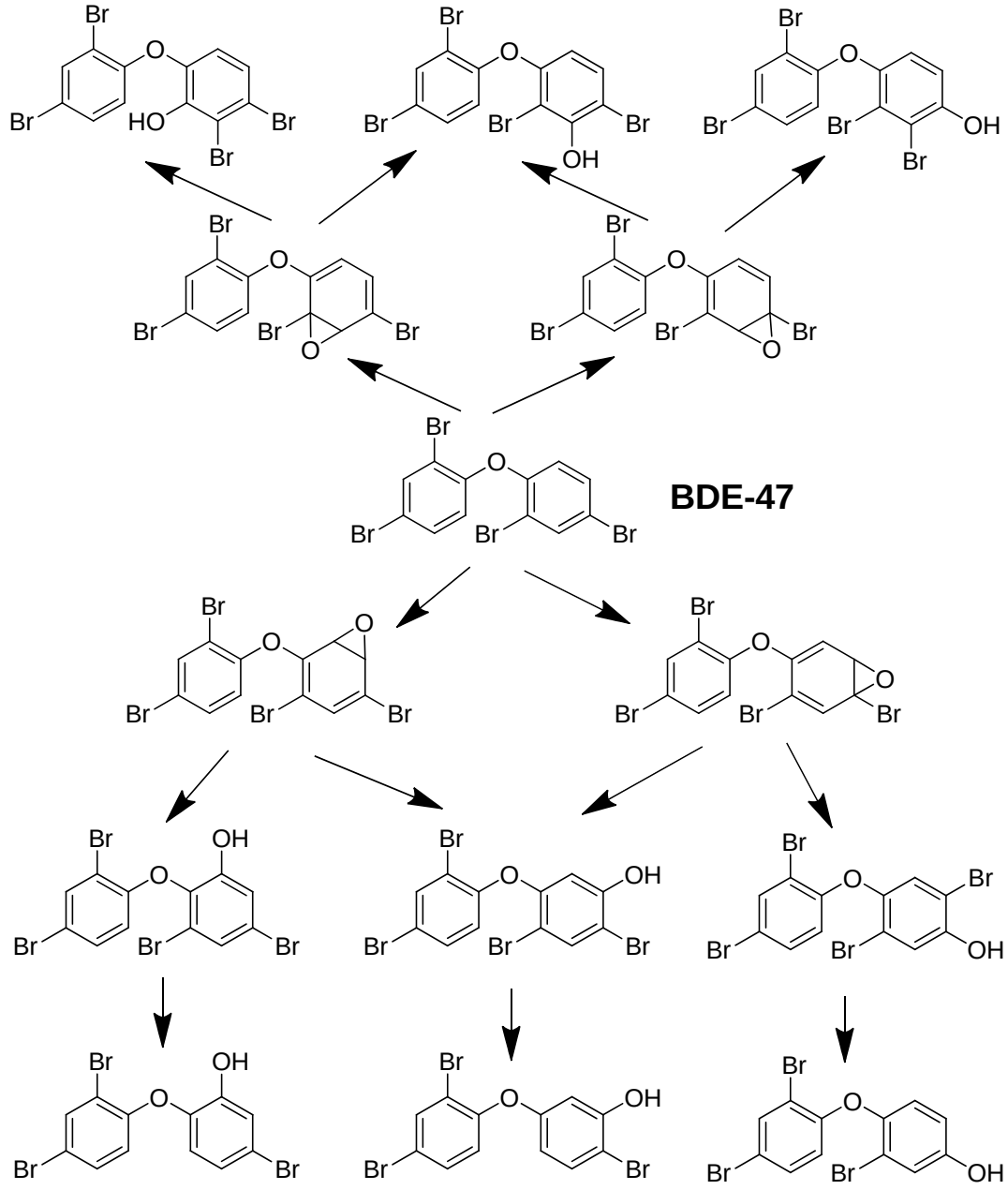

Figure 18: Oxidative and reductive metabolic pathway of BDE-47. A primary four BDE-47 arene oxide intermediates are the parents of six hydroxy-tetraBDE metabolites (upper and second to the bottom row of OH-tetraBDE structures). Each hydroxy-tetraBDE may undergo debromination to form the three hydroxy-triBDE metabolites shown in the bottom row.

BDE-209

Mörck et al. (2003) investigated the metabolic pathways of BDE-209 in rats orally dosed with radiolabelled BDE-209. The BDE-209 substance used in the study was synthesised by a multi-step process involving the bromination of ^{14}C-labelled phenol ultimately giving ^{14}C-BDE-209 (purity determined at > 98 %). The authors analysed the metabolites present in tissues or excreted in faeces, bile and urine. Radioactivity related to BDE-209 was present in the faeces, bile and tissues of exposed rats as a combination of non-extractable residues, lipid-bound residues, water-soluble residues, phenolic metabolites and neutral metabolites/parent compound. Analysis of the phenolic fraction of faeces and tissues indicated the presence of hydroxylated and hydroxy-methoxylated penta- to heptaBDEs. The authors speculated that the potential sequence of events in metabolic transformation of BDE-209 would involve debromination followed by hydroxylation of the benzene ring to form a catechol either directly via an arene oxide or by monohydroxylation followed by secondary oxidation of the resulting phenol. The resulting catechol may then be methylated, potentially by the action of catechol-O-methyltransferase to form the observed hydroxymethoxylated metabolites. The authors also speculated that cytochrome P450 (CYP) enzymes might be responsible for the production of reactive metabolites resulting in a large proportion of bound residues present in the small intestine. The reactive intermediates would also be subject to rapid conjugation via Phase II metabolic processes leading to water-soluble metabolites which would be excreted via bile and faeces, as was observed in the conventional and cannulated rats. The analysis of plasma metabolites in the study performed by Sandholm et al. (2003) in rats orally exposed to ^{14}C-BDE-209 confirmed the formation of debrominated metabolites (mainly different isomers of nonaBDE) as well as hydroxylated metabolites consisting of a hydroxy-octaBDE, a hydroxy-nonaBDE and a hydroxymethoxy-hexaBDE. According to Hakk and Letcher (2003), a likely metabolic pathway between BDE-209 and hydroxylated or hydroxymethoxylated PBDEs is debromination as a first step, followed by the formation of an arene oxide, and subsequent hydroxylation and/or methoxylation. Riu et al. (2008) identified octa- and nonaBDEs and hydroxylated octaBDE as metabolites in tissues and excreta of pregnant rats orally exposed to ^{14}C-BDE-209.

Debromination of BDE-209 was confirmed by Huwe and Smith (2007) in rats. They found that the formation of BDE-197 and -207 from BDE-209 results from *meta* debromination(s), while *para* and *meta* debrominations are responsible for BDE-201 formation. The authors proposed that the action of deiodinase enzymes catalyzing *meta* debromination of BDE-209 was a likely explanation for the increased presence of lower brominated diphenyl ethers congeners.

These data suggest that reductive debromination to nona-, octa- and heptaBDEs is the likely first step in the metabolism of BDE-209. The debrominated metabolites then appear to undergo hydroxylation to form phenols or catechols, potentially via an arene oxide (Figure 19). This could involve the action of CYP enzymes. The catechols are then methylated, potentially by the action of catechol-O-methyltransferase, to form the observed hydroxymethoxylated metabolites which could be further oxidized to quinones, which are highly reactive and would bind to cellular macromolecules. The reactive intermediates and phenolic compounds would also be subject to rapid conjugation via Phase II metabolic processes, leading to water-soluble metabolites which would be excreted via bile and faeces.

It seems likely that nona-BDEs and octa-BDEs are formed in humans after exposure to BDE-209, as supported by the data from a cross-sectional study of rubber workers, using a technical DecaBDE product containing only trace levels of octa- and nonaBDEs and showing substantial concentrations of these congeners in the serum samples (Thuresson et al., 2006). The rate at which this conversion occurs is not known.

Yu et al. (2010) reported the identification, by comparison to authentic reference standards, of three OH-PBDEs: one with nine bromines, 6'-OH-BDE-206, and two with eight bromine substituents, 6-OH-BDE-196 and 6-OH-BDE-199.

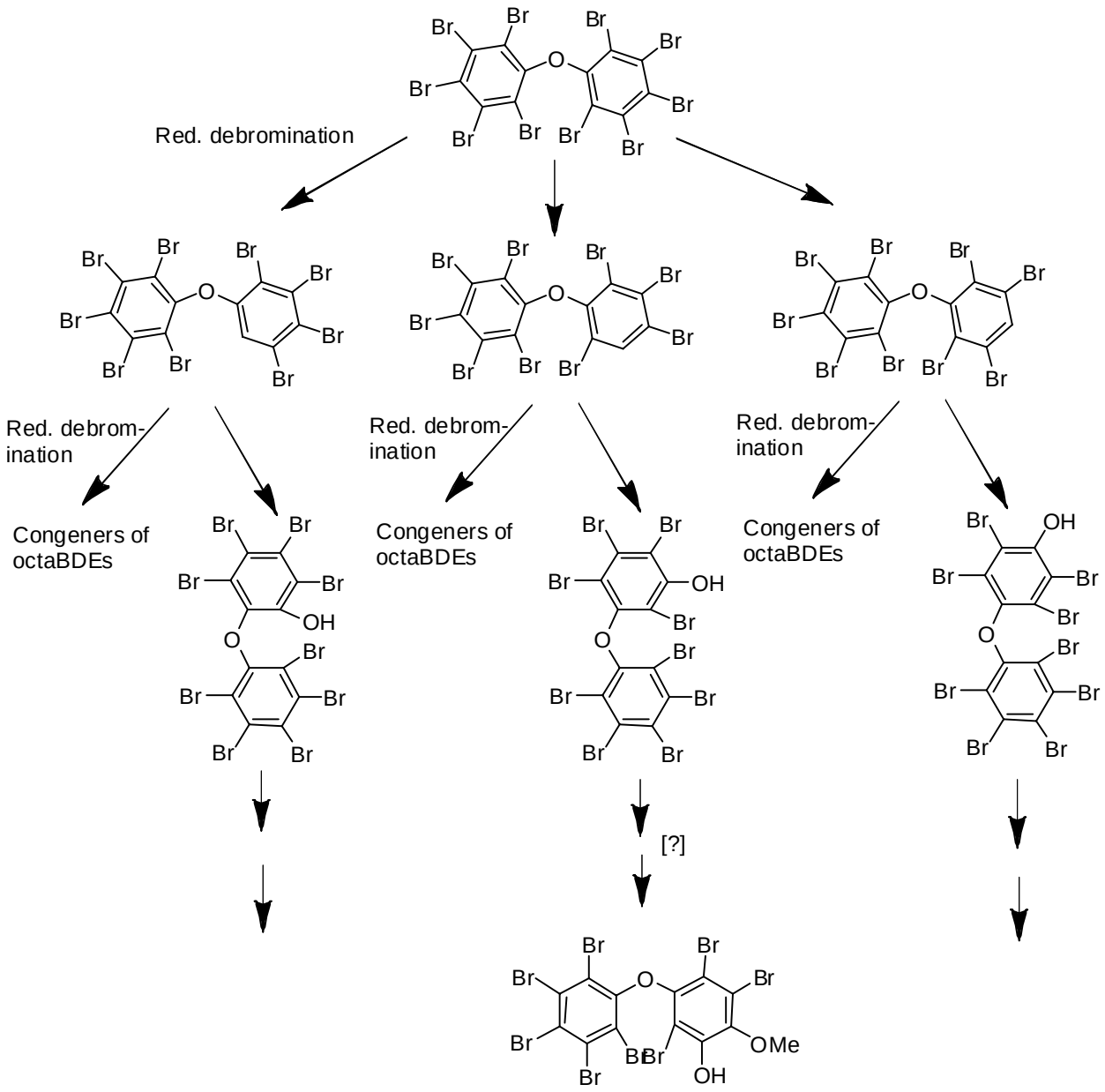

Figure 19: Metabolic pathway of BDE-209. Debromination of BDE-209 is a prerequisite for the formation of hydroxynonaBDE metabolites.

Other PBDE congeners

The metabolism of BDE-99 in rats has been reported by Hakk et al. (2002), detecting small amounts of monohydroxylated metabolites of tetra- and pentaBDEs in faeces. The presence of bound residues in faeces suggests the formation of reactive intermediates. In bile, mono- and dihydroxy-pentaBDEs as well as two thio-substituted pentaBDEs were found. Two dihydrohydroxy-S-glutathionyl and two S-glutathionyl conjugates of BDE-99, 2,4,5-tribromophenol glucuronide, two mono-hydroxylated BDE-99 glucuronides, and three mono-hydroxylated tetrabromodiphenyl ether glucuronides were identified in bile of male rat orally exposed to radiolabelled BDE-99 by Chen and coworkers (Chen et al., 2006b). These authors also identified 2,4,5-tribromophenol and its glucuronide and sulfate conjugates in urine and 2,4,5-tribromophenol, one mono-hydroxylated tetrabromodiphenyl ether, and two monohydroxylated BDE-99 in faeces. These data indicate that BDE-99 undergoes more extensive metabolism than BDE-47. Recently, Stapleton et al. (2009) exposed human hepatocytes to solutions containing 10µM BDE-99 for periods of 24-72 hr. These incubations resulted in the formation of

2,4,5-tribromophenol, two monohydroxylated pentabrominated diphenylether metabolites and an unidentified tetrabrominated metabolite

Mono- and di-hydroxylated metabolites corresponding to the parent compound as well as to lower brominated diphenyl ethers were also detected in the faeces of rats treated with BDE-100 or -154 (Hakk et al., 2006; 2009).

8.1.4. Elimination

Various studies have addressed the excretion of PBDEs in rodents using different routes of administration. These studies indicate that BDE-209 is eliminated faster than some lower brominated diphenyl ethers such as BDE-47. All investigated PBDEs are mainly excreted via faeces, whereas urine represents a minor route of elimination.

8.1.4.1. Excretion routes

BDE-47

Studies with rats and mice showed noticeable differences in excretion rates between the two species. Five days after a single oral dose, cumulative urine excretion represents 10-40 % of the dose in mice, depending on the amount of BDE-47 administered, whereas in similar conditions, only traces (< 1 %) of the oral dose of BDE-47 are present in the urine of rats (Staskal et al., 2005; Sanders et al., 2006). In rats dosed by gavage with ^{14}C-BDE-47, most of the radioactivity was eliminated in the faeces. Less than 5 % of the administered dose remains in the mice 21 days after treatment. However, because the elimination is biphasic, the terminal half-lives are longer than 20 days, suggesting some potential for bioaccumulation.

BDE-209

All the studies conducted in rodents showed that the majority of the orally administered dose was eliminated in the faeces within 24 h, and negligible amounts were eliminated in urine (El Dareer et al., 1987; Mörck et al., 2003). The cumulative excretion of radioactivity in the faeces of rats orally dosed with ^{14}C-BDE-209 was 90 % of the dose (65 % of dose as BDE-209 metabolites) in 7 days (Mörck et al., 2003). Since several authors found that approximately 10 % of the dose can be excreted in the bile as parent molecule or metabolites (El Dareer et al., 1987; Mörck et al., 2003), part of the fecal metabolites could result from nonbiliary sources such as gut microflora biotransformation or intestine wall metabolism which was supported by the presence of covalently bound residues in the small intestine wall.

Evidence exists regarding elimination of BDE-209 in human milk as shown by Antignac et al. (2008) who found that this compound was one of the major PBDE congeners found in human milk collected between the 3rd and 6th day after delivery in 93 volunteer women. The transfer rate of BDE-209 to milk was estimated to be in the 0.16-0.24 % range in lactating cows exposed to a naturally contaminated diet (Kierkegaard et al., 2007).

Other PBDE congeners

The excretion of ^{14}C-2,2',4,4',5-pentaBDE (BDE-99) was investigated in normal and bile-duct cannulated rats that were administered a single dose (10 mg/kg) in corn oil by gavage (Hakk et al. 1999; 2002). The main route of elimination was via the faeces as shown by cumulative faecal recovery of 43 and 86 % of the administered radioactivity in 72 hours in the normal and bile-duct cannulated animals, respectively. In order to explain this difference, the authors suggested that bile salts are needed for the intestinal uptake of BDE-99. Cumulative urinary excretion of radiolabel over 72 hours was about 1 % and 0.3 % of the dose in the normal and bile duct-cannulated rats, respectively. Using a

similar experimental protocol for BDE-100, Hakk and coworkers found that almost 20 % of the dose in conventional male rats and over 26 % in bile-duct cannulated rats was excreted in the faeces, mainly as the unmetabolized parent compound (Hakk et al., 2006).

Over 62 % of the dose in rats orally administred BDE-154 (ca 7.2 mg/kg b.w.) was excreted in faeces during the 72 h period following administration (Hakk et al., 2009) and was composed of parent compound (7.3 %), free metabolites (13.1 %), and covalently bound residues (41.4 %). During the same period urinary excretion was about 1 %.

Information on the elimination of the technical PentaBDE mixture DE-71 and the technical OctaBDE mixture DE-79 is available from studies in which rats were fed diets containing 0.12 µg/kg per day of either mixture in peanut oil for 21 days (Hakk et al., 2001; Huwe et al., 2002). For the PentaBDE mixture, BDE-85 occurred at a relatively high level in the faeces (55.8 % of the administered dose), whereas faecal excretion of the five other tetra- to hexaBDE congeners ranged from 7.6 to 15.8 % of the dose. Regarding the OctaBDE mixture, faecal excretion ranged from 4.9 to 15.9 % of the dose for the hexaBDE congeners, 20.9-31.5 % of the dose for the heptaBDE congeners, and 16.7-44.3 % of the dose for the octaBDE congeners.

8.1.4.2. Half-lives

Rodents

Following the decline of tetra-, penta- and hexaBDEs in animals which had been exposed to a single dose (300 mg/kg b.w.) of the commercial mixture Bromkal 70, von Meyerinck et al. (1990) determined the terminal half-life of these PBDEs in perirenal fat of the rat. The results of this analysis, which indicate half-lives varying from 19 to 119 days, are indicative for the potential for bioaccumulation of PBDEs in the rat (as a reference the half-life of the dioxin 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in rodents lies around 20 days).

Kinetic analyses of individual PBDE congeners are restricted to BDE-47 in mice and BDE-209 in rats. In mice, BDE-47 displayed bi-phasic kinetics with initial and terminal whole body half-lives of 1.5 and 23 days (Staskal et al., 2005; 2006a). In rats, BDE-209 showed mono-phasic elimination kinetic with a carcass half-life of 8.6 days (Huwe and Smith, 2007). Mono-phasic elimination kinetics were also found for the nonaBDEs BDE-208 (half-life: 14.9 days), BDE-207 (half-life: 22.6 days) and BDE-206 (half-life: 7.4 days). Only BDE-203 (octaBDE) showed biphasic elimination kinetics (initial half-life: 1.6 days; terminal half-life: 64.8 days). Furthermore, Sandholm et al. (2003) reported a terminal half-life of 2.5 days for BDE-209 in the rat.

Humans

Jakobsson et al. (2003) mentioned half-lives ranging from 37 to 84 days for octaBDEs, 111 days for BDE-183, 671 days for BDE-153 and 271 days for BDE-154. Similar long half-lives were reported by Sjödin et al. (1999). Thuresson et al. (2006) modeled apparent serum half-lives of PBDEs with 7-10 bromine substituents, using data from from occupationally exposed workers sampled before, during and after a vacation period (Table 30). The data suggests the human PBDEs half-life tends to increase at decreasing bromination of the PBDE congener. The calculated apparent half-life for BDE-209 was 15 days, the three nonaBDEs and four octaBDE congeners were found to have half-lives of 18-39 days and 37-91 days, respectively. The relatively short half-life of BDE-209 as compared with other PBDEs can be explained by a rapid clearance and a susceptibility of BDE-209 to undergo dehalogenation and substitution reactions (Thuresson et al., 2006). Although the conversion rate of BDE-209 to lower brominated PBDEs is not known, this biotransformation probably influence the concentration of nona- and octa- congeners in the serum as well as their apparent half-lives. Unfortunately, the observation period was too short to detect any decrease in the serum level of penta-

or tetraBDEs, suggesting the half-lives of these congeners to exceed that of the hexa-, hepta-, nona- and decaBDEs.

Table 30: Estimated elimination half-lives of higher brominated diphenyl ethers in humans. Calculations are based on observational data on exposure assessments of rubber workers and electronics dimantlers. Values are expressed in days with, between brackets, the 95 % confidence interval. (Data from Thuresson et al., 2006.)

Congener								
BDE-209	**BDE-208**	**BDE-207**	**BDE-206**	**BDE-201**	**BDE-197**	**BDE-203**	**BDE-196**	**BDE-183**
15 (11-18)	28 (17-39)	39 (4-73)	18 (15-20)	72 (0-150)	85 (29-140)	37 (16-59)	91 (0-280)	94 (68- 120)

The above mentioned serum analysis of employees on holiday suggests the human PBDEs half-life tends to increase at decreasing bromination of the PBDE congener. Unfortunately, the observation period was too short to detect any decrease in the serum level of penta- or tetraBDEs, suggesting the half-lives of these congeners to exceed that of the hexa-, hepta-, nona- and decaBDEs.

For tetra- and pentaBDEs, an indirect method to obtain provisional estimates of the half-life has been applied by Geyer et al. (2004) to obtain estimates for the half-lives of BDE-47 (tetraBDE), BDE-99 and -100 (pentaBDEs) and BDE-153 and -154 (hexaBDEs). In this study, the whole body half-lives in humans were estimated from the daily intake and the total body burden under steady conditions in non-occupationally adult humans in Sweden, according to a linear one compartment open pharmacokinetic model. The analysis of Geyer et al. (2004) was extended by Bakker et al. (2008) to the situation in The Netherlands, resulting in similar half-live estimates (see Table 31).

Table 31: Estimated elimination half-lives in days (range) of lower brominated diphenyl ethers in humans.

BDE-47	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**	**Reference**
664 (556-926)	1,040 (663-1,442)	573 (469-660)	2,380 (1,300-4,530)	1,214 (837-1,560)	Geyer et al., 2004
767-803	694-876	730-767	1,387-1,497		Bakker et al., 2008

Trudel et al. (2011) used estimated PBDE uptake values (including oral exposure from food, dust, and soil; inhalation of air; dermal uptake) in combination with PBDE biomonitoring data from the literature as input for a pharmacokinetic model to derive elimination half-lives. In their model, they used the concentration of PBDE congeners measured in human adipose tissue, except for BDE-209, for which the half-life was based on the volume-of distribution concept. Median half-life estimates were 1,100, 510, 280, 670, 2,700, 480 and 1,000 days for BDE-28, -47, -99, -100, -153, -154 and -183, respectively. For BDE-209, a median value of 7 days was found based on the concentration in blood, whereas a median of 4 days was found when calculations were based on levels in both blood and breast milk. Except for BDE-183, which has a median half-life of 1,000 days, as compared with 94 days in the study published by Thuresson et al. (2006), most of these recently derived elimination half-lives are in the same order of magnitude as those previously reported, and confirm that BDE-209 has a different pharmacokinetic behaviour compared to the other PBDE congeners.

8.1.5. Physiologically Based PharmacoKinetic (PBPK) modelling

One-compartmental modelling to describe the accumulation of PBDEs exposure in humans has been described (McDonald, 2005; Bakker et al., 2008; Lorber, 2008). This type of modelling, of course, is restricted to PBDE exposure at the level of the whole body. In order to allow more refined kinetic modelling for developmental exposure Emond et al. (2010) developed a PBPK model for BDE-47 in the rat. Next to an absorption compartment the PBPK model consisted of the following eight compartments: brain, liver, adipose tissue, kidney, placenta, the fetus, the blood and a remaining compartment ("rest of the body"). Transport with the blood to the tissues was perfusion/diffusion limited and tissue affinity was determined by the tissue lipid content (as BDE-47 does not induce specific hepatic sequestration proteins like CYP1A2 the model did not contain this dioxin-like mechanism).

The model was calibrated for the (non-gestational) mature male rats (single oral dose of 0.1 µmol/kg b.w.) as well as pregnant rats (single intravenous (i.v.) dose of 1 mg/kg b.w. at GD18). The calibrated model was verified on several studies (mature male rats: single oral dose of 1, 10, 100 and 1000 µmol/kg b.w.; pregnant rats: single oral dose of 1 mg/kg b.w. on GD18, repeated oral dose of 1 mg/kg b.w. from GD8 through GD18 and single oral dose of 20 mg/kg b.w. on GD18). Although the model resulted in generally good estimations in tissue concentrations and the fetal compartment, improvements of the estimation of exchange of BDE-47 from mother to fetus were not performed. Adipose tissue and tissue lipid content sufficed to describe the distribution of BDE-47 in the rat body. Consequently, as BDE-47 bioaccumulates in lipophilic tissue, the body burden (being linearly related to the body's lipid content) may be used as a predictive dose metric for the accumulation of PBDEs in the body and, hence, its associated toxic risk.

8.2. Biomarkers of exposure

Data on PBDEs in human samples other than human milk were explored through the open literature. The human matrices most frequently analyzed were adipose tissue, serum and blood, liver and placental tissue. PBDEs concentrations were often expressed in ng/g fat and rarely in pg/L or pmol/g. The majority of the studies reported both the median and the range of PBDEs concentration in the samples, while only a few reported average concentrations.

The eight PBDE congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) were found to be the congeners most frequently analysed in these studies. Literature results are presented in three different tables depending on the type of sample analysed: Table 32 reports studies on adipose tissue and liver, Table 33 on blood serum and placental tissue, and Table 34 includes studies which considered paired mother/father/child samples carried out in order to evaluate the exposure of the foetus or the new born (Antignac et al., 2008; Gómara et al., 2007).

Results from different studies need to be compared with caution due to different methodologies, different congeners analysed and different ways of expressing results, e.g. LB or UB approach. Taking this into account, in adipose tissue, BDE-153 resulted to be the most predominant congener (range of mean/median values: 1.0-2.5 ng/g fat) followed by BDE-47 (range of mean/median values: 0.6-6 ng/g fat). A similar profile was observed for liver samples.

Table 33 groups studies conducted on placental tissue, serum or blood. Analysis on serum and blood were performed either on maternal, paternal and umbilical cord samples and also sorted between different age groups. BDE-47 followed by BDE-153 were the two most predominant congeners, with median concentrations ranging from 0.16 to 7 ng/g fat and from 0.021 to 3.7 ng/g fat, respectively among the different studies. When analysed, BDE-209 was the most predominant congener (median values ranging from 0.77 and 37 ng/g fat). In placenta, BDE-47 was the most predominant congener (median concentrations ranging from 0.32 to 0.77 ng/g fat) followed by BDE-153 (median concentrations ranging from 0.20 to 0.44 ng/g fat).

Some studies focused on specific sub-groups of population considered at higher risk such as populations with a high seafood intake (Fängström et al., 2005b) or with a high intake of fish from a PBDE-contaminated lake (Thomsen et al., 2008) and occupational groups (Sjödin et al., 1999) (Table 33). In the population with high seafood intake, BDE-47, -153 and -209 showed the highest levels in serum of mothers and children of 7 years of age with median concentrations of 0.87 and 1.3 ng/g fat, 1.0 and 20.5 ng/g fat and 0.77 and 1 ng/g fat, respectively. In the occupational study, the highest concentrations were found in serum from electronic dismantlers (median concentration for the sum of the congeners analysed: 37 ng/g fat), compared to other occupational groups such as computer clerks (median: 7.1 ng/g fat) and hospital cleaners (median: 5.4 ng/g fat). In the electronic dismantler group BDE-183 was the most abundant congener (median: 7.8 ng/g fat), while in the other two groups BDE-47 show the highest concentrations (median: 1.6 and 1.5 ng/g fat for hospital cleaners and computer clerks, respectively).

While Table 33 groups studies carried out on non-related samples, Table 34 shows studies carried out in paired mother/child samples such as maternal serum, adipose tissue and umbilical cord serum, in order to assess prenatal exposure and exposure via human milk. In the study from Gómara et al. (2007), the congener profile in serum (maternal, paternal and umbilical cord) and in placenta was dominated by BDE-47 and -99. For BDE-47, the highest values were found in umbilical cord serum (median: 3.3 ng/g fat), followed by maternal and paternal serum that presented similar concentrations (median: 2.3 to 2.7 ng/g fat) and placenta (median: 0.25 ng/g fat). When considering BDE-209, the median concentrations were reported to be always below those of BDE-47 and -99, except in the case of placenta, where this congener showed the highest concentrations (1.0 ng/g fat).

Antignac et al. (2009) reported values of the eight PBDE congeners considered in maternal adipose tissue and in maternal and umbilical cord serum. When considering just the sum of seven PBDEs (without BDE-209), maternal adipose tissue showed the highest concentrations (median: 2.590 ng/g fat) followed by maternal serum (median: 0.984 ng/g fat) and umbilical cord serum (median: 0.698 ng/g fat). In maternal adipose tissue BDE-153 was the most predominant congener followed by BDE-47, while in serum, both maternal and umbilical cord, BDE-47 and -99 were the most predominant congeners. When considering BDE-209, it was the most predominant congener in both in maternal and umbilical cord serum, with mean concentrations of 5.783 and 27.110 ng/g fat, respectively.

Frederiksen et al. (2010) determined a number of PBDE congeners, including the eight PBDEs considered, in pairs of maternal and umbilical cord blood. When considering seven selected PBDEs (without BDE-209), sum concentrations (median (range)) were 1.765 (0.640-51.946) and 0.958 (0.213-54.346) ng/g fat for maternal and umbilical cord plasma, respectively. In the majority of the samples BDE-153 was the dominating congener (median: 1.126 and 0.507 ng/g fat for maternal and umbilical cord plasma, respectively) followed by BDE-47. BDE-183 was not detected in any of the samples. In the maternal samples where BDE-209 could be determined, it contributed on average 50 % to the total PBDE concentration. In the umbilical cord samples, the concentrations of BDE-209 were below or close to those found in the blanks.

The study from Gómara et al. (2007) found no differences ($p>0.05$) between the concentration of PBDEs in paternal and maternal serum, whereas differences were found between PBDEs in maternal vs umbilical cord serum and vs human milk samples. Antignac et al. (2009) found no correlation between concentrations of PBDEs in paired samples of maternal and cord serum, significant correlation between levels of sum of seven indicator PBDEs in adipose tissue and human milk, but weak correlation for BDE-209. On the other hand, Frederiksen et al. (2010) reported a high degree of inter-correlation of PBDEs in maternal and umbilical cord plasma.

Table 32: PBDE-levels (mean or median concentration and [range]) (ng/g fat) in human matrices (adipose tissue [AD] and liver [L]) reported in the literature.

Country, Year	*n*	Sample	PBDE congener								Reference
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	Sum 7 PBDEs	BDE-209	
BE, 2000	20	AD	0.05 (±0.06)	1.45 (±1.01)	0.28 (±0.38)	0.48 (±0.34)	2.49 (±1.00)	n.a.	n.a.	-	n.a.	Covaci et al., 2002[(a)]
BE, 2001-03	53	AD	0.2 [<0.06–2.03]	0.88 [<0.06-14.3]	0.47 [<0.09-7.98]	0.72 [<0.09-1.91]	2.40 [0.70–25.1]	0.93 [<0.08-1.28]	0.78 [0.15-15.4]	n.r.	n.a.	Naert et al., 2006[(b)]
BE, 2003-05	25	AD	0.08	1.2	0.55	0.34	2.0	0.9	0.31	n.r.	n.a.	Covaci et al., 2008[(a) (c)]
	25	L	0.06	0.95	0.38	0.17	1.2	0.66	0.21	n.r.	n.a.	
CZ, 2007	98	AD	0.05	0.7	0.2	0.3	1.0	0.1	0.4	n.r.	<2	Pulkrabova et al., 2009[(b)]
ES, 1998	13	AD	n.a.	1.36 [0.20-5.8]	0.42 [<0.07-2.1]	n.a.	1.83 [0.67-4.2]	n.a.	n.a.	-	n.a.	Meneses et al., 1999[(b)]
ES, 2003	20	AD	0.046	0.626	0.236	0.195	1.34	0.034	0.351	n.r.	n.a.	Fernández et al., 2007[(b)]
IT, 2005-2006	12	AD	0.1 (±0.07)	6 (±7)	1.6 (±2.5)	0.8 (±1.1)	<5.2	n.a.	n.a.	-	n.a.	Schiavone et al., 2010[(a)]
SE, 1994	5	AD	[0.05-0.15]	[1.7-4.0]	[0.78-1.7]	[0.15-0.57]	[0.57-1.4]	[0.04-0.09]	n.a.	-	n.a.	Meironyté Guvenius et al., 2001[(b)]
	5	L	[0.05-0.09]	[1.5-4.9]	[1.5-8.0]	[0.24-0.71]	[0.44-4.3]	[0.01-0.29]	n.a.	-	n.a.	

n.a: not analysed. n.r.: not reported in the original publication.
(a): Mean (±SD).
(b): Median values.
(c): Coelution between BDE-154 and the PBB congener BB-153.

Table 33: PBDE-levels (mean or median concentration and [range]) (ng/g fat) in human matrices (blood [B], serum [S] and placental tissue [PL]) reported in the literature.

Country, Year	*n*	Sample	PBDE congeners									References
			BDE -28	BDE -47	BDE -99	BDE -100	BDE -153	BDE -154	BDE -183	Sum 7 PBDEs	BDE -209	
BE, 2007	18	S	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.9 [0.9-7.2]	ND	Roosens et al., 2009[(g)]
DK, 1994-1995	57	S (mother)	n.a.	1.3 [1 - 23]	0.33 [0.2 - 8.2]	0.51 [0.5 - 4.1]	1.0 [0.40 - 11]	n.a.	n.a.	-	0.77 [0.3 - 3.8]	Fängström et al., 2005b[(b)(d)(g)]
	42	S (children age: 7)	n.a.	0.87 [1 - 68]	0.47 [0.2 - 35]	0.14 [0.5 - 14]	2.5 [1.2 - 15]	n.a.	n.a.	-	1.0 [0.3 - 6.4]	
DK, 1997-2001	129	PL	0.03	0.39	0.23	0.11	0.44	0.0	0.0	n.r.	n.a.	Main et al., 2007[(g)]
DK, 2007	50	PL	<0.038 [<0.0077-0.32]	0.32 [0.063 - 2.21]	0.23 [<0.023 - 0.66]	0.066 [<0.018 - 1.14]	0.35 [0.17 - 11.6]	0.089 [<0.027 - 0.27]	<0.10 [<0.057 - 0.24]	n.r.	1.14 [<0.28 - 5.44]	Frederiksen et al., 2009b[(a)(g)]
ES, 1997	92	S (umbilical cord)	0.25 (±0.91)	2.8 (±3.5)	1.3 (±2.2)	1.0 (±3.4)	ND	ND	0.052 (±0.50)	n.r.	n.a.	Carrizo et al., 2007 [(c)]
	244	S	nd	2.9 (±10)	1.2 (±5.4)	0.18 (±1.2)	0.021 (±0.23)	0.054 (±0.49)	ND	n.r.	n.a.	
ES, 2004-2006	174 Valencia	S (umbilical cord)	<LOQ	2.4 [nd-43]	1.5 [nd-41]	ND [nd-46]	ND [nd-9.8]	<LOQ	ND [nd-27]	n.r.	<LOQ	Vizcaino et al., 2011a[(g)]
1997-1998	91 Menorca	S (umbilical cord)	<LOQ	2.1 [nd-17]	ND [nd-12]	ND [nd-26]	ND [nd]	<LOQ	ND [nd-4.8]	n.r.	<LOQ	
ES, 2003-2006	174	S (mother)	(f)	2.3 [nd-72]	0.35 [nd-21]	(f)	2.1 [nd-13]	1.5 [nd-10]	(f)	n.r.	<0.7 [nd-40]	Vizcaino et al., 2011b[(g)]
	174	S (umbilical cord)	(f)	2.3 [nd-43]	1.5 [nd-42]	(f)	<0.23 [nd-9.8]	<0.08 [nd-11]	(f)	n.r.	<1.2 [nd-140]	
FI, 1994-1998	11	PL	0.12	0.77	0.41	n.a.	0.40	n.a.	n.a.	-	n.a.	Strandman et al., 2000[(g)]

Table 33: Continued.

Country, Year	*n*	Sample	PBDE congeners									References
			BDE -28	BDE -47	BDE -99	BDE -100	BDE -153	BDE -154	BDE -183	Sum 7 PBDEs	BDE -209	
FI, 1997-2001	56	PL	0.04	0.60	0.19	0.11	0.20	0.01	ND	n.r.	n.a.	Main et al., 2007[g]
GR, 2007[f]	61	S	0.01 [0.01-0.45]	0.16 [0.16-10.2]	0.09 [0.09-1.51]	0.11 [0.11-1.77]	0.51 [0.30-3.42]	0.02 [0.02-0.53]	0.03 [0.03-0.51]	n.r.	1.18 [1.18-19.10]	Kalatnzi et al., 2011[g]
NL, 2001-2002	12	S (maternal)	n.a.	0.8 [0.04-6.1]	0.2 [ND-2.1]	0.2 [0.03-1.4]	1.6 [0.3-20]	0.5 [0.1-3.5]	n.a.	-	n.a.	Meijer et al., 2008[g]
	69	S (umbilical cord)	n.a.	0.5 [0-2.2]	0.1 [0-0.4]	0.1 [0-0.5]	0.9 [0.2-2.2]	0.3 [0.1-0.7]	n.a.	-	n.a.	
NO, 1990	20 (pool)	S	0.066	0.89	0.24	0.13	0.27	0.23	n.a.	-	n.a.	Thomsen et al., 2002[g]
NO, 1995	19 (pool)	S	0.14	1.4	0.33	0.32	0.52	0.50	n.a.	-	n.a.	
NO, 1999	29 (pool)	S	0.24	1.5	0.31	0.35	0.59	0.35	n.a.	-	n.a.	
NO, 1999	20	S	0.18	1.7	0.53	0.27	1.2	< 0.1	0.15	4.1	10	Thomsen et al., 2007[g]
NO, 2000	20	S	<0.1	1.8	0.68	0.44	1.6	ND	0.14	4.6	37	
NO, 2001	20	S	0.25	1.5	0.35	0.27	1.5	ND	0.13	4.0	<10	
NO, 2002	20	S	0.11	2.8	0.87	0.38	1.4	ND	0.22	5.8	<10	
NO, 2003	20	S	<0.1	1.5	0.40	0.29	1.4	ND	0.12	3.8	10	
NO, 2003	125	S	0 [0-1.09]	1.44 [0-13.2]	0.43 [0-5.20]	0.34 [0-2.47]	1.10 [0-9.56]	0.39 [0-2.90]	0 [0-0.72]	4.01 [0.78-20.2]	n.a.	Knutsen et al., 2008[b][g]
	44 (control)	S	0 [0-0.95]	1.51 [0.20-13.2	0.54 [0-5.20]	0.35 [0-1.23]	0.93 [0-1.95]	0.31 [0-1.5]	0 [0-0.59]	3.74 [0.78-20.2]	n.a.	
NO, 2004-2005	41 (M)	S	0.29 [<LOQ-0.58]	7.0 [0.15-37]	1.3 [0.04-22]	4.5 [<LOQ-26]	3.7 [<LOQ-18]	0.60 [0.08-14]	0.35 [<LOQ-0.49]	18 [0.3-117]	1.7 [<LOQ-11]	Thomsen et al., 2008[g]
	25 (F)	S	0.37 [<LOQ-0.46]	3.3 [0.47-24]	0.98 [0.14-5.7]	1.9 [0.36-19]	1.7 [0.87-14]	0.25 [0.11-3.3]	0.27 [<LOQ-0.32]	8.4 [2.0-66]	1.5 [<LOQ-14]	
RO, 2005	1 (pool)	S	n.a.	0.340	0.120	0.140	0.400	< 0.040	0.040	-	n.a.	Dirtu et al., 2006[g]

Table 33: Continued

Country, Year	*n*	Sample	PBDE congeners									References
			BDE -28	BDE -47	BDE -99	BDE -100	BDE -153	BDE -154	BDE -183	Sum 7 PBDEs	BDE -209	
SE, 2000-2001	15	B (maternal)	0.07 [<0.01-0.2]	0.83 [0.3-5.1]	0.19 [<0.01-1.43]	0.17 [<0.01-0.52]	0.56 [0.27-1.03]	0.04 [<0.01-0.16]	0.06 [0.01-0.44]	n.r.	n.a.	Guvenius et al., 2003(g)
	15	B (umbilical cord)	0.07 [<0.01-0.31]	0.98 [0.33-3.28]	0.07 [<0.01-0.85]	0.07 [<0.01-0.27]	0.17 [<0.01-0.32]	<0.01 [<0.01-0.17]	0.01 [<0.01-0.1]	n.r.	n.a.	
SE	(1) 20 (2) 20 (3) 19	S	n.r.	(1) 1.6 (2) 1.5 (3) 2.9	n.r.	n.r.	(1) 0.57 (2) 0.85 (3) 4.5	(1) 0.38 (2) 0.51 (3) 1.2	(1) 0.12 (2) 0.18 (3) 7.8	-	(1) < 0.7 (2) < 0.7 (3) 4.8	Sjödin et al., 1999(e)(g)
SE, year not specified	5	B	0.25 [<0.412-0.441]	3.9 [3.38-8.29]	<4.1 [<4.10]	0.92 [<1.27-2.06]	1.8 [<0.988-3.86]	0.39 [<0.644-0.683]	< 1.8 [<1.78]	n.r.	10 [<5.54-17.4]	Karlsson et al., 2007(g)
UK, 2003	154	B	<0.14 [<0.14-10]	0.82 [<0.30-180]	<0.16 [<0.16-150]	0.76 [<0.17-390]	1.7 [<0.26-87]	0.60 [<0.15-4.4]	0.30 [<0.14-1.8]	<15 [<15-240]	-	Thomas et al., 2006(g)

ND: not detected. n.a.: not analysed. n.r.: not reported in the original publication. F: females, M: males.
(a): Coelution between BDE-28 and BDE-33.
(b): Coelution between BDE-154 and the PBB congener BB-153.
(c): Mean (±SD).
(d): High seafood intake population
(e): Occupational groups: (1) Hospital cleaners, (2) Computer clerks, (3) Electronics dismantlers.
(f): BDE-28, -100 and -183 were found above the LOD in less than 10 % of the samples.
(g): Median values.

Table 34: PBDE-levels (median concentration and [range]) (ng/g fat) in related human matrices (serum [S], plasma [P], placental tissue [PL], adipose tissue [AD]) reported in the literature.

Country, Year	*n*	Sample	PBDE congeners								Reference
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	Sum 7 PBDEs	BDE-209	
ES, 2003/04 (Vallecas district)	113	S (maternal)	<0.06	2.4 [0.3- 9.0]	2.6 [1.4- 6.9]	1.6 [0.94- 2.4]	0.86 [<0.18- 2.5]	<0.10	0.47 [<0.06- 2.3]	n.r.	1.1 [<1.1- 20]	Gómara et al., 2007
	104	S (paternal)	<0.06	2.3 [0.34-7.3]	2.3 [1.4-5.3]	1.6 [0.94-2.4]	0.81 [<0.18- 3.2]	0.10 [0.10-1.6]	0.60 [<0.06- 2.6]	n.r.	1.1 [<1.1-59]	
	92	S (umbilical cord)	<0.06	3.3 [<0.03- 35]	4.3 [1.8- 17]	2.3 [1.0- 5.7]	0.52 [<0.18- 4.4]	0.13 [<0.10- 1.6]	1.3 [<0.06- 6.0]	n.r.	2.2 [<1.1- 11]	
	30	PL	<0.06	0.25 [<0.001 - 1.0]	0.12 [0.05- 0.52]	0.09 [0.04- 0.27]	0.04 [<0.01- 0.20]	0.004 [0.002-0.77]	0.10 [<0.002- 0.43]	n.r.	1.0 [<0.05-8.4]	
ES, 2003/04 (Getafe district)	113	S (maternal)	<0.06	2.6 [0.51-22]	2.3 [1.1-12]	1.2 [0.77-4.2]	0.77 [<0.18- 3.3]	<0.10	0.06 [<0.06- 2.5]	n.r.	1.1 [<1.1-31]	
	104	S (paternal)	<0.06	2.7 [0.26-6.3]	2.4 [1.1-5.9]	1.3 [0.81-2.1]	0.86 [<0.18- 4.6]	<0.10	0.06 [<0.06- 3.1]	n.r.	1.1 [<1.1- 91]	
	92	S (umbilical cord)	<0.06	3.32 [<0.03-10]	3.0 [0.94- 7.4]	1.5 [0.81- 4.4]	0.32 [<0.18- 8.7]	<0.10	0.15 [<0.06- 2.9]	n.r.	1.4 [<1.1- 24]	

Table 34: Continued.

Country, Year	*n*	Sample	PBDE congeners									Reference
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	Sum 7 PBDEs	BDE-209	
FR, 2004/06	86	AD (maternal)	0.064 [0.018-1.481]	0.651 [0.166-11.883]	0.166 [0.035-5.235]	0.168 [0.054-3.658]	1.136 [0.422-16.580]	0.041 [0.012-1.700]	0.200 [0.066-4.005]	2.590 [0.840-25.850]	0.752 [0.133-4.392]	Antignac et al., 2009
	91	S (maternal)	0.118 [0.042-0.385]	2.831 [0.556-4.844]	1.939 [0.529-18.021]	0.365 [0.107-4.185]	0.721 [0.64-9.658]	0.065 [0.010-0.936]	0.206 [0.032-2.164]	0.984 [0.060-22.912]	5.783 [0.794-37.425]	
	90	S (umbilical cord)	0.000 [2.219-2.219]	<LOQ	7.434 [5.608-15.773]	1.368 [0.679-2.386]	0.485 [0.137-7.376]	0.089 [0.028-0.925]	0.590 [0.141-4.291]	0.698 [0.137-17.066]	27.110 [3.457-363.326]	
DK, 2007	51	P (maternal)	0.0329 [0.00609-0.398]	0.381 [0.011-7.883]	<0.105 [<0.0534-18.554]	<0.104 [<0.053-6.218]	1.126 [<0.013-35.962]	<0.0182 [<0.00891-2.010]	nd	1.765 [0.640-51.946]	1.709 [<0.661-3.849][(b)]	Frederiksen et al., 2010[(a)]
	40	P (umbilical cord)	0.0507 [<0.0175-0.271]	<0.0679 [<0.0214-5.262]	<0.290 [<0.128-7.022]	<0.271 [<0.128-2.733]	0.507 [0.202-9.472]	<0.0462 [<0.0214-0.651]	nd	0.985 [0.213-54.346]	<2.413[(b)]	

LOQ: limit of quantification. nd: not detected. n.r.: not reported in the original publication.
(a): Original values expressed in pg/g.
(b): The number of samples for BDE-209 determination were n=17 and n=12 for maternal and cord plasma, respectively.

8.2.1. Relation between exposure estimates and levels in humans

Few studies address the relation between different exposure pathways and observed concentration of PBDEs in biological material from humans. Although food and particularly seafood appear to be a major source of PBDE exposure in Europe, fish consumption and/or exposure from other foods has only to a low extent explained the observed variability in blood and human milk concentrations. Strong correlations (BDE-209 not included) between fish consumption, estimated dietary intake and serum concentrations of PBDEs were indeed observed in populations consuming PBDE-contaminated fish (Thomsen et al., 2008; Sjödin et al., 2000). However, in a population with high consumption of fish from areas without known point sources of PBDEs, only low correlations between estimated dietary intake and serum concentration of PBDEs were seen, and in men only (Knutsen et al., 2008). In 393 human milk samples, (BDE-209 analysed in a subset of 46 samples) the mothers' diet did not influence the human milk PBDE levels. Other factors such as age, parity, education, having a cohabitant employed as an electrician, and ventilation only explained part of the variability (Thomsen et al., 2010b). Roosens et al. (2009) found no correlation for either diet or dust in 19 students in Belgium. In a study on pregnant women with planned Caesarean section in Copenhagen, Frederiksen et al. (2010) found positive correlations between the concentration of BDE-28, -47, -100 and -209 and sum of PBDEs in 51 maternal plasma samples and the concentrations in house dust. They also found a positive correlation of sum of PBDEs in 40 umbilical cord plasma samples and concentrations in house dust. In placental tissue samples (n=43) in the same study group the concentration of some pentaBDE congeners, but not BDE-209, were found to correlate significantly with concentrations in dust (Vorkamp et al., 2010).

In North America, where one order of magnitude higher PBDE-concentration in dust than in Europe has been reported (Sjödin et al., 2008), high correlations between concentrations in human milk and house dust, and in addition significant correlations between concentrations in human milk and consumption of dairy products and meat were found (Wu et al., 2007). Also, strong correlation between serum concentration of BDE-47, -99 and -100 and concentration in house dust was found (Johnson et al., 2010). A recent large scale study in the US population revealed an association between intake of poultry and red meat and PBDE levels in serum (Fraser et al., 2009).

In summary, weak associations between dietary intake at background concentrations in food and serum concentrations have been found, whereas a higher association was seen at higher contamination level in food in Europe. Other factors such as concentration in dust appear to influence blood/human milk/placenta concentrations significantly, and the relative importance of different exposure pathways for concentration in human tissues is not easy to establish.

8.3. Toxicity

8.3.1. Acute toxicity

No information was available on the acute toxicity of any specific BDE congeners (FAO/WHO, 2006).

PentaBDE has low acute toxicity by the oral and dermal routes. Groups of male and female rats were gavage fed different commercial preparations of PentaBDE at doses up to 10,000 mg/kg b.w. LD_{50} values were between 2,640 and 6,200 mg/kg b.w., all deaths occurring between day 2 and 9 post dosing (ECB, 2001).

OctaBDE has very low acute toxicity. No deaths and normal weight gain was observed in 5 male Charles River CD rats gavage-fed OctaBDE mixture at doses up to 5,000 mg/kg b.w. and observed for 14 days (ECB, 2003). No deaths and no treatment-related lesions were observed at terminal necropsy

in 5 male and 5 female Sprague Dawley rats observed for 14 days after oral exposure to 5,000 mg/kg b.w. (ECB, 2003).

DecaBDE exhibit very low acute toxicity. Female Sprague Dawley rats intubated with single doses of up to 2,000 mg/kg b.w. of a DecaBDE mixture survived with no signs of toxicity during the 14 days observation period (ECB, 2002). Male albino Spartan rats given single dose of up to 5,000 mg/kg b.w. of DecaBDE survived with normal weight gain during the 14 days observation period (ECB, 2002).

8.3.2. Sub-chronic and chronic toxicity

8.3.2.1. Endocrine system

The available data on the effects of PBDEs provide convincing evidence that they have the potential to disrupt endocrine systems at multiple target sites. While the thyroid hormone system appears to be the main target of these compounds, recent studies demonstrated *in vivo* effects on both the estrogen- and androgen-mediated processes as well.

Reproductive organs

A summary of the results of the studies of different PBDEs and their mixtures on reproductive organs is presented in Table 35.

The reproduction and developmental studies in animals of **decaBDE** were conducted by direct dosing of dams to evaluate the effects on development during gestation and lactation, or by direct dosing of pups. The studies of exposure during gestation and/or lactation showed that of a former commercial product, i.e. FR-300-BA (The Dow Chemical Company, Midland, MI, USA) and BDE-209 are not reproductive or developmental toxicants at doses up to 1,000 mg/kg per day (Norris et al., 1975a; Hardy, 2002). In CD-1 mice postnatally exposed to 0-1,500 mg/kg per day BDE-209 from PND21 until PND70, Tseng et al. (2006) observed changes in sperm parameters and set a NOEL at 500 mg/kg per day. Van der Ven et al. (2008b) in a 28 days oral toxicity study in Wistar rats that was designed to improve bioavailability of BDE-209 found that the most sensitive effects in males were increased weight of seminal vesicle/coagulation gland and increased expression of hepatic CYP1A and CYP2B, while in females the most sensitive effect was decreased activity of P450c17 (CYP17), which is a key enzyme in the androgen synthesis pathway, in adrenals. However, BDE-209 given during gestation and/or postnatally generally did not cause reproductive and developmental effects at concentrations of 500 mg/kg b.w. per day and more, whereas in a 28-day toxicity study, van der Ven et al. (2008b) determined a BMDL of 0.2 mg/kg b.w. per day for increase in weight of seminal vesicle/coagulation gland in male rats. The CONTAM Panel noted the large degree of variability of these data with a relatively high BMD/BMDL ratio of 6.2. For a decrease in plasma total triiodothyronine (T3), a $BMDL_{10}$ of 33 mg/kg b.w. per day at a BMD/BMDL ratio of 1.8 was also reported (in female rats). This dose level did not lead to a significant induction of hepatic CYP1A1/CYP1A2 proteins and ethoxy-resorufin-O-deethylase (EROD) activity in female rats, making a contribution of 'dioxin-like' contaminants' to the decrease in T3 highly unlikely.

Reproductive effects of **BDE-99** related to its anti/estrogenicity and antiandrogenicity have been reported in four recent studies. In Wistar rats administered a single low dose of 0.06 or 0.3 mg/kg b.w. on GD6 resulted in female reproductive tract changes in the F1 generation, which were apparent at adulthood and mating of the F1 females with untreated males revealed increased resorption rates in the PBDE groups (Talsness et al., 2005). The same treatment protocol in male offspring permanently impaired spermatogenesis by the means of reduced sperm and spermatid counts (Kuriyama et al., 2005). In another study in which adult female Long-Evans rats were exposed by subcutaneous injection to 1 or 10 mg/kg per day from GD10-18, offspring exhibited unchanged uterine weight but increased ovarian weight (Ceccatelli et al., 2006). The authors showed that prenatal exposure to BDE-99 disrupted the expression of estrogen target genes and their regulation by endogenous

estrogens. They observed down-regulation of progesterone receptor (PR) mRNA in offspring at both BDE-99 doses, while estrogen receptor alpha (ERα), ERβ and insulin-like growth factor-I (IGF-I) were upregulated at the lower dose (Ceccatelli et al., 2006). In Long-Evans hooded rats exposed in a similar way to the same concentrations of BDE-99, Lillienthal et al. (2006) observed a decrease in circulating sex steroids 17β-estradiol (E2) and testosterone (T) at weaning and in adulthood, reduction of anogenital distance and feminization of sexually dimorphic behaviour. In female offspring, puberty onset was delayed at the higher dose level (10 mg/kg b.w. per day), whereas a slight acceleration was detected in low-dose (1 mg/kg b.w. per day) males. The number of primordial/primary ovarian follicles was reduced in females at the lower dose, whereas decline of secondary follicles was more pronounced at the higher dose (Lillienthal et al., 2006).

Reproductive effects of **DE-71** have been reported in two studies. In Wistar rats exposure to DE-71 (Great Lakes Chemical Coorporation, West Lafayyete, IN - Lot 7550OK20A) at doses of 0, 3, 30 and 60 mg/kg b.w. per day from postnatal days (PND) 22-53 caused in males reduction of seminal vesicle (SV) and ventral prostate (VP) weights at 60 mg/kg, and significant delay in preputial separation (PPS) was at 30 and 60 mg/kg. In the female, the 60 mg/kg dose caused a significant delay in the age of vaginal opening (Stocker et al., 2004). The temporal effects of DE-71 on thyroid hormones and liver enzymes were measured in separate group of males and females following 5 days of dosing (PND21 to 26 in females and PND23 to 28 in males). Serum T4 was significantly decreased at 30 and 60 mg/kg following the 5-day exposures and in the 21-day exposed females. Doses of 3, 30 and 60 mg/kg decreased T4 in 31-day exposed males. Serum T3 was decreased and thyroid stimulating hormone (TSH) elevated by 30 and 60 mg/kg in the 31-day exposed males only (Stocker et al., 2004). In the follow up study, the authors observed that the delay in PPS suppression of VP and SV growth were associated with significant increase in luteinizing hormone, a non-significant increase in testosterone, androstenedione and estrone, and positive response for anti-androgenic activity in an immature rat Hershberger assay (Stoker et al., 2005). The authors concluded that the delay in puberty in the male rat and decreased growth of androgen-dependent tissues observed following exposure to DE-71 were likely due to inhibition of androgen receptor (AR) binding by several of the congeners which make up DE-71 mixture.

Van der Ven et al. (2008a) in a 28-days oral toxicity study in Wistar rats used the commercial mixture **DE-71** obtained from Great Lakes Chemical Coorporation, which had been purified to remove all dioxins and dibenzofurans, as well as any other coplanar molecules. The purified DE-71 mixture was analysed to contain 42 % BDE-47, 34 % BDE-99, 9 % BDE-100, 2 % BDE-153, 2 % BDE-154 while the remaining 11 % were other PBDEs. Thus, the mixture contained a pattern of congeners different from previously published data (La Guardia et al., 2006), suggesting a batch-specific composition. The animals received 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7 or 200 mg DE-71/kg b.w. per day by gavage. The purified DE-71, in addition to marked decrease of circulating total T4 caused a dose-dependent decrease in weight of epididymis, seminal vesicles, and prostate, and sperm head deformities in males. In females, induction of CYP17 activity in adrenals was observed. For the reduction in plasma T4, a $BMDL_{10}$ of 1.1 mg/kg b.w. per day was calculated. A sample of the purified DE-71 mixture contained about 0.1 ‰ 1,2,3,4,6,7,8-HpBDF and 0.001 ‰ 2,3,7,8-TBDF . For the latter compound an *in vitro* relative potency of 0.79 has been reported (Behnisch et al., 2003). At a dose level of 1 mg/kg b.w. per day, this contamination would account for 1.0 ng TBDF/kg b.w. per day, which appears unlikely to cause a drop in T4. According to the NTP (2006), TCDD at a dose level of 3 ng/kg b.w. resulted in a slight, non-significant decrease in total T4 in female Sprague-Dawley rats after 14 weeks of treatment, while a significant decrease was found at 22 ng/kg b.w. per days. After 31 weeks of treatment, 10 ng/kg b.w. per day led to a significant decrease. Further information about the presence of 'dioxin-like' contaminants is provided in the paper saying that 'the purified mixture was tested for dioxin-like activity (AhR-agonistic response) in a DR-CALUX *in vitro* system, as published previously (Hamers et al., 2006). EROD activity in the DR-CALUX cells was tested according to de Haan et al. (1996).

BDE-47 (98 % purity; LGC Promochem GmbH, Wesel, Germany) administered by gavage to pregnant Wistar rats at doses of 0, 0.14 or 0.7 mg/kg b.w. on GD6 showed in female offspring a

significant decrease in ovarian weight after exposure to 0.140 mg/kg b.w BDE-47. In the offspring exposed to 0.7 mg/kg BDE-47 alterations in folliculogenesis were observed (a decrease in tertiary follicles and serum estradiol concentrations). On PND100, persistent effects on the thyroid glands included histologic and morphometric changes after exposure to BDE-47 (Talsness et al., 2008). In immature rats injected with 50, 100, and 200 mg/kg b.w. BDE-47 (ChemService, West Chester, PA) significant increase of wet uterine weight was observed at 200 mg/kg b.w. (Dang et al., 2007). The uterotrophic effect has been show to involve ER and ER-mediated signalling pathway (for details see Chapter 8.3.3. Biochemical Effects and Molecular Mechanisms).

To summarize, **BDE-209** given during gestation and/or postnatally, generally did not cause reproductive or developmental effects at doses up to 500 mg/kg b.w. per day. In a 28-day toxicity study, **BDE-99** administered by gavage to rats during gestation showed reproductive and developmental effects in terms of impaired spermatogenesis and changes in female reproductive tract at a LOEL of 0.06 mg/kg b.w. (Kuriyama et al., 2005; Talsness et al., 2005). The study of **BDE-47** given during gestation showed effects on female reproductive organs (LOEL 0.14 mg/kg b.w.) (Talsness et al., 2008). Postnatal exposure of rats to **DE-71** affected male (LOEL 30 mg/kg b.w. per day) and female (LOEL 60 mg/kg b.w. per day) reproductive organs (Stoker et al., 2004). **DE-71** tested in adult rats in a 28-day toxicity test induced sperm head deformities ($BMDL_{10}$ 9.6 mg/kg b.w. per day) (van der Ven et al., 2008a).

Table 35: Summary of effects of PBDEs in the reproductive organs. NOEL/LOEL/BMD(L) values as reported in the original studies.

PBDE	Species	Exposure [(a)]	NOEL/LOEL/ BMD(L) [(b)]	Purity	Effects	Reference
BDE-47	Wistar Rats: GD6	Gavage; 0.14; 0.7	LOEL: 0.14-0.7	98 %	• Decrease in ovarian weight (only at 0.14 mg/kg b.w.) • Alterations in folliculogenesis (0.7 mg/kg b.w.), histologic	Talsness et al., 2008
BDE-47	Immature female Sprague-Dawley rats 24 hours	*s.c.* Injection; 50, 100, 200	LOEL: 200 (uterine weight)	Not specified	• Increase in uterine weight, the induction of CaBP-9k mRNA and protein expression.	Dang et al., 2007
BDE-99	Wistar rats single dose: GD6	Oral: 0.06; 0.3	LOEL: 0.06	98 %	Impaired spermatogenesis in terms of decrease in sperm and spermatic counts (PND140)	Kuriyama et al., 2005
BDE-99	Wistar rats single dose on GD6	Gavage: 0.06 or 0.3	LOEL: 0.06	98 %	• Female reproductive tract changes in the F1 generation, which were apparent at adulthood. increased resorption rates in the PBDE groups of F1 females mated with untreated males	Talsness et al., 2005
BDE-99	Long-Evans rats GD10-18	Subcutaneous: 1, 10	LOEL: 1	99 %	• In male reduced anogenital distance and decrease in circulating sex hormones (E2, T) at weaning and adulthood, In female delayed puberty (10 mg/kg), and reduced ovary folliculogenesis.	Lilienthal et al., 2006
BDE-99	Long Evans rats GD10-18	Subcutaneous: 1; 10 mg	LOEL (ovarian weight): 10	99 %	• Unchanged uterine weight but increased ovarian weight. • Down-regulation of progesterone receptor (PR) mRNA in offspring at both doses; up-regulation of estrogen receptor alpha and beta (ERα, ERβ) and insulin-like growth factor-I (IGF-I) at the lower dose.	Ceccatelli et al., 2006
BDE-209	Sprague-Dawley rats, GD0-GD19	Gavage: 100; 300; 1,000;	NOEL: 1,000	97.34 % BDE-209 2.66 % nona- and octa-BDE	• No reproductive or developmental effects.	Hardy et al., 2002
BDE-209	CD-1 mice PND21-70	Gavage: 10; 100; 500; 1,500;	NOEL: 500	98 % Sigma Aldrich	• Changes in sperm velocity of motion, and sperm count with high mitochondrial membrane potential and with elevated levels of hydrogen peroxide.	Tseng et al., 2006

Table 35: Continued.

PBDE	Species	Exposure [(a)]	NOEL/LOEL/ BMD(L) [(b)]	Purity	Effects	Reference
BDE-209	Wistar Rats: 28 day oral toxicity study	Gavage 1.87; 3.75; 7.5; 15; 30; 30/30[(c)]	BMDL: 0.2 (males)	0.001 ‰ 2,3,7,8-TBDF (probably an artefact of the GC analysis), 0.1‰ 1,2,3,4,6,7,8-HpBDF	In male increased weight of seminal vesicle/coagulation gland. *BMDL derived from data with large variation, not showing a clear dose-response relationship.*	van der Ven et al., 2008b
DE-71	Juvenile Wistar Rats; PND23-53 (male); PND22-41 (female)	Gavage: 3, 30, 60	NOEL: 3 LOEL : 30	58.1% penta-BDE 24.6% tetra-BDE	• In male: delay in perputial separation, reduced ventral prostate and seminal vesicle growth at 30 and 60 mg/kg b.w. per day. • In females: delay in vaginal opening at 60 mg/kg b.w. per day. • Reduction in T4 serum concentration	Stoker et al., 2004
DE-71	Wistar Rats: 28 day oral toxicity study	Gavage; 0.27; 0.82; 2.47; 7.4; 22.2; 66.7; 200	NOEL: 1 for DE-71; 0.45 for pentaBDE BMDL: 9.6 (sperm head deformities)	Purified 42 % BDE-47, 34 % BDE-99, 9 % BDE-100, 2 % BDE-153, 2 % BDE-154	• In males dose-dependent decreased weight of epididymis, seminal vesicles and prostate, and sperm head deformities.	van der Ven et al., 2008a
FR-300-BA	Sprague-Dawley rats, GD5-15	Gavage: 10; 100; 1,000;	NOEL ≥ 1,000	77.4 % DecaBDE 21.8 % NonaBDE 0.8 % OctaBDE	• No reproductive or developmental effects. • Increase in resorptions, but not dose related.	Norris et al., 1975a
FR-300-BA	Sprague-Dawley rats from 60 days prior mating through mating, gestation and lactation	In diet: 3, 30, 100	NOEL: 100	77.4 % DecaBDE 21.8 % NonaBDE 0.8 % OctaBDE %	• No reproductive or developmental effects.	Norris et al., 1975a

NOEL: no-observed-effect level; LOEL: lowest-observed-effect level; BMD: benchmark dose; BMDL: benchmark dose lower confidence limit; b.w.: body weight; GC: gas chromatography; PND: post-natal day; GD: gestational day.
(a): mg/kg b.w. per day if not stated otherwise.
(b): mg/kg b.w. per day.
(c): Due to limited solubility, the highest dose was administered as a duplicate dose of the 30 mg/kg b.w. per day dose, given with an interval of 4 h.

Interactions of PBDEs with the thyroid hormone system

Disruption of thyroid hormone signaling is one of the most sensitive effects found after PBDE exposure. The results of the studies of the effects of different PBDEs and their mixtures on thyroid hormones are summarized in Table 36.

Postnatal exposure of the inbred C57BL6/J mice to a daily oral dose of 0, 6 or 20 mg/kg **BDE-209** from PND2 to PND15, showed a dose-related reduction of serum thyroxine (T4) levels in male animals (Rice et al., 2007). On the contrary, Lee et al. (2010) reported that postnatal exposure of Sprague-Dawley rats to BDE-209 (0, 100, 300 and 600 mg/kg b.w. daily) from PND10 to PND42 caused significant dose dependent decrease in total serum T3, increase in TSH (at 300 and 600 mg/kg b.w.), and no changes in the levels of T4. The histological examinations revealed degenerated follicular epithelium at 300 and 600 mg/kg b.w., and at the highest dose thyroid and adrenal gland weights were increased. A decrease (ca. 21 % at 10 mg/kg and 1,500 mg/kg b.w.) in serum T3 but not T4 were also found in offspring of CD-1 mice administered BDE-209 (0, 10, 500, and 1,500 mg/kg b.w. per day) per gavage from GD0-17 (Tseng et al., 2008). At 500 mg/kg day b.w. per day the authors reported no changes in serum T3, and an insignificant increase in T4, which they explained as possibility of inverted U-shaped curve trend. In the 1,500 mg/kg group there were also mild changes in the thyroid glands. In another study examining the effects of prenatal exposure to BDE-209 (0, 5, 40, or 320 mg/kg b.w. per day) T4 concentrations were significantly lower in F1 offspring of dams exposed to BDE-209 at PND42 and the reduction was more pronounced in the group exposed to higher doses (Kim et al., 2009). Van der Ven et al. (2008b) in a 28 days oral toxicity study in Wistar rats that was designed to improve bioavailability of BDE-209 found no changes in serum T4, wheras serum T3 levels were increased in females only at high dosage ($BMDL_{10}$ 33 mg/kg b.w. per day)

In NMRI mice exposed to either **BDE-99** or **Bromkal 70-5DE** at 452 and 262 mg/kg b.w. per day, respectively, from GD4 to PND17 no changes in serum T4 were found in dams. Plasma T4 levels were reduced in offspring in the Bromkal 70-5DE group, while BDE-99 had no effect on T4 levels, suggesting that other components in Bromkal are responsible for the hypothyroxinemia (Skarman et al., 2005). Also Branchi et al. (2005) found a non-significant decrease of serum T4 on PND22, following developmental exposure to BDE-99 (18 mg/kg b.w. per day from GD6 to PND21) in CD-1 Swiss mice. Kuriyama et al. (2007) evaluated thyroid hormone concentrations, hepatic enzyme activities and tissue concentrations of BDE-99 in Wistar rats (dams and offspring) after treatment by gavage on GD6 with a single low dose of 0, 0.06 or 0.3 mg BDE-99/kg b.w. The dose of 0.3 mg BDE-99/kg b.w. reduced T4 concentration in dams at the beginning of lactation (PGD1), and caused a slight reduction in T4 on PND22, although not statistically significant. In offspring, reduced T4 was observed at PND22, probably due to cumulative effects of BDE-99 during lactation. The adipose tissue concentration of BDE-99 measured in this study was close to those reported for BDE-99 in non-occupationally exposed humans (Kuriyama et al., 2005). No changes in serum T3 and T4 were observed in adult rats exposed to single dose (0.6 and 1.2 mg/kg b.w.) BDE-99, however testosterone and progesterone levels decreased (Alonso et al., 2010).

Fowles et al. (1994) reported decreased levels of circulating T4 in female C57BL/6 mice exposed to single doses of **DE-71** (0, 0.8, 4.0, 20, 100, or 500 mg/kg b.w.), or to daily doses (totalling 250, 500, or 1,000 mg/kg) over a 14 day period. Regarding developmental exposures, Zhou et al. (2001) reported that short term exposure (4 days) of weanling Long-Evans rats to 0, 0.3, 1, 3, 10, 30, 100 or 300 mg/kg b.w. per day DE-71 or **DE-79**, but not **DE-83R** (98 % decaBDE), caused a reduction of serum T4 levels, without altering those of triiodothyronine (T3) and thyroid stimulating hormone (TSH). Serum total T4 was decreased at maximum of 80 % for DE-71 and 70 % for DE-79 in the highest dose, with BMDs of approximately 12.74 mg/kg b.w. per day for DE-71 and 9.25 mg/kg per day for DE-79. In a subsequent study the same authors found that exposure of rats to DE-71 from GD6 to PND21 to 1, 10 and 30 mg/kg b.w. per day caused a significant decrease of serum T4 in dams on GD20 and PND22, and in the foetuses and pups on GD20, PND4 and 14, with a recovery by PND36 (Zhou et al., 2002). Szabo et al. (2009) found that oral administration of **DE-71** (1.7, 10.2 or

30.6 mg/kg per day) to pregnant Long-Evans rats with DE-71 (Great Lakes Chemical Corporation - Lot 7550OK20A) (by gavage) between GD6 and PND21 decreased total serum T4 in a way that was age and dose dependent, whereas the levels of serum T3 remained unchanged. At PND 4, exposure to DE-71 decreased total serum T4 to 57 and 51% of control levels at 10.2 and 30.6 mg/kg per day, respectively. At PND 21 total serum T4 was decreased to 46 and 25 % of controls at 10.2 and 30.6 mg/kg per day, respectively. By PND 60 no differences between control and dose groups were seen. A similar study of DE-71 in rats exposed from GD6 to PND18 showed decrease in serum T4 levels in dams on PND19, and in pups on PND18, with a full recovery by PND31. No changes in T3 and transthyretin (TTR) levels, but increased TSH levels were detected in dams (Ellis-Hutchings et al., 2006). Stoker et al. (2004) reported that in Wistar rats following DE-71 exposure serum T4 was significantly decreased in females at 30 and 60 mg/kg and in males at 3, 30, and 60 mg/kg. Serum T3 was decreased and TSH elevated by 30 and 60 mg/kg in the 31-day exposed males only. Decreased colloid area and increased follicular cell heights (indicative of the hypothyroid state) were observed in thyroids of the 60 mg/kg groups of 20- and 31-day exposed female and males. In a 28-day sub-acute oral toxicity study Wistar rats received 0, 0.27, 0.82, 2.47, 7.4, 22.2, 66.7 or 200 mg of a purified DE-71/kg b.w. per day, the liver appeared to be a key target organ, showing a marked increase of weight and centrilobular hepatocellular hypertrophy, probably due to the observed induction of P450 enzymes, notably CYP1A and CYP2B. A marked decrease of circulating total thyroxine (T4) and an increase of plasma cholesterol were probably secondary to the liver effects (van der Ven et al., 2008a). A recent study in zebrafish (*Danio rerio*) larvae model showed that exposure to DE-71 (1, 3 and 10 µg/L) from fertilization to 14 days thereafter showed significant decrease of T4 level at exposure to 10 µg/L, whereas the changes in mRNA expression of genes involved in hypothalamic-pituitary-thyroid axis were dose dependent (Yu et al., 2010).

Exposure of adult mice and rats to tetraBDE mixture, **BDE-47** or to the commercial mixture **Bromkal 70-5DE**, decreased serum total and free T4 levels, without altering TSH levels (Hallgren and Darnerud, 2002; Hallgren et al., 2001; Darnerud et al., 2007). Darnerud et al. (2007) in their study of exposure of rats to 18 mg/kg b.w. per day BDE-47 or Bromkal 70-5DE for 14 days determined also internal plasma doses of 421 µg BDE-47/g lipid and 463 µg sumPBDE/g lipid which corresponded to the decrease in plasma levels of T4. Exposure to BDE-47 on GD6 was found to decrease T4 levels in dams on PND1, but not on PND22 (Kuriyama et al., 2004b), and to decrease T4 levels in pups on PND14, but not on PND1 or 22 (Talsness et al., 2004). In offspring of Wistar rat dams exposed low-dose BDE-47 (0, 0.002, 0.02 and 0.2 mg/kg b.w.) each 5 days from GD15 to PND20 by intravenous injections significant decrease in total T4 was observed at the highest two dosages. A trend of the decrease in free T4 was also observed but the decrease was significant only at the highest dosage. No changes in T4 levels were detected in exposed dams and no changes in total or free T3 was onserved in pups and dams (Suvorov et al., 2009). The concentrations of BDE-47 in adipose tissue of dams on PND27 (7 days after the last exposure), were in the control group: 7.0 ng/g fat, in the 0.002 mg BDE-47/kg group: 12.6 ng/g fat, in the 0.02 mg BDE-47/kg group: 21.0 ng/g fat, and in the 0.2 mg BDE-47/kg group: 234.3 ng/g fat. In pups, fat BDE-47 concentrations were: in the control group: 5.9 ng/g fat, in the 0.002 mg BDE-47/kg group: 38.9 ng/g fat, in the 0.02 mg BDE-47/kg group: 208.7 ng/g fat, and in the group exposed to 0.2 mg BDE-47/kg: 1,054.7 ng/g fat. BDE-99 and -100 congeners were not detected (Suvorov et al., 2009).

Richardson et al. (2008) reported that in female C57BL/6 mice orally administered 0, 3, 10, or 100 mg/kg per day of **BDE-47** for 4 days BDE-47 caused a significant, 43 % decrease at 100 mg/kg per day, in serum total T4 concentrations. There was no increase in hepatic T4-glucuronidation activity, but significant increases in hepatic Ugt1a1, Ugt1a7, and Ugt2b5 mRNA expression. Induction of pentoxyresorufin O-deethylase (PROD) activity occurred at the lowest dose (3 mg/kg per day). Cyp2b10 mRNA expression increased significantly at 10 and 100 mg/kg per day. These findings suggest that PBDE activates the constitutive androstane receptor (CAR, NR1I3/Nr1i3), which regulated expression of Cyp2b10 mRNA expression and associated enzyme activity (PROD). Decreases in Mdr1a mRNA expression also occurred at the lowest dose administered (3 mg/kg per day BDE-47). BDE-47 exposure also decreased hepatic transthyretin and monocarboxylate transporter 8

(Mct8) mRNA expression, suggesting that while induction of uridine diphosphoglucuronosyl transferases (UGTs) may be partly responsible for T4 decreases, other mechanisms are also involved. The authors concluded that changes in hepatic UGTs and transporters may be involved in decreases in circulating T4 following BDE-47 exposure.

Abdelouahab et al. (2009) showed that *i.v.* administration of pregnant sheep with doses of 0, 0.2, 2 and 20 µg/kg b.w. **BDE-47** (Chromatographic Specialties Inc., Brockville, Ont., Canada) by *i.v.* injection once a week affected thyroid state in lamb. A significant decrease of total serum T3 and T4 was observed in lambs at 2 and 20 µg/kg b.w. without any effects in dams. The concentrations of BDE-47 in fat tissue harvested 30 days after the last injection showed high retentation of BDE-47 in both pregnants sheep and lamb. The authors estimated that in pregnant sheep 6.3-10 % of total administred dose was retained in fat tissue.

To summarize, the hypothalamus-pituitary-thyroid axis appears to be the main target of PBDEs. Exposures to rats to **BDE-209** during gestation caused reduction of serum T4 levels at relatively high doses (LOEL: 320 mg/kg b.w. (330 µM)) (Kim et al., 2009), whereas a decrease of serum T3 was observed at lower doses (LOEL: 10 mg/kg b.w. (10 µM)) (Tseng et al., 2008). In postnatal exposed rats to BDE-209 a decrease in T3 and in TSH was observed at LOEL 300 mg/kg b.w. (213 µM) (Lee et al., 2010). In rats, **BDE-99** caused significant a decrease in serum T4 after single gestational administration at the LOEL of 0.3 mg/kg b.w. (0.53 µM) (Kuriyama et al., 2007). Gestational exposure of sheep (*i.v.*) to **BDE-47** at doses that are relevant to human exposure caused a significant decrease in the levels of total serum T4 and T3 (LOEL 2 µg/kg b.w.; 0.4 nM) (Abdelouahab et al., 2009). In rat (*i.v.*) gestational exposure, a reduction of T4 was observed in pups but not in dames at LOEL 0.02 mg/kg b.w., while T3 levels were not affected (Suvorov et al., 2009). The study of postnatal exposure of rats to BDE-47 showed a decrease in plasma T4 at the LOEL of 100 mg/kg b.w. (206 µM) (Richardson et al., 2008). In the studies of the exposure of rats to **DE-71** during gestation and postnataly, a reduction of serum T4 was observed at concentrations higher than 1 mg/kg b.w. (Zhou et al., 2002; Taylor et al., 2003), whereas in the study of postnatal exposure the BMDL values for the reduction of serum T4 was 0.282 mg/kg b.w. for females and 0.944 mg/kg b.w. for males (Stoker et al., 2004). In the 28-day oral toxicity study of DE-71 in rats, the $BMDL_{10}$ values for a decrease of serum T4 were 1.8 mg/kg b.w. for females and 1.1 mg/kg b.w. for males (van der Ven et. al., 2008a). **BDE-209** under the same exposure conditions had no effect on serum T4 (NOEL 60 mg/kg b.w) but caused an increase of T3 ($BMDL_{10}$ 33 mg/kg b.w.) (van der Ven et al., 2008b).

Table 36: Summary effect of exposure to PBDEs on thyroid hormone homeostasis. NOEL/LOEL/BMD(L) values as reported in the original studies.

PBDE	Species	Exposure [(a)]	NOEL/LOEL/ BMD [(b)]	Purity	Effects	Reference
BDE-47 Bromkal 70-5DE	Sprague Dawley rats and C57BL/6N mice 14 days	Gavage: 18, 36	LOEL: 18	BDE-47: 98 % Bromkal 70-5DE: 40 % BDE-47; 60 % terta- and penta-BDE	• Decrease in total and free T4 by BDE-47 and Bromkal-705DE in mice and rats • No effect on TSH	Hallgren et al., 2001
BDE-47	Sprague Dawley rats (7 weeks old) 14 days	Gavage: 1, 6, 18	NOEL: 6 LOEL: 18	98 %	• Decrease in plasma T4 • No effect on TSH	Hallgren and Darnerud, 2002
BDE-47	Wistar Rats: GD6	Gavage; 0.14; 0.7	LOEL: 0.14-0.7	98 %	• No changes in thyroid gland weight • Histologic and morphometric changes of thyroid glands.	Talsness et al., 2008
BDE-47 Bromkal 70-5DE	Sprague Dawley rats (7 weeks old) 14 days	Gavage: 18, 36 (Bromkal) 1, 6, 18 (BDE-47)		BDE-47: 98 % Bromkal 70-5DE: 33 % BDE-47 34 % BDE-99 13 % BDE-100 3.8 % BDE-138 7.9 % BDE-153 8.2 % BDE-154	• Decrease in free plasma T4 • At 18 mg/kg b.w. decrease in plasma T4 corresponded to internal plasma dose 463 µgsum PBDE/lipid (Bromkal) and 421 µg BDE-47/g fat	Darnerud et al., 2007
BDE-47	Female C57bl/6 mice (9 weeks old) 4 days	Oral: 3, 10, 100	NOEL: 10 LOEL: 100	Not specified	• 43 % decrease in serum total T4 at 100 mg/kg per day associated with induction of Ugt1a1, Ugt1a7 and Ugt2b5 mRNA and decreased hepatic transthyretin (TTR) and monocarboxylate transporter 8 (Mct8) mRNA expression.	Richardson et al., 2008
BDE-47	Wistar rat dams; From GD15 to PND 20 each 5 days	*i.v.*: 0.002, 0.02, 0.2	NOEL: 0.002 LOEL: 0.02	BDE-47 (Chromatographic Specialties Inc. (Brockville, Ont., Canada): 100 % (GC-MS)	• In offspring decrease in total T4 was observed at the highest two dosages. • Free T4 that was significant only at the highest dosage. • No changes in T4 levels in exposed dams • No changes in total or free T3 in pups and dams	Suvorov et al., 2009
BDE-47	Dorset sheep (from 5th till 15th week of gestation)	Weekly iv. injection 0.0002, 0.002 and 0.02	NOEL 0.0002 LOEL: 0.002	Not specified	• Decrease in total T4 and T3 in lambs exposed during fetal stage. • Linear trend for total T4: $F_{3;14}$ value = 3.60; p=0.04 • Linear trend for total T3: $F_{3;14}$ value = 3.32; p=0.05	Abdelouahab et al., 2009
BDE-99	CD-1 Swiss mice GD6-PND21,	Oral; 18	NOEL: 18	Not specified	• Non-significant decrease of T4 on PND22	Branchi et al., 2005

Table 36: Continued.

PBDE	Species	Exposure [a]	NOEL/LOEL/ BMD [b]	Purity	Effects	Reference
BDE-99 or Bromkal 70-5DE	NMRI mice GD4-PND17 every 3 days	Oral; 452 (BDE-99) 262 (Bromkal 70-5DE)	NOEL (BDE-99): 452 LOEL (Bromkal70-5DE): 262	BDE-99: 99 % Bromkal 70-5DE: 2,2',4,4',5-pentaBDE (37 %) and 2,2',4,4'-tetraBDE (35 %)	• Decrease of T_4 in offspring on PND11 in Bromkal 70-5DE group; recovery by PND37. • No changes in serum T4 in dams. • No changes in serum T4 in offspring in BDE-99 group.	Skarman et al., 2005
BDE-99	Wistar rats single dose on GD6	Oral: 0.06; 0.3	LOEL: 0.06	98 %	• In dams reduced T4 at PND1 at 0.06 mg/kg b.w.; • In offspring reduced T4 at PND22 at 0.3 mg/kg b.w.;	Kuriyama et al., 2007
BDE-99	Sprague-Dawley rats: adult, single dose	Gavage: 0.6 and 1.2; observations 45 days after exposure	LOEL (testosterone and progesterone): 0.6	98 %	• No effect changes in serum T3, T4 and free T4. • Decrease in testosterone and progesterone levels,	Alonso et al., 2010
BDE-209	C57BL6/J mice PND2-15	Oral 6, 20	LOEL: 6	99.5 %	• Dose dependent decrease of T_4 in males on PND21	Rice et al., 2007
BDE-209	CD1 mice GD0-17	Gavage: 10, 500, 1500	NOEL: 1,500 (T4) LOEL: 10 (T3)	98 %	• No changes in serum T_4 levels in offspring. • Decrease in serum T_3 in adult male offspring of dames dosed 10 and 1,500 mg/kg-day.	Tseng et al., 2008
BDE-209	Wistar Rats: 28 day oral toxicity study	Gavage 1.87; 3.75; 7.5; 15; 30; 60[c]	NOEL: 60 (T4) BMDL: 33 (T3)	0.001 ‰ 2,3,7,8-TBDF; 0.1 ‰ 1,2,3,4,6,7,8-HpBDF	• In females increase in circulating T3, no effect in males, • No effect on T4.	van der Ven et al., 2008b
BDE-209	Sprague-Dawley Crl:CD female rats GD6-18	Gavage; 5, 40, 320	NOEL: 40 LOEL: 320	98 %	• Decrease of serum free T4 levels of female offspring on PND 42 (at 320 mg/kg) • Increased serum TSH levels in male and female offspring on PND 42 (at 320 mg/kg). • No effects on testosterone levels in F1 male offspring, • Lower estradiol levels only at 5 mg/kg	Kim et al., 2009
BDE-209	Sprague-Dawley Rats: PND10-42	Gavage: 100, 300, 600	NOEL: 100 (T3) NOEL: 300 (TSH)	98 %	• Dose dependent decrease in serum T3 • Increase in TSH (300 and 600 mg/kg b.w.) • No changes in serum T4 • Folicular degeneration in thyroid gland (300 and 600 mg/kg b.w.) Increase in thyroid and adrenal weights (600 mg/kg b.w.)	Lee et al., 2010

Table 36: Continued.

PBDE	Species	Exposure [(a)]	NOEL/LOEL/ BMD [(b)]	Purity	Effects	Reference
DE-71 DE-79 DE-83R	Long-Evans rats PND28-31 (female only)	Oral: 0.3, 1, 3, 10, 30, 100, 300	BMD (DE-71): 12.74 BMD (DE-79): 9.25 NOEL (DE-83R): 300	DE-71: 58.1 % penta-, 24.6 % tetra-BDE DE-79:30.7 % octa-, 45.1% hepta-BDE DE-83R > 98 % decaBDE	• Decrease of T4 on PND 32 by DE-71 and DE-79 • No effects on T3 and TSH	Zhou et al., 2001
DE-71	Female C57BL6 mice	Oral acute: 0.8, 4.0, 20, 100, 500 Sub-chronic: 250, 500, 1000 (14 days)	LOEL: 0.8		• Acute treatment: lower total serum T4 at all concentrations except 100 mg/kg • Sub-chronic treatment: dose dependent decrease of total serum T4	Fowles et al., 1994
DE-71	Long-Evans rats GD 6–PND 21	Oral: 1, 10, 30	NOEL: 1 LOEL: 10	58.1 % penta-, 24.6 % tetra-BDE	• Decrease of T4 in fetuses and pups on GD20 and PND21 (10 and 30 mg/kg) recovery by PND36. • Decrease of T4 in dames on GD20 and PND22	Zhou et al., 2002
DE-71	Sprague-Dawley rats (sufficient - VAS and marginal vitamin A –VAM) GD6-PND18	Oral: 18	LOEL: 18	58.1 % penta-BDEs 24.6 % tetra-BDEs	• Decrease of T4 on PND19 in dams and PND18 in pups with recovery by PND 31. • Increase in TSH level in exposed dams.	Ellis-Hutchings et al., 2006
DE-71	Rats GD6-PND21	Oral: 1, 5, 30, 100,	NOEL: 1 LOEL: 5		• Decrease of T4 on PND5, 14 (5-100 mg/kg)	Taylor et al., 2003
DE-71 (technical)	Long-Evans rats, female (pregnant)	Orally; GD6 to PND21; 1.7, 10.2, 30.6	NOEL: 1.7 LOEL: 10.2	Penta-BDE, lot 7550OK20A (Great Lakes Chemical Corporation (West Lafayette, IN)	• Decrease in total serum T4 at PND4 and 21 in male and female • No changes in total serum T4 at PND60 • No changes in serum T3.	Szabo et al., 2009
DE-71	Juvenile Wistar Rats; PND 23-53 (male); PND 22-41 (female)	Gavage: 3, 30, 60	BMDL female: 0.282 (5 day); 1.16 (20 day) BMDL male: 1.28 (5 day); 0.944 (20 day)	58.1 % penta-BDEs 24.6 % tetra-BDEs	• Decrease in circulating T4 after 5, 20 and 31 days both sexes. $BMDL_5$ female 5-day 0.282, 20-day 1.16; male 5 day 1.28, 31-day 0.944 • At all concentrations; decreased serum T3 and • Elevated TSH by 30 and 60 mg/kg b.w. per day in males after 31 days.	Stoker et al., 2004

Table 36: Continued.

PBDE	Species	Exposure [(a)]	NOEL/LOEL/ BMD [(b)]	Purity	Effects	Reference
DE-71	Wistar Rats: 28 day oral toxicity study	Gavage; 0.27; 0.82; 2.47; 7.4; 22.2; 66.7; 200	BMDL (T4) female: 1.8; male 1.1	Purified 42 % BDE-47, 34 % BDE-99, 9 % BDE-100, 2 % BDE-153, 2 % BDE-154	• Decrease in circulating T4 • Decrease in hepatic apolar retionids (BMDL 0.5 mg/kg b.w. per day in males and 2.3 mg/kg b.w. per day in females).	van der Ven et al., 2008a
DE-71	Zebrafish (*Danio rerio*) larvae from 0 to 14 post fertilization day	Exposure concentrations: 1, 3, 10 µg/L	LOEL T4: 10 LOEL gene expression changes: 3	Wellington Laboratory, INC (Ontario, CA) > 99.9 %	• Significant decrease in body T4 content at 10 µg/l • Up-regulation of genes involved in TH synthesis • Down-regulation of genes involved in TTR synthesis	Yu et al., 2010

NOEL: no-observed-effect-level; LOEL: lowest-observed-effect-level; BMD: benchmark dose; T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone; TTR: transthyretin; b.w.: body weight; GC: gas chromatography; PND: post-natal day; GD: gestational day; BMDL: benchmark dose lower confidence limit; TH: thyroid hormone.
(a): mg/kg b.w. per day if not stated otherwise.
(b): mg/kg b.w. per day.
(c): Due to limited solubility, the highest dose was administered as a duplicate dose of the 30 mg/kg b.w. per day, dose given with an interval of 4 h.

8.3.2.2. Nervous system

The available data point to the nervous system as one of the organs vulnerable to PBDE-induced toxicity. The main concern relates to their potential developmental neurotoxicity. The fact that infants and toddlers have the highest body burden of PBDEs (Fischer et al., 2006; Allen et al., 2007) provides a consistent argument to support the concern, and so do a number of animal studies performed with different congeners. The majority of the available developmental studies are based on oral administration. Prenatal exposures were performed by treating pregnant dams with the selected PBDE via gavage, self-administration or by loading the chemicals on palatable food in volumes adjusted for the body weight. The procedure was continued after the delivery and until weaning (PND21) in order to maintain the exposure also during lactation. Alternatively, the chemicals were administered to the pups via gavage on single or repeated occasions between early postnatal days and weaning.

Generally, alterations in spontaneous behaviour suggestive for impaired habituation in a novel environment and hyperactivity were found consistently in young animals, while impaired learning ability and impulsivity occurred in adult rodents (both mice and rats of various strains) exposed prenatally. A detailed description is given in the following subchapter. Table 37 provides an overview of relevant publications reporting developmental neurotoxic effects, including the most relevant information concerning congeners tested, their purity, animal species, doses, neurobehavioural effects, and, when possible, a NOEL or LOEL.

Neurodevelopmental studies based on single exposures

BDE-47, administered by gastric intubation, induced alterations in habituation and spontaneous behaviour in a novel environment in NMRI mice exposed on PND10. Doses of 0, 0.7 or 10.5 mg/kg b.w. were tested with the estimated LOEL being 10.5 mg/kg b.w. (Eriksson et al., 2001). Gee and Moser (2008) treated C57BL/6 mice with a dose of 0, 1, 10 or 30 mg/kg b.w. BDE-47 on PND10. A non-dose related increase in motor activity was seen all dose groups at 4 month of age. A study on Wistar rats exposed to 0.14 or 0.7 mg/kg b.w. of BDE-47 on GD6 showed increased locomotor activity and decreased anxiety-like behaviour with a LOEL of 0.7 mg/kg b.w. (Kuriyama et al., 2004a). Decreased learning abilities after postnatal exposure to 1, 5 and 10 mg/kg b.w. BDE-47 on PND10 were observed in adult (2 months old) Sprague-Dawley rats with a LOEL being 1 mg/kg b.w. (He et al., 2009a). In a recent study C57BL/6 mice were administered 0, 1, 10, or 30 mg/kg b.w. BDE-47 on PND10 (Gee et al., 2011). An increase in cortical dopamine (DA) on PND15 and 20, as well as in adult mice, was found at 10 mg/kg b.w. No effects were observed in the low and the high dose group.

Studies on **BDE-99** also reported behavioural alterations in different mice strains and rats. NMRI and C57/BL6 mice exposed to BDE-99 (purity > 98 %) on PND3, 10 or 19 via gavage showed decreased habituation and alterations in spontaneous behaviour determined at 2, 5 and 8 months (C57/BL6 mice) or at 4 months of age (NMRI mice). In C57/BL6 mice, a LOEL of 0.8 mg/kg b.w. for spontaneous and 16 mg/kg b.w. for habituation behaviour was determined (Eriksson et al., 2002; Viberg et al., 2004a). In addition, in the 2 month old C57/BL6 mice exposed on PND10, the $BMDL_{10}$ for increase in rearing, locomotion, and total activity (defined by the authors as “all types of vibration within the cage (i.e., those caused by mouse movements, shaking (tremors), and grooming)”) were determined as 1.2, 0.85, and 0.42 mg BDE-99/kg b.w., respectively (Sand et al., 2004). In NMRI mice, only one dose (8 mg/kg b.w.) was tested that showed alterations in spontaneous behaviour in NMRI mice (Eriksson et al., 2002). Deficits in learning and memory abilities determined via Morris water maze were detected in 5 month old NMRI mice exposed to 12 mg/kg b.w. BDE-99 on PND10 (Eriksson et al., 2001). Another group found that BDE-99 induced hyperactivity in Wistar rats exposed to 0.06 or 0.3 mg/kg b.w. on GD6, with a LOEL of 0.06 mg/kg b.w. in animals tested at PND71 and 0.3 mg/kg b.w. in younger animals (PND36), which points to a time-dependent increase in BDE-99 induced neurotoxicity (Kuriyama et al., 2005).

Only one study has been published, so far, on the neurotoxic potential of hexaBDEs. NMRI mice were exposed via gavage to 0, 0.45, 0.9 and 9 mg/kg b.w. **BDE-153** on PND10. A disruption in spontaneous behaviour indicated by decreased habituation and impaired learning and memory capabilities tested in the Morris swim maze were observed with a LOEL of 0.9 mg/kg b.w. BDE-153 purity: 92.5 % hexaBDE and 7.5 % heptaBDE (Viberg et al., 2003b).

BDE-183 was shown to decrease spontaneous and habituation behaviour in NMRI mice exposed to 15.2 mg/kg b.w. via gavage on PND3 (Viberg et al., 2006).

Similarly, **BDE-203** also decreased spontaneous behaviour, habituation, as well as learning/memory performance in NMRI mice exposed via gavage to 16.8 mg/kg b.w. on PND3 or PND10 (Viberg et al., 2006). Decreased habituation behaviour was also induced by **BDE-206** in NMRI mice exposed to 18.5 mg/kg b.w. via gavage on PND3 or PND10 (Viberg et al., 2006). Finally, also **BDE-209** induced changes in spontaneous behaviour and habituation after oral administration of 6.7 mg/kg b.w. in rats and 20.1 mg/kg b.w. in mice on PND3 (Viberg et al., 2003a, 2007).

Neurodevelopmental studies based on repeated exposures

Repeated exposures to PBDE congeners have been performed by exposing dams and/or neonatal rodents at different developmental stages; GD6-18 (Kim et al., 2009); GD6-PND21 (Branchi et al., 2002, 2005); PND2-15 (Rice et al., 2007, 2009); PND6-12 (Dufault et al., 2005); from 4 weeks before mating until PND21 (Ta et al., 2011) followed by behavioural analyses of the offspring at different ages.

BDE-47 (ACS grade) was administered on corn flakes at doses of 0, 0.03, 0.1 and 1 mg/kg b.w. per day, to C57BL/6J female mice, starting 4 weeks before mating, throughout gestation and lactation, until weaning on PND21 (70-80 days in total). The pups exposed to 0.01 and 0.03 mg/kg b.w. displayed shorter crown-rump length and lower body weight. In most behavioural tests pups of treated dams did not show any effect, but on PND60, female pups of the 0.1 and 1 mg/kg b.w. BDE-47 dose group showed less locomotor activity than controls in the open field apparatus. This effect was, however, not dose related. In the Morris water maze test female pups of dams administered 1.0 mg/kg b.w. BDE-47 had a slower swim speed. No effects on behaviour were observed in male offspring. Blood and tissue levels of BDE-47 were measured in dams and in the offspring. Levels in brain of pups from dams admistered 1 mg/kg b.w. declined from about 370 ng/g tissue on PND1 to about 200 ng/g tissue on PND21. Dams of the same dose group showed levels of BDE-47 in adipose tissue of about 21.000 ng/g tissue at the time of mating and during gestation, declining to about 6,900 ng/g tissue at weaning (Ta et al., 2011).

The effects of **BDE-99** were investigated in three different studies performed in rats and mice. CD-1 Swiss mice exhibited hyperactivity and alterations in anxiety-like behaviour after oral administration (by trained self-administration from a modified syringe once a day or via gavage to dams) of 0, 0.6, 6, 18 or 30 mg/kg b.w. from GD6 to PND21 with a LOEL of 0.6 mg/kg b.w. (Branchi et al., 2002, 2005). Sprague-Dawley rats exposed via gavage to 2 mg/kg b.w. from GD6 to PND21 displayed poor short-term memory when tested in the Morris water maze at PND34-36, and lower antioxidant enzyme activity in the brain at PND37 (Cheng et al., 2009). Long-Evans rats exposed by subcutaneous administration to 1 or 10 mg/kg of BDE-99 given to dams from GD10 to GD18 induced feminization in male mice, as shown by an increased sweet preference, and a decreased sexual behaviour in females with a LOEL of 10 mg/kg (Lilienthal et al., 2006; Lichtensteiger et al., 2004).

In a recent study (Daubié et al., 2011) adult Sprague Dawley rats were administered a daily dose 0, 0.15, 1.5 or 15 µg/kg b.w. BDE-99 by oral gavage for 90 days. Before and after the 90 days of exposure, behavioral tests including the open-field, the elevated plus-maze test for locomotor activity and anxiety, and the Morris water maze for spatial learning were conducted. No effects on behavioural parameters were found in any of the dose groups. The mean concentration of BDE-99 in adipose tissue of rats of the highest dose group was 1,925 ng/g fat.

The neurotoxic potential of **BDE-209** was investigated in C57BL6/J mice exposed by oral administration with a micropipette to 0, 6 or 20 mg/kg b.w. BDE-209 from PND2 to PND15. Increased locomotor activity on PND70 and developmental delays in palpebral reflex on PND14 were observed with a LOEL of 20 mg/kg b.w. (Rice et al., 2007). Evaluation of the same mice at later ages (16 month) showed changes in learning and visual discrimination ability also after exposure to 6 mg/kg b.w. Increased impulsivity was observed in young (PND87 ± 4) and older (16 month) animals that were exposed to 20 mg/kg b.w. BDE-209 (Rice et al., 2009).

Further, repeatead exposure to BDE-209 of CD1 Swiss mice (10 weeks of age) by gavage for 15, 30 or 60 days resulted in permanent alterations in acetylcholinesterase (TchE), superoxide dismutase and malonic dialdehyde (MDA) activity in brain tissues with increased activities for TchE and MDA whereas superoxide dismutase (SOD) activity was decreased. A NOEL of 0.1 mg/kg b.w. per day and a LOEL of 40 mg/kg b.w. per day were determined (significant alterations in SOD and MDA activity after exposure to 40 mg/kg b.w. after 15, 30 and 60 days; significant alterations in TchE activity after 80 mg/kg b.w. after 15 days of exposure) (Liang et al., 2010).

Other studies were performed using **DE-71**. Oral administration of 30 mg/kg b.w. DE-71 (25 % tetraBDE, 50-60 % pentaBDE and 4-8 % hexaBDE) impaired learning and visual discrimination in adult Long-Evans rats that were exposed from PND6 to PND12 (Dufault et al., 2005). Transient hyperactivity was also described at PND60, but not at earlier (PND24) or later (PND110, 273) timepoints in Long-Evans rats exposed via gavage to 10.2 mg/kg b.w. from GD6 to PND21 (Kodavanti et al., 2010).

In addition to rodents, Killifish embryos exposed to DE-71 (58.1 % pentaBDE, 24.6 % tetraBDE) from day 0 to 7 post fertilization were analysed for behavioural changes in activity, learning and predation. Hypoactivity was observed after single exposure to 0.001-1 µg/L, whereas multiple exposures to 0.1-1 µg/L induced hyperactivity (Timme-Laragy et al., 2006).

Mechanisms of PBDE-induced neurotoxicity

The mechanisms of PBDE-induced neurotoxicity have been studied in *in vivo* and *in vitro* model systems (see Section on Biochemical effects and molecular mechanisms). Studies from *in vivo* models which have provided information on specific neurotoxicity mechanisms are summarized below.

Biochemical changes due to **BDE-47** exposure have been investigated in two different studies. In one study, Sprague-Dawley rats were exposed to 0, 1, 5 and 10 mg/kg b.w. BDE-47 on PND10. The hippocampus of two month old rats showed alterations in the endoplasmatic reticulum, mitochondria, periplast and cytoplasm in the hippocampal CA1 region, with a LOEL of 5 mg/kg b.w. In addition, changes in the expression of apoptosis related genes and proteins (XIAP, DAPK, casase-3 and -12, cytochrome C) were detected at exposure levels between 1 and 10 mg/kg b.w. BDE-47 (He et al., 2009a). In the second study, C57/BL6 mice were exposed to a single oral dose of 6.8 mg/kg b.w. BDE-47 on PND10. *Ex vivo* analyses on PND17-PND19 showed a reduced hippocampal long-term potentiation and post-tetanic potentiation. Molecular studies on protein level revealed a decreased expression of postsynaptic proteins involved in synaptic plasticity (NR2B, GluR1 and CAMKII) (Dingemans et al., 2007).

BDE-99 was shown to alter expression of proteins involved in neuroplasticity and maturation in the striatum (GAP43, stathmin and synclein) and proteins of metabolism and energy production in the hippocampus (e.g. ATP synthase, α- and γ-enolase) in NMRI mice that were exposed via gavage to 12 mg/kg b.w. BDE-99 on PND 10 after 24 hrs (Alm et al., 2006). Neonatal exposure of NMRI mice to a single oral dose of **BDE-153** (0, 0.9 or 9 mg/kg b.w.) on PND10 exhibited a reduced density of nicotinic receptors in the hippocampus of adult offspring (6 month) (Viberg et al., 2003a). Protein levels of CAMKII and synaptophysin in the hippocampus of neonatal NMRI mice exposed to 16.8 mg/kg b.w. **BDE-203** or 18.5 mg/kg b.w. **BDE-206** on PND10 were found altered already after 24 h (Viberg, 2009). The same mice exposed to 20.1 mg/kg b.w. **BDE-209** as a single oral dose on

PND3 showed alterations in the expression of CaMKII (hippocampus), GAP-43 (hippocampus and cortex), BDNF (hippocampus) and synaptophysin (hippocampus) protein levels 7 days after treatment in different brain regions (Viberg et al., 2008; Viberg, 2009).

In summary, different behavioural studies performed in rats and mice, all PBDEs tested induced long-lasting behavioural alterations, particularly in the motor and cognitive domain. However, it should be noted that only a few studies were designed according to the OECD 426 guideline (OECD, 2007) for developmental neurotoxicity studies. The recommended test guidelines, considering, amongst others, time of exposure between implantation and weanling, way of administration and control for litter effects, have been demonstrated to provide the most reliable and reproducible data for assessing potential developmental neurotoxicity (Makris et al., 2009). In addition, appropriate statistical design and analyses appear essential prerequisites to formulate relevant hypotheses and draw conclusions on toxicity (Holson et al., 2008). Biochemical studies performed after *in vivo* exposure indicate that different PBDE congener interfere with the expression of proteins involved in neuronal maturation, synaptogenesis and neuroplasticity. Further findings show that PBDEs alter the expression of proteins that are involved in apoptotic pathways. Therefore, PBDEs might interfere with essential processes of brain development resulting in alterations in neuronal plasticity and circuitry. However, a correlation between behavioural and biochemical alterations is difficult to establish based on the available data.

Table 37: Neurobehavioural effects of PBDEs. LOEL values as reported in the original studies.

Congener	Species	Age	Exposure level	LOEL	Purity	Outcome	Reference
BDE-47	NMRI mice	PND10	0.7 and 10.5 mg/kg b.w. oral	10.5 mg/kg b.w.	98 %	• Alterations in spontaneous behaviour (2 and 4 month old) • Decreased habituation (2 and 4 month old)	Eriksson et al., 2001
BDE-47	Wistar rats	GD6	0.14 and 0.7 mg/kg oral	0.7 mg/kg		• Increased locomotor activity • Decreased thigmotaxis • Decreased anxiety	Kuriyama et al., 2004a
BDE-47	Sprague-Dawley rats	PND10	1; 5 and 10 mg/kg oral	1 mg/kg	100 %	Alterations in water maze behaviour: • total distance swam increased • ratio in platform quadrant/total distance decreased	He et al., 2009a
BDE-47	C57BL/6 mice	PND10	1, 10, 30 mg/kg b.w. oral	-		• Non-dose related increase in spontaneous locomotor activity (at 4 months of age) in all dose groups	Gee and Moser, 2008
BDE-47	Wistar rats	GD15-PND20	0.002, 0.02, 0.2 mg/kg b.w., *i.v.* every 5 days	0.002 mg/kg b.w.		• Increased spontaneous locomotor activity (PND20)	Suvorov et al., 2009
BDE-47	C57BL/6 mice	Before breeding-PND21	0.03, 0.1, 1 mg/kg b.w. oral	1.0 mg/kg	ACS grade	• Decreased locomotor activity (PND60)	Ta et al., 2011
BDE-47	C57BL/6 mice	PND10	1, 10, 30 mg/kg b.w. oral	-		• Increased cortical dopamine (PND15, 20, adults) at 10 mg/kg b.w. only	Gee et al., 2011
BDE-99	NMRI mice	PND10	0.2, 0.4 and 12.0 mg/kg oral	12.0 mg/kg		Decreased habituation	Viberg et al., 2004b
BDE-99	NMRI mice	PND3 or 10 or 19	8 mg/kg b.w. oral	8 mg/kg on PND3 or 10	98 %	• Alterations in spontaneous behaviour • Decreased habituation	Eriksson et al., 2002
BDE-99	C57/BI mice	PND10	0.4, 0.8, 4.0, 8.0 and 16.0 mg/kg b.w. oral	0.8 - 4 mg/kg	99 %	• alterations in spontaneous behaviour (2, 5 and 8 months old) • Decreased habituation (2 and 8 months old)	Viberg et al., 2004a
BDE-99	Wistar rats	GD6	0.06 and 0.3 mg/kg b.w. oral	0.3 mg/kg (PND36) 0.06 mg/kg (PND71)	98 %	Hyperactivity (PND36 and PND71)	Kuriyama et al., 2005
BDE-99	CD-1 Swiss mice	GD6-PND21	0.6, 6.0 and 30.0 mg/kg oral	0.6-6.0 mg/kg		• Hyperactivity at PND22, 34 and 60, and hypoactivity at PND120 • Decreased thigmotaxis indicating reduced anxiety-like behaviour (PND 60).	Branchi et al., 2002
BDE-99	CD-1 Swiss mice	GD6-PND21	18 mg/kg b.w. oral	18 mg/kg		•Hyperactivity and decreased habituation at PND34 (assessed at PND34, 69, 90 and 120)	Branchi et al., 2005

Table 37: Continued.

Congener	Species	Age	Exposure level	LOEL	Purity	Outcome	Reference
BDE-99	NMRI mice	PND10	0.8 and 12.0 mg/kg oral	0.8 mg/kg	98 %	• Alterations in spontaneous behaviour (2 and 4 months old) • Decreased habituation • Decreased performance in Morris swim maze (12.0 mg/kg; 5 months old) which points to deficits in learning and memory function	Eriksson et al., 2001
BDE-99	Sprague-Dawley rats	GD6-PND21	2 mg/kg oral			• Impaired short-term memory (PND34-36) • Lower antioxidant enzyme activity in the brain (PND37)	Cheng et al., 2009
BDE-99	Long-Evants rats	GD10-18	1; 10 mg/kg b.w. daily sub-cutaneous injection	10 mg/kg	99 %	Increased sweet preference indicates feminization (starting on PND120).	Lilienthal et al., 2006
BDE-99	Long-Evants rats	GD10-18	1; 10 mg/kg b.w. daily sub-cutaneous injection	10 mg/kg	99 %	• Decreased female sexual behaviour	Lichtensteiger et al., 2004
BDE-99	Sprague Dawley rats	Adults, 90 days exposure	0.15, 1.5, 15 µg/kg b.w. per day, oral	-	98 %	• No effect on behaviour, locomotor activity, spatial learning, anxiety.	Daubié et al., 2011
BDE-153	NMRI mice	PND10	0.45, 0.9, 9.0 mg/kg b.w. oral	0.9 mg/kg	92.5 % hexaBDE, 7.5 % heptaBDE	• Disruption of spontaneous behaviour indication decreased habituation (2, 4 and 6 month old) • Decreased performance in Morris swim maze indicating impaired learning and memory capability (6 months old)	Viberg et al., 2003b
BDE-183	NMRI mice	PND3 or 10	15.2 mg/kg b.w. oral		98 %	• Decreased spontaneous behaviour when administered on PND3 (determined in 2 months old animals) • Decreased habituation	Viberg et al., 2006
BDE-203	NMRI mice	PND3 or 10	16.8 mg/kg b.w. oral		98 %	• Decreased spontaneous behaviour when administered on PND3 and PND 10 (determined in 2 months old animals) • Decreased habituation • Decreased performance in Morris swim maze (determined in 3 months old animals)	Viberg et al., 2006
BDE-206	NMRI mice	PND3 or 10	18.5 mg/kg b.w. oral		98 %	Decreased habituation	Viberg et al., 2006

Table 37: Continued.

Congener	Species	Age	Exposure level	LOEL	Purity	Outcome	Reference
BDE-209	NMRI mice	PND3 or 10 or 19	PND10: 1.34, 13.4 and 20.1 mg/kg PND3: 2.22 and 20.1 mg/kg b.w. oral	20.1 mg/kg		PND3: Alterations in spontaneous behaviour and habituation (2, 4 and 6 month old) PND10 and PND 19: no alterations detectable	Viberg et al., 2003a
BDE-209	Sprague-Dawley rats	PND3	6.7 and 20.1 mg/kg b.w. oral	6.7 mg/kg	98 %	• Alterations in spontaneous behaviour indicating decreased habituation (2 months old) • Alterations in nicotine response (2 months old)	Viberg et al., 2007
BDE-209	C57BL6/J mice	PND2-15	6 and 20 mg/kg b.w. oral	20 mg/kg	99.5 %	•Hyperactivity (PND70) •Developmental delay in palpebral effect	Rice et al., 2007
BDE-209	C57BL6/J mice	PND2-15	6 and 20 mg/kg b.w. oral	6 mg/kg		• Impaired learning in old (16 months old), but not in young (3 months old) mice • Impulsivity in the high dose (20 mg/kg)	Rice et al., 2009
DE-71	Long-Evans rats	PND6-12	30 mg/kg b.w. oral		25 % tetraBDE, 50-60 % pentaBDE, 4-8 % hexaBDE	Impaired learning in visual discrimination in adult rats	Dufault et al., 2005
DE-71	Long-Evans rats	GD6-PND21	1.7, 10.2 and 30.6 mg/kg b.w. oral	10.2 mg/kg		• Hyperactivity only at PND60	Kodavanti et al., 2010
DE-71	Killifish	Embryos	0.001-100 µg/L	0.001	58.1 % pentaBDE, 24.6 % tetraBDE	• Hypoactivity	Timme-Laragy et al., 2006

LOEL: lowest-observed-effect level; PND: post-natal day; GD: gestational day; b.w.: body weight; *i.v.*: intravenous.

8.3.2.3. Immune system

It has been suggested that PBDEs might exert toxic effects to the immune system by reducing resistance to infections by microorganisms. Only few experimental studies on immunotoxicity in which contamination of the test substance with brominated dioxins and/or furans have been controlled were identified.

Mice (male balb/c, n=5/group) were infected with human coxsackievirus B3 (CBV3) on day 0, exposed orally to 0 or 20 mg/kg b.w. of **BDE-99** or **Bromkal 70-5 DE** on day 1, and put to death on day 3. Amount of CBV3 in liver and pancreas and serum levels of 21 cytokines were measured. PBDE exposure caused a marked decrease of IL-13, MIP-1β, RANTES, IFN-γ and KC in non-infected mice (Lundgren et al., 2009). Viral replication in lung, pancreas and liver during early CVB3 infection was not affected by PBDEs exposure (Lundgren et al., 2009, 2007a, 2007b). The BDE-99 used had 99 % purity and did not contain PBDD, PBDF or PBB above LOD (0.05 ng/g). The Bromkal-mixture contained detectable amounts (135 ng/g-5,377 ng/g) of some PBDF congeners. The same Bromkal-mixture (20 mg/kg) did not induce CYP1A1 in liver, lung or pancreas, and no increase in liver EROD activity was observed (Lundgren et al., 2007a, 2007b).

Host immunity to respiratory syncytial virus (RSV) was investigated after exposure of five weeks old mice to 1 % **DecaBDE** (purity not stated) in the diet (approximately 1,700 mg/kg b.w. per day) for 28 days followed by RSV infection. No effect on the subsequent pulmonary viral titre was observed (Watanabe et al., 2010a). Offspring of mice exposed to DecaBDE (0, 1000, 10,000 mg/kg diet, purity 98 % or more) from GD10 to weaning at PND21 were infected with RSV on PND28. Based on average food consumption and b.w., the highest DecaBDE dose corresponded to 3,300 mg/kg b.w. per day. Increased virus titres were found in the highest PBDE dose group at 1 and 5 days after infection. This was accompanied by reduced TNFα and IL-6 levels and increased IL-1β secretion one day after infection (Watanabe et al., 2010b).

In a study of **DE-71** in ranch mink (male, 20 weeks old, n=10/group) the animals were dietary exposed to 0, 1, 5 or 10 mg/kg food (estimated intake 0, 0.069, 0.457 or 0.777 mg/kg b.w. per day, based on mean feed consumption), for eight weeks. Sum of PBDE concentration in liver at termination of experiment was 58.8, 5,067, 18,505 and 27,909 mg/kg lipid, but the lipid level did however decrease by increasing exposure. Mink in the two highest treatments groups had significantly increased antibody production, lower haematocrit, increased neutrophils percentage, decreased lymphocytes percentage, and reduced b.w. compared to unexposed mink. Exposed mink also had larger spleen, adrenal and liver masses relative too b.w. than control mink. Animals in the highest exposure group had spleens with increased germinal centre development and increased incidence of B-cell hyperplasia. Early T-cell response was not affected. DE-71 was analysed for brominated dioxins and furans, all were below LOQ/LOD of < 0.03 ng/g (Martin et al., 2007), but still EROD activity, which is sensitive for AhR-mediated activation of transcription, was increased in all treated mink.

In summary, immunotoxic effects were observed after eight weeks exposure of ranch mink with 0.457 or 0.777 mg DE-71/kg b.w. per day. A single exposure of mice to Bromkal 70-5 DE or BDE-99 (20 mg/kg b.w.) did not affect susceptibility to CBV3 infection, but increased RSV titres were seen in offspring of dams exposed to 3,300 mg DecaBDE/kg b.w. per day from GD10 to PND21.

8.3.2.4. Liver

The liver was reported to be a target organ for a variety of PBDEs and PBDE mixtures (Table 38). The major effects observed in rodents were liver enlargement and histopathological changes, mainly centrilobular hepatocellular hypertrophy. In a variety of species, including non-mammalian vertebrates, induction of enzymes of hepatic drug metabolism was observed. Furthermore, a loss of apolar retinoids, normally stored in the liver, was obtained. Finally, the decrease in serum thyroxin

(T4) seen in several species was attributed, at least in part, to an increased hepatic metabolism of the hormone.

Zhou et al. (2001) administered orally technical mixtures DE-71, DE-79 or DE-83R to 28 days old female Long-Evans rats over four days. DE-71 and DE-79 led to liver enlargement, induced hepatic EROD and pentoxyresorufin-O-deethylase (PROD), and UGT activities, and decreased serum T4. The most sensitive effects PBDEs for a 50 % increase in PROD activity were 0.81 mg/kg b.w. per day for DE-71 and 0.53 mg/kg b.w. per day for DE-79.

Oral dosage of technical DE-71 or single PBDEs (BDE-47, -99 and -153) to adult male F344 rats on three consecutive days resulted in a weak up-regulation of hepatic CYP1A1 mRNA compared to the effect of a corresponding dose of technical DE-71 (Sanders et al., 2005). The authors conclude that planar contaminants in the technical PentaBDE mixture are responsible for Ah receptor-mediated effects. Furthermore, they observed a marked induction of the constitutive active receptor- (CAR-) and Pregnane X Receptor (PXR, NR1I2/Nr1i2) regulated CYP2B and CYP3A transcripts in the liver.

Ellis-Hutchings et al. (2006) treated dams (Sprague-Dawley rats) from gestation day 6 to lactation day 12 or 18 with PentaBDE mixture by oral gavage. In the pups, hepatomegaly was induced at PNDs 12, 18 and 31. Furthermore, PentaBDE lowered liver vitamin A levels both in dams and pups.

In a 28 days oral toxicity study van der Ven et al. (2008b) treated Wistar rats orally (by gavage) with DecaBDE. The most sensitive effects in the liver were induction of CYP1A and CYP2B (BMD_{10}s 0.5-0.7 mg/kg b.w. per day for a 10 % increase).

Van der Ven et al. (2008a) reported that a purified commercial PentaBDE mixture (containing approximately 45 % pentaBDE congeners), given orally (gavage) to Wistar rats over 28 days resulted in increased liver weight, centrilobular hepatocellular hypertrophy, decrease in apolar hepatic retinoids, and induction of hepatic CYP1A and CYP2B enzymes. The $BMDL_{10}$ were 7.6 mg/kg b.w. per day for liver enlargement, 1.1 (males) and 1.8 (females) mg/kg b.w. per day for decreased plasma T4, 0.5 (males) and 2.3 (females) mg/kg b.w. per day for decreased apolar liver retinoids, and 0.07 (males) and 0.8 (females) mg/kg b.w. per day for increased CYP2B1 mRNA. The authors also found increased serum alanine aminotransferase activities in treated males only ($BMDL_{10}$ 15.5 mg/kg b.w. per day). Taken together, the authors suggest that most effects seen in the liver were mediated by activation of the nuclear receptor CAR which regulates, among others, the expression of CYP2B1. CAR activation was reported to be more sensitive in male than in female rats.

Richardson et al. (2008) treated female C57BL/6 mice orally (by gavage) with 0, 3, 10, or 100 mg/kg b.w. BDE-47 for four days. At 100 mg/kg b.w. per day hepatic UGT1A1, 1A7, and 2B5 were significantly induced. At the same dose level a significant decrease in serum total T4 was observed. Induction of hepatic PROD activity was detected at the lowest dose (3 mg/kg b.w. per day). BDE-47 also decreased hepatic transthyretin and monocarboxylate transporter 8 (Mct8) mRNA expression suggesting that induction of hepatic UGTs may be partly responsible for decreases in circulating T4 following BDE-47 exposure.

Dunnick and Nyska (2009) treated F344/N rats and B6C3F1 mice with DE-71(Great Lakes Chemical Corporation - Lot 2550OA30A) by oral gavage over 13 weeks. Hepatocellular hypertrophy and vacuolization occurred in rats at 50 mg/kg b.w. per day and above, in mice at 100 mg/kg b.w. per day and above. Liver CYP1A1, 1A2, and 2B levels were increased at exposure levels of 50 mg/kg b.w. per day and above in both species. The most sensitive parameter found was liver enlargement which occurred at 5 mg/kg b.w. per day and above in rats and at 50 mg/kg b.w. per day and above in mice. The authors suggest that these changes may be indicative for a tumor-promoting potential of the commercial PentaBDE mixture in rodent liver.

Szabo et al. (2009) found that treatment of pregnant Long-Evans rats with DE-71 (Great Lakes Chemical Corporation - Lot 7550OK20A) (by gavage) between GD6 and PND21 decreased serum T4,

and induced various hepatic CYPs and UGTs in the male pups. Furthermore, SULT1b1 expression was increased, transthyretin and deiodinase I expression was decreased, and a variety of hepatic export pumps such as Mdr1, Mrp2, and Mrp3 and the import transporter Oatp1A4 were induced. Taken together, the authors conclude that various hepatic effects can explain the observed decrease in serum T4.

Albina et al. (2010) treated adult male SD rats with a single dose of 0, 0.6 or 1.2 mg/kg b.w. of BDE-99 by gavage. After 45 days, they found significant increases in hepatic SOD activity, GSSG levels, and glutathione disulfide/glutathione (GSSG/GSH) ratio while GSH levels were decreased. Catalase activity was reduced at the highest dose. The authors concluded that PentaBDE can lead to oxidative stress in rat liver at a dose level of 0.6 mg/kg b.w. and above.

Bruchajzer et al. (2010) treated by gavage female Wistar rats with 0, 2, 8, 40 or 200 mg/kg b.w. per day PentaBDE or with 10, 100 or 1,000 mg/kg b.w. per day DecaBDE for 7, 14, 21, or 28 days. After 28 days of treatment, the autors report an increase in hepatic GSH at the lowest dose of PentaBDE (2 mg/kg b.w. per day). With DecaBDE, this effect was observed at the lowest dose (10 mg/kg b.w. per day) after 21 days but not after 7, 14, and 28 days. At 200 mg/kg b.w. per day, PentaBDE led to an increase in hepatic malondialdehyde levels, while DecaBDE did not cause such effects. Furthermore, Penta BDE (at 2 mg/kg b.w. per day) markedly induced hepatic EROD and PROD activities, whileDecaBDE had a marginal inducing effect. At the highest dose of PentaBDE hepatic steatosis and increases in serum ALT and AST were also observed.

Öberg et al. (2010) treated by gavage male and female Sprague-Dawley rats over 28 days with 0, 2.5, 25 and 250 mg Bromkal 70-5DE/kg b.w. per day. In treated animals increased hepatic EROD and PROD activities, enhanced liver weight and depletion of hepatic retinoids were observed. Furthermore, treatment led to histopathological changes (hepatocellular hypertrophy, fatty degeneration). Chemical analysis of the PBDE mixture by GC-MS showed impurities of polybrominated dibenzofurans and to a lesser extent dibenzodioxins, in total levels of about 7.0 µg/g of Bromkal 70-5DE. The animals were thereby exposed to an estimated dose of dioxin-like equivalents corresponding to 1.3-131 ng TEQ/kg b.w. The authors did not rule out that TEQ contaminations had contributed to these effects.

Summarising, the liver is a major target organ for PBDEs. The most prominent hepatic effects are organ enlargement and hepatocellular hypertrophy and vacuolization. Furthermore, PBDEs induce a number of enzymes of hepatic drug metabolism such as various CYPs, UGTs, and transmembrane pumps, leads to a decrease in hepatic retinoids, and seems to cause oxidative stress. Most of these effects are in agreement with mechanisms mediated by the CAR and/or the PXR. The possibility of a contribution of dioxin-like impurities in the PBDEs used is also discussed by several authors. Since this pattern of effects is characteristic for rodent liver tumour promoters, a tumor-promoting potencty of PBDEs appears plausible. In fact, there is some evidence for an increase in liver adenoma in rats and liver adenoma and carcinoma in mice treated with decaBDE (see Chapter 8.3.2.6.). Activation of the aryl hydrocarbon receptor (AhR) mostly seen with technical PBDE mixtures, is supposed to be mainly due to minor 'dioxin-like', non-PBDE contaminants. The $BMDL_{10}$ value for pentaBDE-mediated hepatic CYP2B induction in male rats was 0.07 mg/kg b.w. per day. No clear evidence for marked differences in CYP-inducing potency of tetraBDEs, pentaBDEs or decaBDE can be derived from the available literature. Changes in hepatic drug metabolism and transthyretin expression seem to play a key role in the decrease in serum T4 observed in rodents.

Table 38: Liver toxicity/hepatic effects of PBDEs. LOEL/NOEL/BMD(L) values as reported in the original studies.

Congener	Species	Exposure and level(s) [a]	LOEL [b]	NOEL [b]	BMD(L) [b]	Purity/impurities	Outcome	Reference
BDE-47	C57 BL/ 6 mice female	Orally (by gavage) with 3, 10, 100 mg for 4 days.	100 mg/kg b.w.	-	-	> 98 %	Induced UGT1a1, 1a7, 2b	Richardson et al., 2008
			3 mg/kg b.w.	-	-		Induced PROD activity	
BDE-99	SD rats, male	0, 0.6, 1.2 by gavage	Liver GSSG/GSH, GSSG, GSH, SOD: 0.6	LOELs at lowest dose studied			Increased GSSG, GSSG/GSH, SOD activity, decrease in liver GSH	Albina et al., 2010
BDE-99 (technical)	Wistar rats, female	2, 8, 40, 200 orally, by gavage	Liver GSH:2 Malondialdehyde:8 Steatosis, increased ALT, AST: 200 EROD, PROD: 2	LOEL at lowest dose: 2. 40 LOEL at lowest dose		> 98 %	Increased activity liver GSH, EROD,PROD, Malondialdehyde, ALT and AST	Bruchajzer et al., 2010
BDE-209	Wistar rats, male and female	orally (by gavage) 28 days 1.9, 3.8, 7.5, 15, 30, 60 mg	-	-	$BMDL_{10}$: 0.5 - 0.7	0.00001 % of 2,3,7,8-TBDF; 0.001 % of 1,2,3,4,6,7,8-HpBDF	Induced CYP1A and CYP2B activities and mRNAs.	van der Ven et al., 2008b
BDE-209	Wistar rats, female	10, 100, 1.000 orally by gavage	EROD, PROD:10	LOEL at lowest dose		> 98 %	Induction EROD, PROD	Bruchajzer et al., 2010

Table 38: Continued.

Congener	Species	Exposure and level(s) [a]	LOEL [b]	NOEL [b]	BMD(L) [b]	Purity/impurities	Outcome	Reference
BDE-47, BDE-99, BDE-153, DE-71 (technical)	F344 rats, male, (3 days)	Orally, Technical DE-71: 1.5, 15, 150 BDE-47: 0.49, 4.9, 49 BDE-99: 0.57, 5.7, 57 BDE-153: 0.6, 6.4, 64	Technical DE-71: 15 BDE-47: 49 BDE-99: 57 BDE-153:64	Technical DE-71: 1.5 BDE-47: 4.9 BDE-99: 5.7 BDE-153: 6.4	-	Technical DE-71: 81 % BDE-47: 99 % BDE-99: 96 % BDE-153: 96 %	CYP1A induction	Sanders et al., 2005
			Technical DE-71: 15 BDE-47: 4.9 BDE-99: 5.7 BDE-153:6.4	Technical DE-71: 1.5 BDE-47: 0.49 BDE-99: 0.57 BDE-153:0.6	-	Containing 2,3,7,8-TBDD and other PBDD/Fs	CYP2B induction	
			Technical DE-71: 150 BDE-47: 49 BDE-99: 57 BDE-153: 6.4	Technical DE-71: 15 BDE 47: 4.9 BDE 99: 5.7 BDE-153: 0.6	-		CYP3A induction	
DE-71 (cleaned, technical)	Zebrafish	0.1, 1.0 mg/L water	-	-	-	Cleanup procedure to remove PBCD/Fs: <0.8 ng TEQ/g BDE-71.	Induction of CYP1A in hepatic blood vessels only limited with uncleaned BDE-71.	Kuiper et al., 2008
DE-71 and DE-79 (technical)	SD rats female, 28 days old (4 days)	orally, DE-71: 0.3, 1, 3, 10, 30, 100, 300 DE-79: 0.3, 1, 3, 10, 30, 60, 100	-	DE-71 (79): EROD: 3 (10) PROD: 3 (3) UGT: 10 (10)	BMD 50 % for DE-71 (79): EROD: 1.8 (2.5) PROD: 0.5 (0.4) UGT: 5.8 (11.0)	no information	Liver enlargement induced hepatic EROD, PROD, and UGT activities.	Zhou et al., 2001
DE-71 (technical)	SD rats female	GD6 to PND12 or 18 18 mg intra-gastrically	-	-	-	no information	Pups: hepatomegaly at PND 12, 18 and 31 Dams and pups: vitamin A levels decreased.	Ellis-Hutchings et al., 2006

Table 38: Continued.

Congener	Species	Exposure and level(s) [a]	LOEL [b]	NOEL [b]	BMD(L) [b]	Purity/impurities	Outcome	Reference
DE-71 (technical)	Wistar rats, male and female	orally (by gavage) 28 days 0.27, 0.82, 2.47, 7.4, 22.2, 66.7, 200 mg	-	-	$BMDL_{10}$: 7.6 (females)	90 ng 2,3,7,8-PBDFs per g BDE 71	Increased liver weight, centrilobular hepatocellular hypertrophy.	van der Ven et al., 2008a
			-	-	0.5 (males) and 2.3 (females)		Decrease in apolar hepatic retinoids.	
			-	-	0.07 (males) and 0.8 (females)		Induction of CYP2B1.	
			-	-	males only: 15.5		Increased serum alanine aminotransferase.	
DE-71 (technical)	F344/N rats B6C3F1 mice	oral gavage, 13 weeks, 5 days a week, 0.01, 5, 50, 100, 500	5 (males) 100 (females)	0.01 (males) 50 (females)	-	0.0066 % PBDD/Fs	hepatocellular hypertrophy, vacuolization	Dunnick and Nyska, 2009
			50	5	-		CYP 1A1, 1A2, 2B, UGT levels increased	
			5 (rats) 50 (male mice) 100 (female mice)	0.01 (rats) 5 (male mice) 50 (female mice)	-		Liver enlargement	
DE-71 (technical)	Long-Evans rats, female (pregnant)	Orally; GD6 to PND21; 1.7, 10.2, 30.6	At PND4 (21): CYP1A1, EROD CYP2B1, 2B2, PROD: 1.7 (1.7) CYP3A1: 30.6 (10.2) BROD: 10.2 (1.7)	Various LOELs at lowest dose studied	-	No information	Male pups: CYPs, UGTs, SULT1b1, Mdr1, Mrp2, Mrp3, Oatp1A4 increased; transthyretin, deiodinase I decreased.	Szabo et al., 2009

Table 38: Continued.

Congener	Species	Exposure and level(s) [a]	LOEL [b]	NOEL [b]	BMD(L) [b]	Purity/impurities	Outcome	Reference
Bromkal 70-5DE	SD rats	2.5, 25, 250 orally, by gavage	Males: EROD: 2.5 histop. changes:25 PROD:25 hepat. retinoids:250 Rel. liver weight: 25 Females: Liver weight: 250 Histop. changes: 25 Hepat. retinoids: 25 EROD:2.5 PROD: 2.5	LOEL at lowest dose. histop. changes:2.5 PROD: 2.5 hepat. retinoids:25 rel. liver weight: 2.5 Relative liver weight: 25 Histop. Changes: 2.5 Hepatic Retinoids: 2.5 LOEL at lowest dose PROD: 2.5		7 µg PBDD/PBDF per g	Induction EROD, PROD histopath. Decreased relative liver weight Decrease in hepatic retinoids	Öberg et al., 2010

LOEL: lowest-observed-effect level; NOEL: no-observed-effect level; BMD: benchmark dose; BMDL: benchmark dose lower confidence limit; UGT: uridine diphosphoglucuronosyl transferase; GSSG: glutathione disulfide; GSH: glutathion; SOD: superoxide dismutase; ALT: alanine transferase; AST: aspartate transferase; EROD: ethoxy-resorufin-O-deethylase; PROD: pentoxyresorufin-O-deethylase; b.w.: body weight; PND: post-natal day; GD: gestational day; CYP: cytochrome P450.
(a): mg/kg b.w. per day if not stated otherwise.
(b): mg/kg b.w. per day.

8.3.2.5. Genotoxicity

The genotoxic potential of commercial grade Deca-, Octa-, and PentaBDEs has been examined in several, mostly unpublished, studies (IPCS, 1994). Mutagenicity tests carried out on four strains of *Salmonella typhimurium* with a technical product of **DecaBDE** (HFO-102) and commercial **DecaBDE** with and without metabolic activation were negative. Similarly, studies in eukaryotic cells utilizing yeast (*Saccharomyces cerevisiae*) and the TK locus of the mouse lymphoma cell line L5178Y with and without metabolic activation were negative. Commercial decaBDE did not induce chromosomal aberrations or sister chromatide exchanges in Chinese hamster ovary cells with or without metabolic activation. Results were also negative in cytogenetic examination of bone marrow cells from parent rats exposed to DecaBDE (at dose levels up to 100 mg/kg b.w. per day in a reproduction study) and their weanlings (Norris et al., 1975a; 1975b).

A commercial **OctaBDE** preparation did not induce mutations in *S. typhimurium* or *S. cerevisiae* nor caused sister chromatide exchanges in Chinese hamster ovary cells with or without metabolic activation. Mutagenicity studies with a commercial pentaBDE preparation in four strains of *S. typhimurium* and in *S. cerevisiae* with and without metabolic activation were all negative (IPCS, 1994). It was also found to be negative in the unscheduled DNA synthesis assay in the human fibroblast cell line WI-38 with and without metabolic activation.

More recent studies showed that PBDEs induce oxidative DNA damage. **BDE-47** (1, 5, 10, μM) induced oxidative DNA damage measured as 8-OHdG adducts in SH-SY5Y (human neuroblastoma) cells (Gao et al., 2009). In SH-SY5Y cells exposed to BDE-47 (1, 2, 4, 8 mug/mL/24 h) ROS formation was detected at concentration 2 mug/mL and was associated with dose dependent incease in DNA damage (comet assay), micronuclei and nucleoplasmatic bridges indicating clastogenic effects (He et al., 2008a). Similarly, in rat hippocampal neurons BDE-47 (2.06, 20.6 and 42.2 muM) induced oxidative stress (ROS, MDA, GSH-Px changes) along with DNA strand breaks (comet assay) in dose related manner at all concentrations (He et al., 2008b).

BDE-99 did not induce gene mutations in the Ames test neither chromosomal aberration in the Allium test (Evandri et al., 2003).

A series of brominated compounds including **BDE-47** were negative in DRAG assay which measures differential killing effect in wild type compared to DNA repair deficient CHO cells (Johansson et al., 2004). Two hydroxylated PBDE metabolites: 2-OH-BDE-47 and 2-OH-BDE-85 were cytotoxic at micro molar concentration with 2-OH-BDE-85 being more toxic than 2-OH-BDE-47, while no DNA damage and no evidence of AhR-mediated, dioxin-like toxicity was observed. At micromolar concentration of OH-PBDEs induced transcriptional changes associated with endoplasmic reticulum stress and the unfolded protein response (Song et al., 2009).

Recently Ji et al. (2011) studied the genotoxicity of BDE-47, -49, -99, -138 and -209 and the tetraBDE metabolites 6-OH-BDE-47 and 4-OH-BDE-49 in chicken DT40 cells, including wild type cells, and in a panel of mutant cell lines deficient in DNA-repair mechanisms. Chromosomal aberrations and DNA damage (double strand breaks) were observed for all tested compounds, with lower brominated congeners and the OH-metabolites being more potent. The authors suggested that the observed effects can be explained by the induction of reactive oxygen species (ROS).

Overall, the available studies indicate that PBDEs do not induce gene mutations, but recent studies indicate that they can cause DNA damage through the induction of ROS.

8.3.2.6. Carcinogenicity

Only limited information is available on the potential carcinogenicity of PBDEs. Carcinogenicity studies have been conducted with decaBDE but no such studies appear to have been undertaken with the other PBDEs. The rodent bioassays with decaBDE have been reviewed by a number of groups, including ATSDR (2004) and FAO/WHO (2006). Studies in mouse were performed by the National Toxicology Program (NTP) and in the rat by both NTP (1986) and Kociba et al. (1975).

In the NTP mouse study (NTP, 1986), decaBDE (purity 94-97 %) was administered to groups of 50 male and female B6C3F1 mice in the diet to provide estimated doses of 0, 3,200 and 6,650 mg/kg b.w. in males and 3,760 and 7,780 mg/kg b.w. in females, respectively, for 102 weeks. Treatment had no effect on body weight or survival. There was an increase in liver granulomas in low-dose males, and in liver hypertrophy in males of both dose groups. The combined incidence of hepatocellular adenomas and carcinomas was statistically significantly increased in males (8/50 in controls, 22/50 in low-dose and 18/50 in high-dose males) but there was no significant trend. The incidence of hepatocellular carcinoma alone was not significantly increased in either group of male mice. There was a small, non-significant increase in the combined incidences of thyroid follicular cell adenomas and carcinomas in both males (0/50 in controls, 4/50 in low-dose and 3/50 in high-dose) and females (1/50 in controls, 3/50 in low-dose and 3/50 in high-dose). There was evidence for an increase in thyroid follicular cell hyperplasia in males and females of both dose groups, the effect being greater in males than in females (high-dose males 19/50; high-dose females 7/49). This study was limited by an early, statistically significant, loss of control male mice during the first year of the study, most likely due to fighting.

In the study by Kociba et al. (1975), male and female Sprague-Dawley rats, 25 per sex per group, were administered decaBDE, which also contained 21.8 % nonaBDE and traces of octaBDE, 0.8 %, in their diet for 100-105 weeks. The doses were 0, 0.01, 0.1 or 1 mg/kg b.w. per day. There was no effect of treatment on body weight, clinical signs or survival. No adverse effects were observed, including any change in tumour incidence. However, it has been noted that the dose levels use in this study were very low (IARC, 1990).

In the NTP rat study (NTP, 1986), Fischer 344/N rats (50/sex/group) received decaBDE (purity 94-97 %) in their diet for 103 weeks, to give estimated dose levels of 0, 1,120 and 2,240 mg/kg b.w. per day in males and 0, 1,200 and 2,550 mg/kg b.w. per day in females, respectively. Treatment had no effect on body weights. At the end of the study, survival in low-dose males was significantly reduced, but this may not have been compound related. Histopathological changes were observed in liver, spleen and forestomach of high dose males. There was a statistically significant increase in the incidence of 'neoplastic nodules' in the liver (presumably adenomas) in both males (1/50 in controls, 7/50 in low-dose and 15/49 in high-dose; $P < 0.001$, for trend) and females (1/50 in controls, 3/49 in low-dose and 9/50 in high-dose females; $P = 0.002$, for trend). The assumption that all of the hepatic neoplastic nodules observed in this study were hepatic adenomas is conservative. There was no difference in the incidence of hepatocellular carcinomas in males or females at either dose level. Although there was a high incidence of mononuclear cell leukaemia in treated animals, this is unlikely to be of biological significance because there was also a high incidence in control animals (males: 30/50, 33/50, and 35/50; females: 14/50, 21/50, and 18/50 at control, low and high doses, respectively), the difference between controls and treated groups was marginal and not statistically significant. In this study, there was a dose-related reduction in the incidence of C-cell hyperplasia in the thyroid gland of both males and females (12/50, 6/49, and 2/49 in males and 14/50, 7/49, and 2/50 in females at control, low-dose, and high-dose groups, respectively).

Whilst BDE-209 has not been tested for carcinogenicity, decaBDE has been studied in rats and in mice, with some evidence for an increase in liver adenoma in rats and liver adenoma and carcinoma in mice. Hence, it is possible that BDE-209 could have similar effects in rodent liver. DecaBDE and BDE-209 are not genotoxic, hence the mode of action for any hepatocarcinogenic response presumably involves non-genotoxic processes. BDE-209 caused hepatic hypertrophy and induction of

CYP enzymes typical of activation of CAR/PXR receptor(s). Other compounds that act in this way, such as phenobarbitone, are tumour promoters in rodent liver. Tumours occur only after prolonged, high dose exposure, and precursor effects are reversible. There is evidence that CAR/PXR activation in humans does not support a number of the key events necessary for tumour promotion, such as hepatic hyperplasia. It is therefore concluded that BDE-209 does not present a carcinogenic risk to humans.

DecaBDE has been classified by IARC as Group 3 (not classifiable as to its carcinogenicity to humans) (IARC, 1990).

8.3.2.7. Teratogenicity

Commercial **DecaBDE** (containing 77.4 % decaBDE, 21.8 % nonaBDEs and 0.8 % octaBDE) has been studied for teratogenicity with Sprague-Dawley rats at doses of 0, 3, 30 or 100 mg/kg b.w. per day given in diet or 10, 100, or 1,000 mg/kg b.w. per day given by oral gavage (IPCS, 1994; Norris et al., 1975a, 1975b). No compound related effect was observed after giving the compounds in diet. After gavage, no maternal toxic effects were observed, while fetal toxicity was observed in terms of increased rate of resorptions (at 100 mg/kg) and subcutaneous edema and delayed ossification (at 1,000 mg/kg). Analysis of maternal and fetal livers for bromine concentration (reflecting liver concentration of DecaBDE) showed significantly increased concentrations only in maternal livers at the 1,000 mg/kg b.w. per day dose, given by oral gavage.

Teratogenicity of **DE-79** was studied in rats that were given the test compound by gavage at doses 0, 2.5, 10, 15, 25, or 50 mg/kg b.w. per day (IPCS, 1994). Reduced maternal body weight gain and slightly increased cholesterol levels were observed at the highest dose of 50 mg/kg b.w. per day. Fetal toxicity that was indicated by increased numbers of late resorptions, significantly reduced mean fetal weights, severe generalized edema, reduced ossification of the skull, various unossified bones, bent limb bones and bent ribs. The NOEL for maternal toxicity is 25 mg/kg b.w. per day and for fetal effects 15 mg/kg b.w. per day (IPCS, 1994).

Teratogenicity of **Saytex 111** (a commercial mixture containing 0.2 % penta-, 8.6 % hexa-, 45 % hepta-, 33.5 % octa-, 11.2 % nona- and 1.4 % decaBDE) was studied in Charles River (Sprague-Dawley) rats that were administered the test substance by gavage at doses 0, 2.5, 10, or 25 mg/kg b.w. per day (US EPA, 1986). The test substance was more toxic to the fetuses than to the dams. A dose-dependent reduction of fetal body weight was observed at the two highest dose levels. At 25 mg/kg per day the number of early and late resorptions, delayed skeletal ossification, and induced fetal malformations such as enlarged heart and rear limb malformations, was increased. Teratogenicity of **Saytex 111** was also studied in New Zealand white rabbits by Breslin et al. (1989). The rabbits were administered the test substance by gavage at 0, 2, 5, or 15 mg/kg b.w. per day. Maternal toxicity was exerted as a decrease in body weight of dams that was statistically significant at 15 mg/kg b.w. per day (93 % of control weight) and an increase in the absolute relative liver weight at this dose level. Signs of fetal toxicity were slight (nonsignificant) decreases in fetal body weights (≥ 5 mg/kg), delayed ossification (≥ 2 mg/kg), fetal variants included increased incidences of retrocaval ureter and fused sternebrae (≥ 5 mg/kg).

A teratogenicity study with a commercial **PentaBDE** preparation was carried out in rats that were exposed by gavage at 0, 10, 100, or 200 mg/kg per day (IPCS, 1994). Maternal body weight gain was decreased at 100 and 200 mg/kg per day, and a slight (non significant) reduction of fetal body weight was observed at 200 mg/kg per day.

These reproduction and developmental toxicity studies showed that in general fetuses are more sensitive to PBDEs than mothers. Although it is known that maternal toxicity can influence fetal ossification (Khera, 1983), the fetal effects seem to appear at lower doses than those indicative of maternal toxicity.

8.3.3. Biochemical effects and molecular mechanisms

In this chapter, studies on modes of action underlying the mechanisms of toxicity of PBDEs are summarized. The majority of mechanistic studies have been focused on prevalently occurring PBDEs (congeners BDE-47, -99, -100 prevalent in PentaBDE mixtures, hepta-brominated BDE-183 in OctaBDE mixtures, BDE-209 in DecaBDE mixtures, and BDE-153 occurring in lower concentrations but highly persistent) and PBDE metabolites (6-OH-BDE-47).

AhR-dependent ("dioxin-like") activity

Several PBDEs have been reported to be AhR agonists in DR-CALUX assay using rat hepatoma H4IIE cell line stably transfected with luciferase reporter gene (Hamers et al., 2006). BDE-153 was the most potent PBDE under study with EC_{50} at 0.6 μM; estimated EC_{50} for 6-OH-BDE-47 was 1.3 μM. Interestingly, partial antagonistic activities were found at micromolar concentrations of PBDEs as well. Another *in vitro* study showed no significant AhR-dependent induction of CYP1A1 activity in human breast cancer MCF-7 cell line, human hepatocarcinoma HepG2 cells and rat hepatoma H4IIE cells (Peters et al., 2004). The same group confirmed antagonistic activities of PBDEs against AhR-dependent gene expression (Peters et al., 2004, 2006).

Chen et al. (2001) reported relatively strong potencies of BDE-77 and -126 to bind to AhR and to induce AhR-dependent EROD activity in various *in vitro* models including hepatoma and colon cells. Environmentally occuring PBDEs BDE-100, -153 and -183 were only partial agonists with EC_{50} values < 10 μM. BDE-47 and -99 were inactive in the assay. Toxicity equivalency factors (TEF approach) showed that toxic equivalents of individual PBDEs were 3-4 orders of magnitude less than toxic equivalents of PCDD/PCDFs and PCBs (Chen and Bunce, 2003). However, recent studies with purified PBDEs showed that some weak dioxin-like activity might be due to presence of trace concentrations of brominated furans in both standard chemicals and commercial PBDE mixtures (Sanders et al., 2005; Wahl et al., 2008).

Activation of CAR and PXR receptors

Transcription factors CAR and PXR play key roles in regulation of the enzymes of oxidative metabolism of xenobiotics and endogenous lipophilic compounds including steroid hormones. PBDEs have been reported, similar to non-dioxin-like PCBs, as inducer of CAR- and PXR-mediated gene expression *in vitro* (Pacyniak et al., 2007; Wahl et al., 2008; Fery et al., 2009) as well as *in vivo* (Sanders et al., 2005; Fery et al., 2009; Szabo et al., 2009). BDE-47, -99 and -209 induced PXR-dependent gene expression in mice. On the other hand, no induction of AhR-dependent gene expression was reported (Pacyniak et al., 2007). Importantly, reporter gene assays, using either murine PXR (mPXR) or human PXR (called steroid X receptor, SXR) transfected into HepG2 cells, revealed only a partial induction of mPXR-dependent gene expression in comparison to significant SXR activation after at 10 μM exposure to BDE-47 or -99. BDE-209 showed only weak induction potencies (Pacyniak et al., 2007). In another study, a PentaBDE mixture was also significantly more potent inducer of CAR/PXR-dependent CYP3A4 enzyme in human HepG2 cells and luciferase activity in a reporter assay, compared to only weak induction in both rat hepatocytes and luciferase-transfected rat hepatoma H4IIE cells (Fery et al., 2009). These findings suggest higher sensitivity and toxicological importance of activation of PXR in humans than in rodents.

Wahl et al. (2008) found induction of biotransformation enzymes such as CYP2B and CYP3A involved in metabolism of steroids and thyroid hormones in primary rat hepatocytes exposed to BDE-47. Similarly, purified BDE-47, -99 and -153, but not BDE-209, induced CYP2B1 and CYP3A1/3 mRNA in primary rat hepatocytes (Wahl et al., 2010). Moreover, activation of biotransformation enzymes was found also in liver of rats exposed to BDE-47 (Suvorov and Takser, 2010) and to commercial pentaBDE mixture DE-71 (Szabo et al., 2009). Szabo et al. (2009) reported increased expression of Phase II and Phase III enzymes and transporters, and decreased serum T4, transthyretin and deiodinase 1. These findings provide a direct link between CAR/PXR activation and

decreased levels of circulating E2, testosterone and T4 reported in a series of *in vivo* studies (van den Ven et al., 2008a,b; Richardson et al., 2008; Szabo et al., 2009). Therefore, PXR activation, especially in humans, may be the critical mode of action of PBDEs.

Induction of hepatic uptake transporters (organic anion-transporting polypeptides) and their differential substrate specificity against individual PBDE congeners might affect half-lives and toxic potencies (Szabo et al., 2009). The greater abundance of BDE-47 in human liver samples compared to that of BDE-99 can be attributed to a greater uptake efficiency as well as lower rate of metabolism (Pacyniak et al., 2010).

Recently there is some evidence that PBDEs can affect growth. Ceccatelli et al. (2006) found up-regulation of insulin-like growth factor-1 (IGF-1) in Long-Evans rats exposed to BDE-99. Recently, increased plasma IGF-1, glucose uptake and body weight were reported in Wistar rats exposed to BDE-47 (Suvorov et al., 2009). Activation of metabolic pathways, including metabolism of lipids and carbohydrates, has been reported in the global gene expression study (Suvorov and Takser, 2010). The implications of these limited findings for human health are unknown at present, however disrupted metabolic pathways may represent novel targets and processes affected by PBDEs.

Neurotoxicity

Most of data have been developed in studies in experimental animals or in model *in vitro* systems. However, these studies may provide support for effects and modes of action in humans. Major reported neurotoxic effects are summarized in Table 39. Several studies in mostly neuronal or astroglial cell lines have been performed to characterize PBDE-induced neurotoxicity. Non-cytotoxic concentrations of BDE-47 seem to interfere with migration of human neuronal progenitor cells and neural differentiation (Schreiber et al., 2010), while at higher concentrations a decrease in number of cells in neuronal cells and tissue occur via induction of apoptosis. Micromolar concentrations of BDE-47 induce apoptosis in neuroblastoma cell line SHSY5Y (He et al., 2009b). These findings are supported by results obtained from primary hippocampal neurons isolated from 18-day old Sprague-Dawley rats (He et al., 2008a). Further, BDE-47 interferes with the expression of cytochrome c, caspase 12 and procaspase 3, which might indicate that BDE-47 alters the apoptotic machinery in neuronal cell lines (He et al., 2009b). BDE-47 induced oxidative stress in hippocampal neurons in parallel to a reduced expression level of antioxidative proteins and enzymes (GSH, SOD, GSH-Px), which might lead to induction of apoptosis (He et al., 2008a). In addition, alterations in calcium homeostasis were observed in mitochondria prepared from rat brain (Coburn et al., 2008) and SHSY5Y cells (He et al., 2009b).

BDE-99 was shown to induce similar effects. Cytotoxicity as measured by MTT reduction was detected in the neuroblastoma cell line SK-N-MC (Tagliaferri et al., 2010) and the human astrocytoma cell line (132-1N1) (Madia et al., 2004). In addition, alterations in neural migration/differentiation of human neural progenitor cells (Schreiber et al., 2010) and modulations of calcium uptake determined in rat mitochondria (Coburn et al., 2008) have been reported. Large-scale proteomic analyses with non-toxic and cytotoxic concentrations showed that BDE-99 alters the expression of cytoskeletal proteins already at low concentrations in cerebellar cortical cells isolated from rat fetuses on GD21 (Sprague-Dawley rats). Since the effects occurred already 1 hour after the exposure, BDE-99 might induce non-cytotoxic, post-translational modifications affecting cytoskeletal organisation (Alm et al., 2010). A recent study has shown a single administration of BDE-99 in adult rats induced a decrease in the antioxidant enzymes (Bellés et al., 2010). DE-71 is reported to induce apoptosis in several primary neural cells such as cerebellar granule cells isolated from rats (Reistad et al., 2006) and mice, hippocampal and cortical neurons and hippocampal astrocytes (Giordano et al., 2009). Additionally, effects of PBDEs on neurotransmitter systems have been reported (Mariussen and Fonnum, 2003). The pentaBDE mixture DE-71 inhibited uptake of dopamine in rat brain synaptic vesicles *in vitro* at low concentrations (IC_{50}; 3-8 μM), while highly brominated OctaBDE and DecaBDE mixtures had no effect on plasma membrane uptake of dopamine, glutamate and GABA. DE-71 reduced dopamine

concentrations in synaptosomes, which was suggested to be mediated through inhibition of dopamine transporters (Dreiem et al., 2010).

The mechanism of BDE-209-induced neurotoxicity was investigated in primary cultures of neonatal rat hippocamal neurons. In this model system, BDE-209 (approximately 10 μM was the lowest concentration used in the study) caused an increase in p38 expression, calcium concentrations and reactive oxygen species, which was associated with increased apoptosis. In addition, malondialdehyde content, a marker of lipid peroxidation, was increased and a decrease in superoxide dismutase activity and global gene DNA methylation was observed (Chen et al., 2010). BDE-100, -153 and -209 caused suppression of thyroid hormone receptor-mediated gene transcription, and a decrease in T4-dependent dendrite arborization and synaptogenesis of Purkinje cells (concentrations range 10^{-11} to 10^{-9} M). BDE-47 and -99 had no effect (concentration range 10^{-9} to 10^{-7} M) (Ibhazehiebo et al., 2010). BDE-209 was found to inhibit differentiation of rat neural stem cells into neurons and neurite outgrowth (Zhang et al., 2010).

A comparative study with BDE-47, -99, -100, -153 and -209 performed in cerebellar granule cells isolated from 7-day old mice supports the hypothesis that PBDE elicit oxidative stress that may be associated to apoptosis. The rank order of toxic potential was the same as that for the intracellular accumulation rate of the different PBDE congeners (BDE-100 > -47 > -99 > -153 >> 209) (Huang et al., 2010b), in contrast to the report of Ibhazehiebo et al. (2010).

The available *in vitro* studies suggest that the majority of PBDE congeners, with exception of BDE-209, share similar mechanisms of neurotoxicity including (i) induction of oxidative stress, reduction of the antioxidant capacity, mitochondrial alterations, and apoptosis; (ii) interference with calcium homeostasis, and (iii) effects on neurotransmitter systems. Recent data indicate that non-cytotoxic PBDE concentrations can interfere with neural migration, differentiation and cytoskeleton organisation in neural precursor cells in culture.

Table 39: Mechanistic studies of PBDE neurotoxicity.

Congener	*In vitro* model	Exposure level	Effect: LOEL	Purity	Reference
BDE-47	Human neuroblastoma cell line SK-N-MC	0.1 – 100µM; 24 hrs	Cytotoxicity MTT: 5µM		Tagliaferri et al., 2010
BDE-47	Sprague-Dawley rats. Hippocampus from 2 month old rats.	1; 5; 10 mg/kg oral on PND10	Alterations in CA1 (affected neuronal structures: endoplasmatic reticulum, mitochondria, periplast, cytoplasm): 5-10 mg/kg mRNA expression changes: • x-chromosome linked inhibition of apoptosis (XIAP): ♀:1 mg/kg; ♂:10 mg/kg • death associated protein kinase (DAPK): 10 mg/kg • caspase 12: 5 mg/kg • caspase 3: 5 mg/kg • cytochrome C: ♂:10 mg/kg Protein expression: • XIAP: 1 mg/kg • cytochrome C: ♀:5 mg/kg; ♂:1 mg/kg • caspase 12: 5 mg/kg • procaspase 3: 1 mg/kg	100 %	He et al., 2009a
BDE-47	SHSY5Y	1; 5; 10µmol/L	Cytotoxicity (MTT): 5 µmol/L Intracellular Ca^{2+}: increase at 1 µmol/l Apoptosis:1 µmol/L (2 %); 5 µmol/L (3 %); 10 µmol/L (10 %) mRNA level: • DAPK:1 µmol/L • caspase 3: 1 µmol/l • caspase 12: 10 µmol/L • cytochrome C: 10 µmol/L Protein expression level: • cytochrome C: 10 µmol/L • caspase 12: 1 µmol/L • procaspase 3: 1µmol/L	100 %	He et al., 2009b

Table 39: Continued.

Congener	*In vitro* model	Exposure level	Effect: LOEL	Purity	Reference
BDE-47	Mitochondria and microsomes prepared from rat brain (frontal cortex; cerebellum, hippocampus, hypothalamus)	3; 10, 30µM	Inhibition of Ca^{2+} uptake microsomes:10-30 µM mitochondria: 10 µM	-	Coburn et al., 2008
BDE-47	Primary human neurospheres	0.1; 1; 10µM	Migration: 1µM Neural differentiation: Reduction in • Tuj1 positive cells: 1 µM • O4 positive cells: 1µM • nestin mRNA expression: 10 µM	-	Schreiber et al., 2009
BDE-47		6.8 mg/kg at PND10	• reduction of hippocampus long-term potentiation and post-tetanic potentiation (analysis PND17-19) • decreased expression of postsynaptic proteins NR2B, GluR1, CAMKII • alterations in Ca^{2+} signalling: PC12 cells exposed to 20 µM BDE-47	99 %	Dingemans et al., 2007
BDE-47 + BDE-99	Human neuroblastoma cell line SK-N-MC	BDE-47 1µM + BDE-99 5µM, 3hrs	ROS formation: BDE-47 1 µM + BDE-99 5 µM	-	Tagliaferri et al., 2010
BDE-99	Human astrocytoma cells 132-1N1	1; 10; 25; 50; 100µM	Cytotoxicity MTT: 25µM PKC translocation:100 µM Apoptosis: 50 µM p53 expression: 50 µM	-	Madia et al., 2004
BDE-99	Human neuroblastoma cell line SK-N-MC	0.1 – 100µM; for 24 hrs	Cytotoxicity MTT: 10 µM	-	Tagliaferri et al., 2010
BDE-99	Mitochondria and microsomes prepared from rat brain (frontal cortex; cerebellum, hippocampus, hypothalamus)	3; 10, 30µM	Inhibition of Ca^{2+} uptake microsomes:3-30 µM mitochondria: 10-30 µM	-	Coburn et al., 2008

Table 39: Continued.

Congener	*In vitro* model	Exposure level	Effect: LOEL	Purity	Reference
BDE-99	Primary human neurospheres	0.1; 1; 10 µM	Migration: 1 µM Neural Differentiation: Reduction in • Tuj1 positive cells: 0.1 µM • O4 positive cells: 1 µM Migration: 1 µM Differentiation: Reduction in • Tuj1 positive cells: 1 µM • O4 positive cells: 1 µM • nestin mRNA expression: 10 µM	-	Schreiber et al., 2009
BDE-99	Adult Sprague-Dawley rats. hippocampus and cerebellum.	0.6 and 1.2 mg/kg b.w. oral	• Lower antioxidant enzyme activity in cortex.	-	Bellés et al., 2010
BDE-99	Hippocampus, Striatum dissected 24 h after the exposure (proteomics study)	12 mg/kg PND10	Alterations in protein expression: • increase in GAP43 • decrease in stathmin • increase in synuclein	-	Alm et al., 2006
BDE-153	Hippocampus (time point after exposure?)	0.45, 0.9 and 9 mg/kg b.w.at PND10	Decreased amount of cholinergic receptors: 9 mg/kg	92.5 % hexa-PBD 7.5 % hepta-BDE	Viberg et al., 2003b
BDE-209	Hippocampus; analyses were performed at PND10	20.1 mg/kg at PND3	Alterations in the expression of CAMKII (increased in hippocampus), BDNF (dereased in hippocampus), GAP43 (increased in hippocampus; decreased in cortex)	98 %	Viberg et al., 2008
BDE-209	Primary neonatal hippocampal neurons (GD19-21 Sprague-Dawley rats)	10, 30 and 50 µg/ml for 24 h	• induction of apoptosis (AnnexinV/PI staining) with a LOEL of 10 µg/mL • induced p38 MAPK expression (protein level) with a LOEL of 10 µg/mL • increase in ROS and NO levels with a LOEL of 10 µg/mL • increased calcium ion content with a LOEL of 10 µg/mL • increased expression of malondialdehyd (MDA) with a LOEL of 30 µg/mL • decreased SOD activity with a LOEL of 10 µg/mL • decrease in global DNA methylation with a LOEL of 10 µg/mL • induction of cytotoxicity (MTT) with a LOEL of 10 µg/mL	-	Chen et al., 2010

Table 39: Continued.

Congener	*In vitro* model	Exposure level	Effect: LOEL	Purity	Reference
BDE-209	Brain samples from 10 week old CD1 Swiss mice. Analyses performed 20, 40 or 60 days after exposure.	Chronic toxicity: 0.1, 40, 80, 160 mg/kg b.w. per day by gavage for 15, 30 or 60 days	• Increased activity of acetylcholinesterase with a LOEL of 80 mg/kg b.w. per day after 15 days of exposure • decreased SOD activity with a LOEL of 40 mg/kg b.w. per day after 15, 30 and 60 days of exposure • induction of MDA activity with a LOEL of 40 mg/kg b.w. per day for 15, 30 and 60 days of exposure. The reported alterations seemed to be permanent since were observed at all times points analysed after exposure.		Liang et al., 2010
BDE-209	Hippocampal neural stem cells from neonatal Sprague-Dawley rats	0.01, 0.03 and 0.05 mM. Exposure: 7 days.	• MTT assay: decreased viability of neural stem cells. • Suppression of neurite outgrowth • Suppression of the differentiation of neural stem cells into neurons in a concentration dependent manner. • Enhanced differentiation of neural stem cells into glial cells.	-	Zhang et al., 2010
DE-71	Cerebellar granule cells from rat PND7.	2, 5, 10 and 20 µM	Cytotoxicity (Trypan blue exclusion): 10 µM Apoptosis (Hoechst staining, DNA fragmentation): 5 µM		Reistad et al., 2006
DE-71	• Cerebellar granule cells (PND7) • mouse hippocampal neurons (PND0.5) • mouse cerebral cortical neurons (PND0.5) • mouse astrocytes from hippocampus (PND0.5) • mouse cerebral cortex (PND7)	1 – 50 µM	Cytotoxicty (MTT): IC_{50}: • CGN 7.7±2.3 µM • Hippocampal neurons: 2.2±1.7 µM • cerebral cortical neurons:11.5±0.9 µM • astrocytes from hippocampus: 52.3±3.4 µM • astrocytes from cerebral cortex: 61.3±4.8 µM • astrocytes from cerebellum: 39.6±1.8 µM Apoptosis (Hoechst staining): IC_{50}: • CGN 11.2±1.5 µM • Hippocampal neurons: 2.3±0.8 µM • cerebral cortical neurons:47.8±1.8 µM • astrocytes from hippocampus: 89.1±3.8 µM • astrocytes from cerebral cortex: 86.2±2.0 µM • astrocytes from cerebellum: 118.6±3.5 µM	44 % BDE-99, 32 % BDE-47, 9 % BDE-100, 4 % BDE-153, 11 % other BDE; No chemical analysis to exclude contamination with PBDF or PBDD performed	Giordano et al., 2009
DE-71	Striatal synaptosomes from Long-Evans rat pups (PND7, PND14 and PND21)	10, 20 and 40 µM	• Reduction of dopamine concentrations in synaptosomes from PND7 and PND14 (20 and 40 µM). • No alteration in total (sum of medium and synaptosomes) 3,4-dihydroxyphenylacetic acid (DOPAC) concentration.		Dreiem et al., 2010

Table 39: Continued.

Congener	*In vitro* model	Exposure level	Effect: LOEL	Purity	Reference
DE-71 DE-79 (OctaBDE) DE-83R (DecaBDE)	Wistar rat brain synaptosomes and synaptic vesicles	2, 5, 10 amd 20 µM	• Inhibition of vesicular uptake of dopamine (IC_{50}: 8 µM) • No effect on dopamine uptake • No effect on dopamine uptake	- - -	Mariussen and Fonnum, 2003
BDE-28, -47, -66, -85, -99, -100, -153, -154, -175, -183, -209, DE-71; OH-BDE-47, -49, -68	• CV-1 cell line (monkey fibroblast-derived) • Cerebellar Purkinje cells (PND0)	10fM-1µM	Suppression of TR-mediated transcription (CV-1): BDE-100 1nM, BDE -209 10pM Dissociation of TR from TRE (CV-1): BDE-209 1nM T4-dependent arborisation of cerebellar Purkinje cells: BDE-209 0.1nM (only partially rescued by increasing T4 concentration)	PBDEs >99 % OH-PBDE >98 % DE-71: BDE-99 44 % BDE-47 32 % BDE-100 9 % BDE-153 4 % other 11 %	Ibhazehiebo et al., 2010

MTT: 3-(4,5-Dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide; PND: post-natal day; XlAP: x-chromosome linked inhibitor of apoptosis; DAPK: death-associated protein kinase; LDH: lactic dehydrogenase; GSH: glutathione; GSH-Px: glutathione peroxidase; SOD: superoxide dismutase; MDA: malondialdehyde; ROS: reactive oxidative species; PKC: protein kinase C; PI: propidium iodide; DOPAC: dihydroxyphenylacetic acid; CGN: cerebellar granule neuron; TR: thyroid hormone receptor; TRE: thyroid hormone receptor response.

Disruption of thyroid hormone signalling

Disruption of thyroid hormone signalling appears to be one of most important modes of action of PBDEs due to a direct association with developmental processes. PBDEs may affect thyroid hormone signaling at three different levels: 1) by binding to thyroid hormone transport proteins, 2) by activation of thyroid hormone metabolizing enzymes which results in alterations in thyroid hormone concentrations; 3) by affecting transcription activation of thyroid hormone receptors (TR). Meerts et al. (2000) reported a very potent competition binding for various BFRs (even stronger than natural ligand T4) in TTR binding assay. However, PBDEs, including BDE-47, have been reported to be effective only at high micromolar concentrations and to compete with T4 more efficiently after metabolic activation. In a subsequent study, 6-OH-BDE-47 has been found to be the most potent of PBDEs and PBDE metabolites, with IC_{50} value of 180 nM (Hamers et al., 2006). Therefore, perturbations of the thyroid hormone transport to target cells and tissues appear to be one of the most sensitive mechanisms possibly leading to adverse effects of BDE-47 exposure. Other environmentally occurring PBDEs have shown low or negligible activity in these models.

While disruption of thyroid hormone transport is limited to BDE-47 and its metabolite(s), suppression of thyroid hormone concentration represents a major mode of action of PBDEs. The activation of CAR- or PXR- (also known as SXR-) dependent gene expression of monooxygenase and transferase biotransformation enzymes seems to be the key process involved.

The results of T-screen, a cell proliferation assay reflecting the activation of TR, have suggested that several environmentally less relevant PBDEs, e.g. BDE-127 and -185, may elicit only weak agonistic activities towards TR (Hamers et al., 2006). Recently, weak antagonistic effects of hydroxylated PBDEs (and not parent PBDEs) on TRα- and TRβ-dependent gene expression in transgenic Chinese hamster ovary (CHO) cells have been reported (Kojima et al., 2009; Li et al., 2010). However, in another model (in CV-1 monkey fibroblast-derived cells co-transfected with expression vectors for TRβ1 (or TRα1) and luciferase reporter constructs containing direct repeats of thyroid response elements), BDE-209, -100, -153 and -154 at pico- or nanomolar concentrations have been shown to suppress TRβ-mediated gene expression (Ibhazehiebo et al., 2010). This effect was not observed with BDE-47, as also found by Suvorov et al. (2010). Therefore, suppression of TR-dependent gene expression by BDE-209, -100, -153 and -154, which might be associated with interference of thyroid hormone-induced neurodevelopment, could be considered as another relevant mode of action.

Estrogenicity/antiestrogenicity of PBDEs

The estrogenic effects of some PBDE congeners have been reported based on the estrogen receptor (ER)-dependent luciferase reporter gene expression assay. BDE-47, -100 and some other congeners had EC_{50} values at low micromolar concentrations and their relative potencies (related to 17β-estradiol) were about 10^{-6} (Meerts et al., 2001; Hamers et al., 2006). BDE-183 and several other higher brominated diphenyl ethers were antiestrogenic at micromolar concentrations. The most potent antiestrogenic compound was 6-OH-BDE-47, a major hydroxylated metabolite of BDE-47, with IC_{50} value 0.45 μM. However, BDE-99, -153 and -209 did not modulate ER-dependent gene expression (Hamers et al., 2006). These findings were partly confirmed in another model system, using CHO cells transfected with expression plasmids encoding full-length human estrogen receptor alpha (ERα) or beta (ERβ) proteins and a luciferase reporter plasmid. BDE-99, -100 and -153 did not induce ER, but they were weakly antiestrogenic at concentrations 3^{-10} μM in the models containing either ERα or ERβ (Kojima et al., 2009). Up-regulation of ERα, ERβ and increased ovarian weight have been reported in Long-Evans rats exposed to BDE-99 (Ceccatelli et al., 2006).

Besides the ER-mediated activity, other mechanisms exist that may affect the endocrine system, including modulations of steroidogenesis and induction of drug-metabolizing enzymes leading to changes in serum steroid hormones. Major metabolites 6-OH-BDE-47 and 6-OH-BDE-99 inhibited aromatase (CYP19) activity, a key enzyme of biosynthesis of estrogens, at concentrations > 2.5 and

5 μM, respectively in H295R human adrenocortical carcinoma cells (Cantón et al., 2005; 2008). Strong inhibition of CYP17, another enzyme of steroidogenesis, by 6-OH- and 6-methoxy-BDE-47 at 1 μM concentration has been reported as well (Cantón et al., 2006). 6-OH-BDE-47 effectively suppressed expression of other steroidogenic genes such as CYP11B and StAR in the H295R cells at the concentration 0.025 μM (Song et al., 2009). PBDEs could modulate also metabolism (inactivation) of steroid as well as thyroid hormones via induction of CAR/PXR-mediated gene expression of biotransformation enzymes including CYP and transferase enzymes (Pacyniak et al., 2007; Fery et al., 2009; Suvorov and Takser, 2010). On the other hand, IC_{50}s for inhibition of estradiol sulfatation (the effect leading to higher natural estrogen concentrations) were 0.8 and 1.4 μM for BDE-47 and 6-OH-BDE-47, respectively (Hamers et al., 2006). The antiestrogenicity of lower concentrations of BDE-47 could be related to ER-inhibiting potency of the major hydroxylated metabolite 6-OH-BDE-47 (Hamers et al., 2006) and induction of drug and steroid-metabolizing enzymes (Suvorov and Takser, (2010). Similarly, based on both *in vitro* and *in vivo* findings, it can be concluded that increased oxidative metabolism of steroids may be at least partly responsible for antiestrogenic action of BDE-99, -100, -209 and probably also BDE-153.

Antagonistic activities of PBDEs on AR-, PR- and GR-dependent gene expression

The AR-antagonistic effects have been determined in the AR-CALUX bioassay (Hamers et al., 2006). The reported IC_{50} values were from nanomolar to micromolar concentrations with BDE-19 and -100 being the most potent congeners (IC_{50} values: 0.06 and 0.1 μM, respectively). The IC_{50} values for BDE-47, 6-OH-BDE-47, BDE-99 and -153 were 1.0, 2.8, 7.8 and 13 μM, respectively. Kojima et al. (2009) reported antiandrogenic effects of PBDEs in the human AR transactivation assay using CHO cells. The most potent AR antagonists were BDE-100 followed by BDE-47 and -99.

PBDEs were antagonistic but less potent in the PR-CALUX assay. BDE-100 and 6-OH-BDE-47 had IC_{50}s of 3.4 μM and 5.0 μM, respectively (Hamers et al., 2006). Similarly, only weak antagonistic effects of PBDEs on glucocorticoid receptor-mediated gene expression were found in CHO transgenic cells (Kojima et al., 2009).

Comparison of in vitro toxic potencies of PBDEs

PBDEs seem to operate through multiple modes of action. The results of the toxic mechanism-oriented studies, using *in vitro* models, are in good agreement with the data coming from the experimental *in vivo* studies. However, quantitative relative toxic potencies cannot be calculated from the majority of the available studies.

PBDEs have not been reported to elicit direct genotoxic effects *in vitro*. Nevertheless, the oxidative stress generated may lead to DNA damage as well as to activation of apoptosis in various cellular systems. The effects associated with neurotoxicity and neurodevelopmental toxicity of PBDEs including induction of oxidative stress, perturbation of calcium homeostasis and activation of apoptosis have been reported (at concentrations 10-40 μM). The lower, noncytotoxic concentrations (0.1- 10 μM) of BDE-47 and -99 may disturb migration and differentiation of neural cells (Schreiber et al., 2010). Significant decrease in differentiation of normal human neural progenitor cells occurred at 0.1 and 1.0 μM for BDE-99 and -47, respectively. Inhibition of migration in the same cellular model was seen at 1 μM concentration for both BDE-47 and -99 (Schreiber et al., 2010). Intracellular calcium release and apoptosis induction was observed after the exposure to 1 or 5 μM BDE-47 in human neuroblastoma SH-SY5Y cells as well as oxidative DNA damage at 10 μM BDE-47 (He et al., 2008b; Gao et al., 2009). Moreover, suppression of TR-mediated gene expression has been reported even after nanomolar exposure to BDE-100, -153, -154 and -209; PBDEs inhibited also dendrite arborization (differentiation process) in Purkinje cells (Ibhazehiebo et al., 2010). Due to a high accumulation of PBDEs in neural cells and relatively strong *in vitro* toxic potencies, neurodevelopmental and neurotoxic effects might be taken in account in hazard characterization of PBDEs. Disruption of the hormone receptor-mediated gene expression or hormonal transport and metabolism (of note are

especially the effects on thyroid hormone signalling) may affect normal endocrine functions, which can in turn lead to reproductive and neurodevelopmental defects. To this time the following endocrine disrupting events have been reported as possibly the most sensitive endpoints (Hamers et al., 2006): antiandrogenic activity of BDE-100 and -47 with IC_{50}=0.1 and 1.0 μM (according to Kojima et al. (2009) also BDE-47, -99 and some metabolites are bioactive at nanomolar concentrations), inhibition of estradiol sulfatation (BDE-47, IC_{50}=0.8 μM), TTR binding and antiestrogenic activity of 6-OH-BDE-47 with IC_{50} values 0.18 and 0.45 μM, respectively. The ER-mediated activity, anti-PR-, AhR- and anti-AhR activities were reported only at micromolar concentrations, suggesting only a minor significance of these processes. On the other hand, CAR and PXR activation by PBDEs may lead to induction of biotransformation enzymes and increase in metabolism of steroids and thyroid hormones (Pacyniak et al., 2007; Wahl et al., 2008; Richardson et al., 2008; Szabo et al., 2009). Induction of oxidative metabolism of steroids may substantially contribute to antiestrogenic and antiandrogenic action of PBDEs and their interference with thyroid hormone signalling.

In another study, dihydroxy-BDE-47, 2,4-dibromophenol, dihydroxylated BDE-99 and 2,4,5-tribromophenol have been reported as major metabolites of BDE-47 and BDE-99, respectively, in human liver microsomes (Lupton et al., 2009). Importantly, Kojima et al. (2009) found potent antiandrogenic activities of hydroxy- and methoxy-metabolites of PBDEs at nanomolar concentrations, suggesting the involvement of these metabolites in reported toxic modes of action of PBDEs. Oxidative biotransformation of BDE-47 enhanced significantly its toxic modes of action and 6-OH-BDE-47 represents one of the most potent disruptors of thyroid hormone signaling and ER-mediated gene expression (Hamers et al., 2008). 6-OH-BDE-47 and not BDE-47 was a partial agonist of the GABA receptor and an antagonist of the nicotinic acetylcholine receptor (Hendriks et al., 2010). Competitive displacement of thyroid hormones from transport proteins (thyroxin-binding globulin and transthyretin) has been reported for a series of hydroxylated PBDEs (including 6-OH-BDE-47) at nanomolar concentrations (Cao et al., 2010).

8.4. Observations in humans

8.4.1. Effects on thyroid hormone disruption

Hyperthyroidism is characterised by higher serum levels of free T4 and T3 and lower levels of TSH. Subclinical thyrotoxicosis is defined as clinical euthyroidism in the context of normal serum T4 and T3 levels, with TSH levels lower than normal. Patients usually are euthyroid without the specific signs or symptoms associated with overt hyperthyroidism but this condition may induce abnormalities in several organs, including the heart and bones.

Subclinical (or mild) hypothyroidism is a syndrome defined by presence of an elevated serum TSH in the setting of normal thyroid hormone levels, in the absence or presence of non-specific symptoms.

Epidemiologic data on the effects of PBDEs on thyroid hormones in adults are summarized in Table E1 **(**Appendix E). Most of the studies suggest an association between PBDEs and/or single congeners with clinical or suclinical hyperthyroidism.

In a study performed by Gascón et al. (2011), a prospective birth cohort in Menorca (Spain) enrolling 482 pregnant mothers between 1997 and 1998, the association between pre- and postnatal PBDE exposure and thyroid hormones levels in children at age 4 years was examined. PBDE concentrations were measured in cord blood (N=88) and in serum of 4 years olds (N=244). Among all congeners analyzed (BDE-12/13, -17, -32, -28/33, -47, -66, -71, -85, -99, -100, -116, -119, -126, -138, -153, -154,-155, -183 and -190) only BDE-47 was quantified in a reasonable number of samples (LOQ=0.002 ng/mL). Exposure to BDE-47 was analyzed as a dichotomous variable: concentrations above the LOQ (exposed) and concentrations below (referents). Levels of TSH, total T3 and free T4 were not associated with PBDE exposure.

In a study performed by Abdelouahab et al. (2011) in Canada, fifty men were recruited in a fertility clinic. Serum thyroid hormones and the concentration of BDE-47, -99, -100 and -153 were measured. In a multiple regression analysis, T4 levels were negatively associated with serum BDE-47 ($p < 0.05$), BDE-99 ($p < 0.05$), sum of PBDEs ($p < 0.05$), controlling for age and other covariates. No relations were observed between T3, TSH and any of the chemicals measured.

Chevrier et al. (2010) presented a study to determine whether PBDE serum concentrations (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154 and -183) are associated with thyroid hormone levels (free T4 (ng/dL), total T4 (ng/dL), log10-TSH (mIU/L)) in pregnant women. They reported a negative association between the sum of PBDEs and BDE-28, -47, -99, -100 and -153, and TSH serum concentrations in pregnant women around the 27th week of gestation, whereas no association was found between PBDEs and free and total T4.

Wang et al. (2010) suggested that people having worked on an electronic waste recycling and dismantling plant had significantly lower TSH compared to the control group ($p<0.01$). A total of 6 PBDE congeners were analysed (BDE-77, -85, -126, -205, -203 and -209). A positive relation was found between the levels of BDE-126 and T4.

Dallaire et al. (2009) investigated the relationship between exposure to several polyhalogenated compounds (PHCs) and thyroid hormone homeostasis in Inuit adults from Nunavik. Plasma concentrations of BDE-47 were moderately correlated with BDE-153 levels ($r = 0.36$; $p < 0.001$). Although exposure to PBDEs in Inuit men and women is lower than levels reported in other North American populations, this study found a positive association of total T3 with BDE-47 but no association with BDE-153. The association between total T3 and BDE-47 weakened after controlling for fish consumption.

In a study aiming to investigate the influence of prenatal exposure to organohalogen compounds (OHCs), including BFRs, on motor, cognitive and behavioural outcome in healthy children of school age (Roze et al., 2009, see description of study in Table E2). BDE-47 correlated with higher concentrations of T3 ($r=0.322$, $p=0.021$) as did BDE-99 ($r=0.311$, $p=0.031$) and BDE-100 ($r=0.291$, $p=0.038$).

The results of Turyk et al. (2008), where four PBDE congeners were analysed (BDE-47, -99, -100 and -153) as well as PCBs, are consistent with the decreased TSH in Hagmar et al. (2001) study and with the positive direction of the free T4 associations of Meeker et al. (2009), Bloom et al. (2008) and Julander et al. (2005).

Free T4 and TSH were not significantly associated with PBDEs in 36 New York anglers, although the associations of PBDE congeners with free T4 were consistently positive (Bloom et al., 2008). The authors estimated that 318 persons (a nine-fold increase in sample size) would have been required to reach significance for the association of PBDEs with free T4.

A longitudinal study of 11 electronic waste recycling employees found no significant associations of PBDE congeners (BDE-28, -47, -100, -99, -154, -153 and -183) with TSH, total T3, or free T4 (Julander et al., 2005), but did note non-significant trends for increasing free T4 with BDE-28, -153, and -183.

Hagmar et al. (2001) found a significant negative association of BDE-47 with TSH but no significant association with free and total T3 and T4 in 110 men with high consumption of fish from the Baltic Sea.

The findings of a positive association of PBDEs with T3, T4 and/or decreased TSH in the above discussed studies are not consistent with results of laboratory animal studies (see Chapter 8.3.2.1.) and with two other human studies, suggesting an association of PBDEs with subclinical hypothyroidism (Herbstman et al., 2008; Yuan et al., 2008). The study by Yuan et al. (2008) found higher TSH serum

levels in 23 highly exposed Chinese electronic waste workers (median of the sum of PBDEs, 382 ng/g fat) relative to 26 controls who also had elevated serum concentrations of the sum of PBDEs (median, 158 ng/g fat). In Herbstman et al. (2008), prenatal PBDE exposures (BDE-47, -100 and -153) were associated (mainly with no statistical significance) with reduced total T4 and free T4.

Another study by Mazdai et al. (2003) examined the association between serum PBDE levels and thyroid hormones concentrations in 9 women during pregnancy. No associations were found between the sum of PBDEs and free or total T4 in serum samples collected shortly before delivery.

In conclusion, the sample size was often not appropriate to study the exposure-human effects relationship, and the cross-sectional nature of some studies limits causal inference. In addition, the strong correlation among PBDE congeners hampered the ability to distinguish their independent association. Reverse causation, for instance, cannot be excluded because thyroid hormones regulate a number of metabolic pathways, including lipid metabolism and the activity of some cytochrome P450 enzymes (Takahashi et al., 2010; Yen, 2005), which may alter PBDE serum concentrations. In addition, the mechanism of action for reduced TSH has not been clearly established. Possibly because of their structural similarity with T4 and T3, hydroxylated PBDEs (OH-PBDEs) have been shown to bind to thyroid receptors α1 and β and may thus inhibit the release of TSH by the pituitary (Marsh et al., 1998). The possibility of reverse causation of cross-sectional surveys, could have been overcome if prospective longitudinal studies would have addressed the biologic pathways by which PBDEs affect thyroid hormones homeostasis.

8.4.2. Neurodevelopmental effects

The results of studies on the association between *in utero* exposure levels of PBDEs and possible developmental alterations have been summarized in Table E2 (Appendix E). A recent article also reviews the effects of BFRs on the developing nervous system (Dingemans et al., 2011).

In a study performed by Gascón et al. (2011) (see Chapter 8.4.1.) children of 4 years of age were assessed for motor and cognitive function (McCarthy Scales of Children's Abilities), attention-deficit, hyperactivity and impulsivity (ADHD-DSM-IV) and social competence (California Preschool Social Competence Scale). PBDE concentrations were measured in cord blood (N=88) and in serum of 4 years olds (N=244). Among all congeners analyzed only BDE-47 was quantified in a reasonable number of samples (LOQ=0.002 ng/mL). Exposure to BDE-47 was analyzed as a dichotomous variable: concentrations above the LOQ (exposed) and concentrations below (referents). Scores for cognitive and motor functions were always lower in children pre- and postnatally exposed to BDE-47 than in referents, but none of these associations was statistically significant. Postnatal exposure to PBDE 47 was statistically significantly related to an increased score on the attention deficit subscale of ADHD symptoms (RR (95 % CI)=1.8 (1.0, 3.2)), but not to hyperactivity symptoms. A statistically significant higher risk of poor social competence symptoms was observed as a consequence of postnatal BDE-47 exposure (RR (95 % CI)=2.6 (1.2, 5.9)). Adjustment for other organochlorine compounds did not influence the results.

A study was performed in a New York longitudinal cohort of 329 pregnant women (Herbstman et al., 2010). A subset of 152 children with cord PBDE measurements participated in the tests. There were 118, 117, 114, 104, and 96 children with available cord PBDE measurements assessed at 1, 2, 3, 4, and 6 years, respectively. Cord blood total mercury and lead concentrations were also measured to exclude the possibility that these covariates affected the relationship between PBDE concentrations and developmental indicators. On average, children with the higher prenatal concentrations of BDE-47, -99, and -100 scored lower than the rest of the population on nearly all neurodevelopmental indices at all time points (1-4 and 6 years). There are indications that children who had a higher cord blood concentration of BDE-47, -99 and -100 scored lower in some tests for mental and physical development.

A cohort study with 90 healthy pregnant women was performed in the Netherlands (Roze et al., 2009). Concentrations of PCP, CB-153, 4OH-CB-107, 4OH-CB-146, 4OH-CB-187, BDE-47, -99, 100, -153, -154, and HBCDD were measured in maternal blood from women at the 35th week of pregnancy. Sixty-two children were followed up and at 5-6 years of age their neuropsychological functioning was assessed: motor performance (coordination, fine motor skills), cognition (intelligence, visual perception, visuomotor integration, inhibitory control, verbal memory, and attention), and behaviour. Table 41 reports specific congener results. In summary, PBDEs correlated positively and negatively with neurodevelopmental outcome: worse fine manipulative abilities, worse attention, better coordination, better visual perception, and better behaviour according to international behavious scales, were found for the analysed compounds. The study could not attribute the effects to any specific class of compounds. Concentrations of PCBs were much higher than concentrations of PBDE congeners.

Summarising, in the three human studies described above, effects on neuropsychological functioning were associated with exposure to PBDEs, but these results were heterogeneous. Although one study controlled for PCBs, DDT, DDE and HCB, in general, exposure to other halogenated contaminants could have interfered with the outcome of these studies.

8.4.3. Cancer

There are limited epidemiological data on any association between exposure to PBDEs and the risk of cancer (Table E3, Appendix E).

Four studies from Sweden studied the association of serum or adipose tissue levels of single congeners and/or the sum of PBDEs with Non Hodgkin's lymphoma (NHL), testicular and pancreatic cancer. A non-statistically significant association between NHL and exposure to BDE-47 was found when lowest and highest concentration (ng/g fat) groups were compared. In Hardell et al. (2009), no association for BDE-47 and NHL was found. An interaction between Epstein-Barr virus (EBV) and pesticides in the aetiology of NHL had been shown in the study by Nordstrom et al. (2000). A statistically significant association was found between BDE-47 (medians both below and over 1.8 ng/g fat) and titres of EBV EA IgG over 40 for diffuse large B-cell NHL subtype. No statistically significant association was found for survival for pancreatic cancer (p=0.09) and no statistically significant association for risk of pancreatic cancer (OR 3.9 95 % CI 0.93-16.3) and tissue concentrations of ΣPBDE (Hardell et al., 2007).

In a case control study of testicular cancer no differences were found in serum concentrations of ΣPBDE in cases and controls (Hardell et al., 2006). There was an association between the elevated risk (OR 2.5 95 % CI: 1.02-6.0) for testicular cancer with blood levels of the sum of PBDEs in the 44 case mothers. The study has limitations including that current concentrations in mothers' blood do not necessarily reflect body burden about 30 years before, as being median age for the cases. Confounding by diet, other persistent halogenated compounds or other factors was not controlled for in this study.

McElroy et al. (2004) presented results of a population based case-control study of 1,481 breast cancers and 1,301 controls and recent consumption of sport-caught fish, a source of PBDEs among other organic contaminants. Exposure was assessed by telephone interviews. Overall, no association was found (OR: 1.0, CI 0.86-1.17) although there was an excess risk in pre-menopausal women (OR: 1.7 95 % CI 1.16-2.50).

In a study of PBDE levels in breast adipose tissue of 23 Californian women (11 breast cancer cases, 3 ductal carcinoma *in situ*, 7 controls) there was no correlation between disease status and total PBDE concentrations (She et al., 2002).

In 1989, an IARC Working Group (IARC, 1990) evaluated BDE-209 as having limited evidence for the carcinogenicity in experimental animals, with the statement of no data available from studies in

humans and an overall evaluation of BDE-209 as not classifiable as to its carcinogenicity to humans (Group 3).

Overall, there was no association between high fish consumption and breast cancer and levels of PBDEs in breast cancer tissues. No associations were found in case-control studies of testicular and pancreatic cancer. However, the small sample size, and confounding by other contaminants and/or lifestyle factors limit the interpretation of these studies.

8.4.4. Diabetes and metabolic syndrome

Associations of serum concentrations of chlorinated POPs with diabetes were shown in the National Health and Nutrition Examination Survey (NHANES, an ongoing survey designed to measure since 1999 the health and nutritional status of the civilian non-institutionalized U.S. population) (Lee et al., 2006; 2007a). The associations were much stronger in obese than in normal weight diabetic patients suggesting that as people get fatter, the retention of POPs related to the risk of diabetes may increase.

Although specific associations differed depending on chemicals (Lee et al., 2007b, 2008), POPs were associated with most components of metabolic syndrome. The metabolic syndrome is defined as a cluster of risk factors for atherosclerotic disease and type II diabetes mellitus comprising obesity, insulin resistance, hypertension and dyslipidemia. Overall, the conclusion of these authors was that pending confirmation in prospective studies, lipophilic xenobiotics, including brominated POPs stored in adipose tissue, may be involved in the pathogenesis of diabetes and metabolic syndrome, but that inference should be made cautiously in light of the multiple comparisons intrinsic in their investigations.

Two cross sectional studies (Table E4 in Appendix E) were designed in the NHANES and Great Lakes sport fish consumers cohort to specifically investigate if concentrations of PBDEs were associated with diabetes and/or metabolic syndrome.

A sample of 1,367 adults from NHANES was examined with respect to diabetes status (Lim et al., 2008). For metabolic syndrome, analyses were restricted to 637 participants with a morning fasting blood sample. Serum concentrations of BFRs were measured, including PBDEs (BDE-28, -47, -99, -100 and -153) and detected in ≥ 60 % of participants. Compared with subjects with serum concentrations below the LOD, prevalent diabetes had a dose-response association with serum concentrations of BDE-153. Adjusted odds ratios across quartiles of serum concentrations for BDE-153 were 1.0, 1.6, 2.6, 2.7, and 1.8 (P for quadratic term < 0.01). Corresponding figures for metabolic syndrome were 1.0, 2.1, 2.5, 2.4, 1.7 (P for quadratic term = 0.02). The authors conclude that BDE-153 was the only PBDE congener that had an association with diabetes and metabolic syndrome. However, the effects of other halogenated compounds were not controlled for.

In the Great Lakes sport fish consumers cohort (Turyk et al., 2009), there was no association of the sum of eight PBDEs, BDE-47 and -153, with diabetes prevalence in un-stratified analysis. No significant association between PBDEs and diabetes was found, neither in the whole study population of subjects, nor in the subgroup with (n=38) or without hypothyroid disease (n=465).

In summary, some studies link diabetes and metabolic syndrome prevalences to serum concentrations of POPs. The above discussed cross-sectional study by Lim et al. (2008), suggests associations of BDE-153 exposure with diabetes and metabolic syndrome. The study by Turyk et al. (2009) found a non-significant association of PBDEs with diabetes only in subjects with hypothyroid disease. The CONTAM Panel noted that cross-sectional studies may not be the most appropriate study design to investigate the relationship between diabetes and exposure to PBDEs, as they cannot rule out reverse causation in which diabetes may enhance POPs accumulation or inhibit their clearance.

8.4.5. Effects on fertility or offspring

In epidemiological studies little attention has been given to the associations between exposure to PBDEs and birth outcome and female fertility (Table E5 in Appendix E).

In a study performed by Abdelouahab et al. (2011) in Canada (see Chapter 8.4.1), semen counts were analysed for each of the fifty-two men recruited in a fertility clinic. Sociodemographic questionnaires were administered to each participant and all medical data were obtained from medical record. Semen mobility was negatively related to BDE-47, -100 and sum of PBDEs, after controlling for other covariates including age and smoking. No relations were observed with other semen parameters.

Chao et al. (2010) studied whether high human milk PBDE levels in 46 reproductive-age females lead to interference with menstruation characteristics. The sum of PBDEs and certain individual PBDEs appear to have potential to prolong the length of average menstrual cycle and delay the age when menstruation periods begin coming regularly. The findings are difficult to interpret because of the small sample size and the time lag between the start of menstruation and the sampling of the human milk.

Harley et al. (2010) studied the association of maternal concentrations of PBDEs in serum during pregnancy with time to pregnancy (TTP) and menstrual cycle. Increasing levels of BDE-47, -99, -100, -153 and the sum of the four congeners were all associated with longer TTP (decreased odds of pregnancy each month): BDE-47 (OR:0.7, 95%CI 0.5-1.0), BDE-99 (OR:0.7, 0.5-1.0), BDE-100 (OR: 0.6, 0.4–0.9), BDE-153 (OR: 0.5,0.3-0.8), sum of four congeners (OR: 0.7, 0.5-1.0). PBDEs were not associated with menstrual cycle characteristics.

In the study from Tan et al. (2009) the prevalence of POPs, including PBDEs, were determined in 41 cord blood samples collected during the year 2006 in Singapore. Relatively few PBDE congeners (BDE-28, -47 and -99) were detected in more than half of the samples. BDE-47 and -99 were positively associated with Apgar score (a standard way of evaluating the newborn baby on a scale from zero to 10 based on 5 criteria including respiration and pulse). Interpretation of results is hampered by no correction for multiple comparisons.

Akutsu et al. (2008) carried out a pilot study on the relationship between human serum PBDEs and sperm quality and testis size. Blood serum and sperm samples were collected on a monthly basis in the year 2003 from 10 young Japanese males. Of the 29 PBDE congeners monitored, 4 congeners (BDE-47, -99, -100 and -153) were mainly detected in human serum samples. Inverse correlations were observed between the serum BDE-153 concentration and sperm concentration ($r = -0.841$, $p = 0.002$) and testis size ($r = -0.764$, $p = 0.01$). No significant relationships were observed between the serum concentrations of the other congeners and the sperm concentration (r ranged from -0.187 to -0.099, $p = 0.605–0.786$) or testis size (r ranged from -0.216 to -0.054, $p = 0.548$-0.883). The CONTAM Panel noted that the small size of the study group and the limitations of the analysis and the presentation of the data hampered the interpretation of the study.

In a prospective Danish-Finnish study, 1997-2001, Main et al. (2007) investigated whether exposure to PBDEs was associated with cryptorchidism. The study analyzed whole placentas (for 95 cryptorchid/185 healthy boys) and individual human milk samples (62/68) for 14 PBDEs. In 86 placenta-milk pairs, placenta PBDE concentrations in fat were lower than in human milk, and a larger number of congeners were nondetectable. There was no significant difference between boys with and without cryptorchidism for individual congeners, the sum of 5 most prevalent, or all 14 congeners. The concentration of PBDEs in human milk was significantly higher in mothers of boys with cryptorchidism than in controls (sum of BDE-28, -47, -66, -99, -100, -153 and -154: median, 4.16 vs. 3.16 ng/g fat; $p < 0.007$). There was a positive correlation between the sum of PBDEs and serum luteinizing hormone ($p < 0.033$). PBDE levels in human milk, but not in placenta, showed an association with congenital cryptorchidism.

A small study (n=20) (Chao et al., 2007) reported that higher PBDE levels in human milk were associated with shorter pre-pregnancy menstrual cycle length (<30 days). Findings were not statistically significant when models were adjusted for maternal age, body mass index (BMI) and parity, while increased PBDEs in human milk was related with impaired birth outcome, particularly decreased birth weight and length, chest circumference, and decreased BMI of infants.

In summary, recent studies have reported associations of serum and/or milk single PBDE congeners and/or the sum of PBDEs with longer time to pregnancy, longer length of average menstrual cycle, shorter pre-pregnancy menstrual cycle length, delay of age when menstruation periods begin regularly. Impaired birth outcome, particularly for decreased birth weight and length, chest circumference, and BMI of infants were reported in offspring. Inverse correlations were observed between the serum BDE-153 concentration and sperm concentration and testis size. In one study, semen mobility was negatively related to BDE-47 and BDE-100 and to the sum of BDE-47, -99, -100 and -153. PBDE levels in human milk, but not in placenta, showed an association with congenital cryptorchidism.

The CONTAM Panel noted that most of the associations between exposure to PBDEs and effects on fertility or offspring are either based on one single study or are inconsistent through studies. Further issues, such as small sample size, multiple comparisons (significant associations that might have occurred by chance due to the large number of statistical tests) and study design hamper interpretation of these results.

8.5. Consideration of critical effects and possibilities for derivation of a health based guidance value

Toxicological studies with PBDEs were performed with technical mixtures or with a limited number of individual PBDE congeners (i.e. BDE-47, -99, -153 and -209). The purity of the individual congeners and technical mixtures varied considerably and it has been demonstrated that dioxin-like polybrominated furans can be present in the technical mixtures. Therefore, the results of the toxicity studies with PBDE mixtures need to be judged with respect to the possible impact of dioxin-like constituents in the effects observed. Studies with purified mixtures, however, have confirmed that effects on the liver, thyroid and developmental effects are attributable to the PBDEs themselves and not to possible contaminants. In contrast to technical mixtures, it is unlikely that individual PBDE congeners would contain PBDDs or PBDFs, since, based on the production method used, they are not expected to be formed as byproducts during the synthesis of individual PBDE congeners.

Toxicokinetic data for PBDEs are rather limited. Following oral exposure, BDE-209 is absorbed to a limited extent (<25 % of the administered dose) and is mainly distributed to adrenals, kidneys, and liver. Absorption of the other congeners is typically 70-80 % of the administered dose, with lipophilic tissues as the preferred sites for deposition. Elimination characteristics of PBDE congeners in animals and humans differ considerably, with elimination half-lives for individual congeners in rats ranging from about 2 to 20 days, whereas for humans half-lives in the range of 926 days (BDE-47) to about 1,560 days (BDE-153) have been reported. This large difference in kinetics hampers a direct extrapolation of animal dose-response data to humans.

Toxicological studies have been carried out using different experimental designs with single or repeated administration during gestation, postnatally or in adulthood. Most of the studies were performed according to non-standard protocols and do not provide results that are suitable for risk assessment purposes. Main targets for PBDE toxicity were the liver, thyroid hormone homeostasis, and the reproductive and the nervous system.

Animal studies with individual PBDE congeners or technical mixtures provided evidence for disturbance of thyroid homeostasis. Two recent 28 day sub-acute oral toxicity studies were conducted in adult rats with BDE-209 (van der Ven et al., 2008b) and DE-71 (van der Ven et al., 2008a). The CONTAM Panel noted that the observed effects on thyroid hormone levels were not always

consistent. For BDE-47, the LOEL for effects on thyroid hormones (T4) in different studies was between 0.7 mg/kg b.w. (single exposure on GD6, Talsness et al., 2008) and 18 mg/kg b.w. (2 week exposure of adult rats, Hallgren et al., 2001; Hallgren and Darnerud, 2002). For BDE-99, three studies showed no effects on thyroid hormones (T4) either after prenatal exposure (single exposure or from GD4 to PND17) (Branchi et al., 2005; Skarman et al., 2005) or in adults (single exposure) (Alonso et al., 2010), whereas in one study with single exposure on GD6 a decrease of T4 was found with a LOEL of 0.06 mg/kg b.w. (Kuriyama et al., 2007). For BDE-209 a LOEL of about 300 mg/kg b.w. was found based on a reduction of T4 in one study after exposure at GD6-18 (Kim et al., 2009). Effects on T3 and TSH and no changes in T4 were found in another study in rats exposed to a similar dose at PND10-42 (Lee et al., 2010). Mice seem to be more susceptible to BDE-209 with a NOEL between 10 and 20 mg/kg b.w., however again in one study the NOEL is based on a decrease of T4 (Rice et al., 2007) and in another on decrease of T3 (Tseng et al., 2008). The CONTAM Panel was not able to identify an explanation for these contradictory results, which makes it difficult to draw a clear conclusion on the effects of PBDE on thyroid hormone homeostatsis.

The extrapolation of effects on thyroid hormone homeostasis observed in rodents to humans is complicated by differences in levels and binding capacity of circulatory transporting proteins, i.e. transthyretin and thyroid binding globulin (Capen, 1997; Hill et al., 1998). In the case of PBDEs differences in changes in total serum T4 between rodents and humans may arise from the differences in activation of pregnane X receptors that leads to up-regulation of hepatic catabolic enzymes and a subsequent decline in circulating T4 concentrations (Schuetz et al., 1998). *In vitro* reporter gene assays showed that PBDEs (BDE-47, -99 and a PentaBDE technical product) are inducers of human and rodent PXR (Pacyniak et al., 2007; Fery et al., 2009). Although comparable information on the CAR is not available, it is likely that this receptor is also activated by PBDEs. Effects on TTR by BDE-47 (Hamers et al., 2006) and suppression of TR dependent gene expression in neural cells by BDE-100, -153, -154 and -209 (Ibhazehiebo et al., 2010) represent additional mechanisms for changes in thyroid hormone homeostasis and signalling. It is noted that thyroid hormone insufficiency in both humans and in experimental animals may lead to neurodevelopmental effects (Miller et al., 2009). Therefore rodent data on the effects of PBDEs on thyroid hormone homeostasis or signalling might be of relevance for human health risk assessment.

Experimental neurodevelopmental studies conducted in rodents show that PBDEs affect behavioural responses to a novel environment. For BDE-47 the LOEL reported from a single prenatal exposure of rats on GD6 (0.7 mg/kg) (Kuriyama et al., 2004a) was similar to the one from postnatal exposure of mice on PND10 (1 mg/kg). In contrast, the reported LOEL for BDE-99 varied from 0.06 mg/kg (single exposure on GD6 in rats, Kuriyama et al., 2005) to 0.8 mg/kg (single exposure on PND10 in mice; Eriksson et al., 2001). For BDE-99, where exposure took place from GD6 to PND21, Branchi et al. (2002; 2005) found LOELs for neurobehavioural changes in mice in the range of 0.6 to 18.0 mg/kg b.w. per day. A recent study in mice treated with BDE-47 from 4 weeks before mating until weaning (Ta et al., 2011) revealed neurobehavioral effects in female offspring with a LOEL of 1 mg/kg b.w. per day.

The CONTAM Panel noted that most of the information comes from studies with mice exposed to a single administration given by gavage on PND10. The available data, although limited, do not point to large differences in outcome when the same congener was administered during and/or after gestation.

In a number of neurobehavioural studies using single administration the litter effect was not taken into account appropriately since often more than one pup per litter was allocated to a specific dose group in behavioural tests. Since a difference in litter response may occur, uneven distribution of littermates over dose groups without statistical consideration of the litter as the experimental unit may bias the results of the analyses (Holson et al., 2008).

Most of the behavioural studies in rodents have been performed in the same laboratory addressing a limited number of behavioural parameters. As studies of neurodevelopmental effects on behaviour can be very variable (Crofton et al., 1991), it is important that where such an effect is to be used as the

basis of a risk assessment, it should be independently verified. In the case of the PBDEs, there is only a limited number of other studies addressing neurodevelopmental effects on behaviour and the results obtained differed in some important respects, the reasons for which are not clear, e.g. for BDE-209 (Rice et al., 2007). This inconsistency hampers a conclusive evaluation of the toxicological significance of these findings for human health risk assessment.

In addition to the limitations and the concerns regarding the single administration protocol, the CONTAM Panel noted that there are also arguments supporting the use of the results from these studies. First, they provide the lowest doses leading to neurobehavioural effects, and therefore need particular consideration. Second, due to the fact that effects are observed, these studies apparently cover a relevant neurodevelopmental period in experimental animals. Third, the half-lives and the lipophilic nature of a number of PBDE congeners are such that even a single dose would maintain exposure for an appreciable period of time. Therefore, the CONTAM Panel concluded that in this specific case, single-dose studies should be considered for the assessments of risk to human health.

The liver is a target organ for effects of PBDEs. The most prominent hepatic effects are organ enlargement and hepatocellular hypertrophy and vacuolization. Furthermore, PBDEs induce a number of enzymes of hepatic drug metabolism, including those responsible for glucuronidating thyroid hormones. Changes in hepatic drug metabolism and transthyretin expression seem to play a key role in the decrease in serum T4 observed in rodents. In addition, PBDEs seem to cause oxidative stress.

The available genotoxicity studies indicate that PBDEs do not induce gene mutations, but they can cause DNA damage through the induction of ROS.

There are no long-term toxicity/carcinogenicity studies available for individual PBDE congeners or technical mixtures, with the exception of decaBDE, and no tumor promotion studies are available. For decaBDE there is some evidence for an increase in liver adenoma in rats and liver adenoma and carcinoma in mice, but in the view of the CONTAM Panel this was due to a secondary mode of action.

Most epidemiological studies suggested an association between PBDEs and (sub)clinical hyperthyroidism, but two studies (Herbstman et al., 2008; Yuan et al., 2008) showed an association with (sub)clinical hypothyroidism. In a few studies (Roze et al., 2009; Herbstman et al., 2010; Gascón et al., 2011) effects on neuropsychological functioning were associated with exposure to PBDEs. Overall, epidemiological results were inconsistent and it was noted that exposure to other halogenated contaminants could have interfered with the outcome of these studies.

The CONTAM Panel considered the potential for additivity of the different congeners, recognizing that there are some similarities in the effects of the various PBDE congeners, e.g. interactions with nuclear receptors. However, the divergent responses of the different toxicological endpoints, as indicated above, and the limited information available, preclude establishment of a common mode of action. Therefore, the CONTAM Panel decided to perform the risk assessment on the basis of the individual congeners.

Of the eight PBDE congeners (BDE-28, -47, -99, -100, -153, -154, -183 and -209) considered by the CONTAM Panel to be of primary interest for dietary exposure, 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.

Based on the information on the effects on the thyroid hormone homeostasis, neurobehaviour and effects on sperm quality and reproductive performance in animal experiments 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. Not all studies appeared to be useful for a dose-response analysis. Several studies were excluded *a priori* because they only applied one dose-level, and in other studies a clear dose-response relationship was lacking. In its assessment, the CONTAM Panel chose a benchmark response (BMR) of 10 % to avoid extrapolation beyond the

observable range (EFSA, 2009). In addition, the evaluation was restricted to studies with oral administration. For effects on thyroid hormone disturbance by BDE-47 two studies used *i.v.* administration (Suvorov et al., 2009; Abdelouahab et al., 2009). Although these studies provided information on the internal dose, the CONTAM Panel concluded that these studies were not suitable for the risk assessment of PBDEs, because *i.v.* administration would have led to higher peak concentrations than oral (gavage) dosing. In addition, in the study of Abdelouahab et al. (2009) carried out in sheep, the reported concentrations in fat did not show a clear relationship with the administered *i.v.* dose.

The lowest BMD_{10} and $BMDL_{10}$ (see Appendix G) for the critical effects are presented in Table 40. For more detailed information about the studies see Tables 36 and 37.

Table 40: BMD_{10} and $BMDL_{10}$ values for critical effects for individual PBDE congeners and body burden at $BMDL_{10}$ based on external doses of single administration studies. For details of the dose-response assessment see Appendix G.

Congener	Critical endpoint	BMD_{10} µg/kg b.w.	$BMDL_{10}$ µg/kg b.w.	Body burden at $BMDL_{10}$ µg/kg b.w.	Reference
BDE-47	Mice, locomotion	338	309	232	Eriksson et al., 2001
BDE-99	Mice, total activity	22	12	9	Viberg et al., 2004b
	Rat, locomotion	116	82	Not used	Kuriyama et al., 2005
BDE-153	Mice, total activity	107	83	62	Viberg et al., 2003
BDE-209	Mice, total activity	3,200	1,700	*No body burden calculated*	Viberg et al., 2007
	Mice, T4 reduction	11,500	6,800	*No body burden calculated*	Rice et al., 2007

Comparing the $BMDL_{10}$ for neurodevelopmental effects on behavior for the respective congeners with NOEL's (or LOEL's) for other endpoints of toxicity (e.g. effects on thyroid hormone homeostatis and the liver) discussed earlier in this chapter, the CONTAM Panel noted that the $BMDL_{10}$'s given in Table 40 provide the lowest reference point to be used in the hazard characterization of the respective PBDEs. This comparison also included results from studies with repeated administration, that would have resulted in considerably higher body burdens.

In Chapter 8.1.4.2 it has been indicated that the elimination kinetics of most PBDEs in rodents and humans differ considerably. The consequence of this difference in elimination kinetics is that exposure to similar external doses for BDE-47, -99 and -153 will result in higher concentrations in the human body than in the rodent. Therefore, external dose levels of these congeners associated with toxic effects in animals are not appropriate dose metric for the extrapolation to humans for the risk assessment. Instead, the body burden provides a more appropriate dose metric for a direct comparison of internal effect doses in animals and in humans. Body burdens corresponding with effects of the various PBDEs in rodents, even resulting from studies with different dose regimens (e.g. single vs. repeated administration), can readily be transformed (see Chapter 9) into estimated human daily intakes that on a chronic basis would be expected to lead to similar body burdens in humans.

For BDE-209 the half-life in animals and humans is similar, and therefore the external dose level ($BMDL_{10}$) as obtained from animal studies can be applied for the human health risk assessment.

Because the $BMDL_{10}$ values for BDE-47, -99 and -153 of 309, 12, and 83 µg/kg b.w., respectively (see Table 40) were derived from studies applying a single oral dose and considering an oral absorption for these congeners in rodents of about 75 %, for these PBDE congeners the body burden at the BMDL can directly be calculated by multiplication of the BMDL with the absorbed fraction. This results in a body burden at the $BMDL_{10}$ of 232, 9 and 62 µg/kg b.w for BDE-47, -99 and -153, respectively.

These body burden values at the $BMDL_{10}$ for BDE-47, -99 and -153 could in principle be used as the basis to derive 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 data base on PBDEs, the derivation of a health based guidance value was not appropriate. Instead, the Panel used a margin of exposure (MOE) approach for the risk characterization of PBDE congeners.

9. Risk characterization

Assuming that human exposure to PBDEs occurs mainly via food, the chronic dietary intake ($D_{r,h}$) which corresponds with the body burden in the average human can be calculated. In general this calculation needs kinetic modeling, but since PBDEs are expected to distribute predominantly in the adipose tissue in humans, a one compartmental model will suffice here (for clarification see Appendix F). To calculate the chronic human dietary intake ($D_{r,h}$) which is associated with the steady state body burden at the BMDL, only two additional parameters are needed, the fraction of the daily intake which is absorbed in the body and the rate constant for the elimination of the compounds from the body. Therefore $D_{r,h}$ can be calculated as follows:

$$D_{r,h} = \frac{BB_a \cdot k_{el,h}}{F_{abs,h}} \qquad (1)$$

$k_{el,h}$ Rate constant for the elimination from the human body (day^{-1})
$F_{abs,h}$ Fraction of the chemical in food which is absorbed into the human body (dimensionless)
$D_{r,h}$ Chronic human daily dietary intake (amount/kg b.w. per day)
BB_a Body burden in the experimental animal (amount/kg b.w.)

It should be noted that in a one-compartment model as applied in this case, the relationship holds that $k_{el} = \ln 2/t_{1/2}$ (with $t_{1/2}$ being the elimination half-life in the body, i.e. the time needed for half of the amount of a chemical to be cleared from the body once the exposure has stopped).

9.1. Margin of exposure (MOE)

By comparison of the calculated human dietary intake associated with the body burden at the BMDL ($D_{r,h}$) with the estimated dietary intake provided in Chapter 7.4 for the general population or for specific subgroups of the population, the margin of exposure (MOE) can be calculated, where MOE = $D_{r,h}$ (amount/kg b.w.) / estimated dietary intake (amount/kg b.w.).

The CONTAM Panel estimated the MOE for average and high adult consumers, for a specific subgroup of the general population (high and frequent fish consumers) and for young children (1-3 years of age) with an average and high consumption. Dietary intake of infants (< 1 year) was not considered because the Panel was of the opinion that the available data were too limited to facilitate a realiable assessment of the MOE. However, the MOE for breast-fed infants could be estimated.

As indicated in Chapter 8.5, for **BDE-47** the body burden at the $BMDL_{10}$ is 232 µg/kg b.w. As a "worst case" the longest human half-life identified for BDE-47 (see Chapter 8.1.4.2) of 926 days was used. In the absence of robust information, the human absorption of BDE-47 is assumed to be 100 % ($F_{abs,h}$ = 1). The same absorption fraction is also applied for the other PBDE congeners. Substituting

these figures into formula 1 leads to an estimated chronic human dietary intake ($D_{r,h}$) of 172 ng/kg b.w. per day associated with the body burden at the $BMDL_{10}$ for BDE-47.

For BDE-47, the minimum LB and the maximum UB dietary intake across European countries for average adult consumers of the general population is 0.29 and 1.91 ng/kg b.w. per day, respectively (Table 26). This provides a MOE of 590 and 90, respectively, when compared with the estimated chronic human dietary intake ($D_{r,h}$) of 172 ng/kg b.w. per day associated with the body burden at the $BMDL_{10}$ for BDE-47. For high adult consumers (P95) the minimum LB and the maximum UB dietary intake across European countries is 1.1 and 4.51 ng/kg b.w. per day, respectively. This provides MOEs of about 160 and 38. For high and frequent fish consumers the minimum LB and the maximum UB dietary intake across European countries is 5.39 and 7.27 ng/kg b.w. per day, respectively. This results in MOEs of about 32 and 24. For young children (1-3 years) with an average consumption the minimum LB and the maximum UB dietary intake is 1.04 and 6.40 ng/kg b.w. per day, respectively. This results in MOEs of 165 and 27. Young children (1-3 years) with a high consumption (P95) have a minimum LB and a maximum UB dietary intake of 4.44 and 15.6 ng/kg b.w. per day, respectively. The resulting MOEs are 39 and 11, respectively.

The body burden at the $BMDL_{10}$ for **BDE-99** is 9 µg/kg b.w. (see Chapter 8.5). The longest human half-life for BDE-99 is 1,442 days (see Chapter 8.1.4.2). Substituting this figure into formula 1 leads to an estimated chronic human dietary intake ($D_{r,h}$) of 4.2 ng/kg b.w. per day associated with the body burden at the $BMDL_{10}$ for BDE-99.

For BDE-99, the minimum LB and the maximum UB dietary intake across European for average adult consumers of the general population is 0.11 and 0.65 ng/kg b.w. per day, respectively (Table 26). This provides a MOE of 38 and 6.5, respectively, when compared with the estimated human dietary intake of 4.2 ng/kg b.w. per day associated with the body burden at the $BMDL_{10}$ for BDE-99. For high adult consumers (P95) the minimum LB and the maximum UB dietary intake across European countries is 0.3 and 1.07 ng/kg b.w. per day, respectively. This provides MOEs of about 14 and 3.9. For high and frequent fish consumers the the minimum LB and the maximum UB dietary intake across European countries is 0.60 and 1.40 ng/kg b.w. per day, respectively. This results in MOEs of about 7 and 3. For young children (1-3 years) with an average consumption the minimum LB and the maximum UB dietary intake is 0.58 and 2.99 ng/kg b.w. per day, respectively. This results in MOEs of 7 and 1.4. Young children (1-3 years) with a high consumption (P95) have a minimum LB and a maximum UB dietary intake of 1.36 and 6.16 ng/kg b.w. per day, respectively. The resulting MOEs are 3 and 0.7, respectively.

The body burden at the $BMDL_{10}$ for **BDE-153** is 62 µg/kg b.w. (see Chapter 8.5). The longest human half-life for BDE-153 (see Chapter 8.1.4.2) is 4,530 days. Substituting this figure into formula 1 leads to an estimated chronic human dietary intake ($D_{r,h}$) of 9.6 ng/kg b.w. per day associated with the body burden at the $BMDL_{10}$ for BDE-153.

For BDE-153, the minimum LB and the maximum UB dietary intake across European for average adult consumers of the general population is 0.03 and 0.42 ng/kg b.w. per day, respectively (Table 26). This provides a MOE of 320 and 23, respectively, when compared with the estimated chronic human dietary intake of 9.6 ng/kg b.w. per day associated with the body burden at the $BMDL_{10}$ for BDE-153. For high adult consumers (P95) the minimum LB and the maximum UB dietary intake across European countries is 0.07 and 0.67 ng/kg b.w. per day, respectively. This provides MOEs of about 138 and 14. For high and frequent fish consumers the the minimum LB and the maximum UB dietary intake across European countries is 0.24 and 0.89 ng/kg b.w. per day, respectively. This results in MOEs of about 40 and 11. For young children (1-3 years old) with an average consumption the minimum LB and the maximum UB dietary intake is 0.09 and 1.62 ng/kg b.w. per day, respectively. This results in MOEs of 107 and 6. Young children (1-3 years old) with a high consumption (P95) have a minimum LB and a maximum UB dietary intake of 0.20 and 3.18 ng/kg b.w. per day, respectively. The resulting MOEs are 48 and 3, respectively. An overview of the calculated MOEs for the different consumers groups is presented in Table 41.

Table 41: Overview of the margins of exposure (MOEs) for BDE-47, -99 and -153 for different population groups, based on the minimum lower bound (LB) and maximum upper bound (UB) of the dietary intake (ng/kg b.w.).

Exposed population	PBDE congeners														
	BDE-47					BDE-99					BDE-153				
	Estimated intake (ng/kg b.w.)		$D_{r,h}$ [(a)] (ng/kg b.w.)	MOE		Estimated intake (ng/kg b.w.)		$D_{r,h}$ [(a)] (ng/kg b.w.)	MOE		Estimated intake (ng/kg b.w.)		$D_{r,h}$ [(a)] (ng/kg b.w.)	MOE	
	LB	UB		LB	UB	LB	UB		LB	UB	LB	UB		LB	UB
Children (1-3 years), average consumers	1.04	6.40	172	165	27	0.58	2.99	4.2	7	1.4	0.09	1.62	9.6	107	6
Children (1-3 years), high consumers	4.44	15.6	172	39	11	1.36	6.16	4.2	3	0.7	0.20	3.18	9.6	48	3
Adults, average consumers	0.29	1.91	172	590	90	0.11	0.65	4.2	38	6.5	0.03	0.42	9.6	320	23
Adults, high consumers	1.10	4.51	172	160	38	0.30	1.07	4.2	14	3.9	0.07	0.67	9.6	138	14
Adults, high fish consumers	5.39	7.27	172	32	24	0.60	1.40	4.2	7	3	0.24	0.89	9.6	40	11

b.w.: body weight; LB: lower bound; UB: upper bound; MOE: margin of exposure.
(a): $D_{r,h}$ = chronic human daily dietary intake associated with the body burden at the $BMDL_{10}$.

Elimination half-lives for **BDE-209** of 2.5-8.6 days were reported for rats, whereas for humans an elimination half-life of 15 days (range 11-18) was reported (see Chapter 8.1.4). In contrast to the other PBDEs, the elimination half-life of BDE-209 does not differ by orders of magnitude between animals and humans. Therefore, in this case, the animal $BMDL_{10}$ of 1.7 mg/kg b.w. expressed as an external dose can be compared with the estimated human dietary exposure.

For BDE-209, the subgroup of the population with the highest intake are children of 1-3 years old with a high consumption (P95) with a maximum UB of 17.6 ng/kg b.w. per day (Table 26). For this group the MOE is about 97,000. For the other population groups the MOE is even higher.

Usually for non-genotoxic compounds a MOE of 100 is considered sufficient to conclude that there is no health concern (WHO, 1999). This MOE covers uncertainties and variability with regard to both kinetic and dynamic differences between experimental animals and humans (factor 4 × 2.5 = 10), and within the human population (factor 3.2 × 3.2 = 10). Given the fact that the MOE approach is based on a body burden comparison between animals and humans, the potential kinetic differences have been accounted for. Equally, by focussing on the body burden associated with a $BMDL_{10}$ for neurobehavioural effects in mice induced during a relevant period for brain development (i.e. representing the most sensitive fraction of the population), and applying this body burden for the entire life span in humans, individual difference in susceptibility has been covered by the approach taken. Therefore, the calculated MOE should be sufficient to cover inter-species differences in sensitivity for the effects observed (i.e toxicodynamic differences between experimental animals and humans). Usually, in a traditional hazard characterization a default assessment factor of 2.5 (WHO, 1999) is applied to account for inter-species difference in toxicodynamics. In addition, by using the longest half-lives as reported for the various individual PBDE congeners, the estimation of the chronic human intake associated with the body burden calculated at the respective BMDLs is on the conservative side. This implies that in the case of PBDEs in principle any MOE larger than 2.5 indicate that there is unlikely to be a health concern. The larger the MOE is, the smaller is the potential health concern.

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 subpopulations 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 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 high concentration of BDE-99 could have led to overestimation of the exposure. On the other hand it was recognised 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 with respect to current dietary exposure to BDE-99.

For breast-fed infants with average human milk consumption the highest values of the estimated mean daily exposure of BDE-47, -99, -153 and -209 across European countries are 13.8, 5.05, 11.0, and 13.3 ng/kg b.w., respectively (Table 26). For infants with high human milk consumption the values are respectively 20.6, 7.6, 16.5 and 20.0 ng/kg b.w. For BDE-47, -99 and -153 the MOE with the intake associated with the BMDL is 12, 0.8 and 2.5 for infants with an average human milk consumption. For infants with a high human milk consumption, the MOEs are 8, 0.6 and 1.45, respectively. For BDE-209, the MOE is about two orders of magnitude. The Panel concluded that the intake of BDE-47 and -209 by breast-fed infants does not constitute a health risk. For BDE-99 and -153, the MOE is equal or smaller than a factor of 2.5 and thus might pose a potential health concern. The CONTAM Panel noted, however, that the highest mean exposure estimates across European countries were used

for the MOE calculation and that the lowest estimated mean values for average and high consumption of human milk are respectively about 40 and 25 times lower (see Tables 20 and 21). In addition, it should be noted that it takes 3-4 half-lives to reach steady state, i.e. 10 or more years for BDE-99 and -153 in humans. Hence, the MOEs for these PBDEs, as calculated for breast-fed infants, based on the body burden would be an overestimation of the risk. Therefore the CONTAM Panel concluded that the MOEs for BDE-99 and -153 in human milk are unlikely to raise health concern to breast-fed infants.

PBDEs in house and car dust, particularly BDE-209, can be important sources of exposure for children. Exposure to BDE-209 for young children (1-3 year) is estimated to range from about 0.5-80 ng/kg b.w. (see Chapter 7.6). Although the upper end of this range is higher than the estimated dietary exposure for this age group, the CONTAM Panel noted that the estimated total exposure (dietary plus non-dietary) is far below the $BMDL_{10}$ for BDE-209 of 1.7 mg/kg b.w. per day.

9.2. Comparison of body burdens

Since human half-lives of PBDEs have not been directly measured, but estimated based on assumption of steady state intake and concentration in humans, the CONTAM Panel also considered information on biomarkers of exposure to assess the health risk of exposure to PBDE congeners. This was done for comparison with the results of the MOE approach as presented above. In Chapter 8.2 information on levels of individual PBDE congeners in human adipose tissue, liver, (cord) blood, serum and placental tissue has been presented. Of these tissues, the CONTAM Panel identified information on PBDE concentrations in adipose tissue as being most relevant, because they best reflect long-term exposure to PBDE congeners. In order to facilitate a direct comparison of the actual human body burdens with the body burden at the $BMDL_{10}$ for BDE-47, -99 and -153 of 232, 9 and 62 µg/kg b.w., respectively, the CONTAM Panel converted reported concentrations in adipose tissue in humans to an overall body burden by assuming an average fat content of the human female adult body of 25 % (van der Molen, 1998).

The highest reported mean concentrations in adipose tissue for BDE-47, -99 and -153 of 6, 1.6 and 2.5 ng/g fat (see Table 32) correspond to a body burden of 1.5, 0.4 and 4 µg/kg b.w., respectively. Compared with the body burden at the $BMDL_{10}$ of 232, 9 and 62 µg/kg for BDE-47, -99 and -153, this results in a margin of 155, 22, and 100, respectively. Even when the highest reported individual fat concentrations for BDE-47, -99 and -153 of respectively 14.3, 11.9 and 25.1 ng/g fat were used, the resulting body burdens of 3.6, 3 and 6.3 µg/kg b.w. provide a margin of 65, 3 and 10, with the respective body burden at the $BMDL_{10}$.

For chemicals accumulating in the body the concentration in human milk is often used as proxy for the body burden. Therefore the CONTAM Panel also considered information on levels of PBDE congeners in human milk (see Chapter 5.2.2) to compare human body burdens with animal body burdens at the $BMDL_{10}$. Highest mean concentrations across European countries for BDE-47, -99, and -153 have been reported to be 3, 1.1 and 2.4 ng/g fat, respectively. These concentrations are comparable with the respective concentrations in adipose tissue and will thus result in similar margins with the respective body burdens at the $BMDL_{10}$ for BDE-47, -99, and -153.

The CONTAM Panel concluded that this comparison of body burdens between animals and humans provided similar margins for BDE-47, -99 and -153 as the MOEs derived in Chapter 9.1. and therefore supports the conclusions presented above.

10. Uncertainty

The evaluation of the inherent uncertainties in the assessment of exposure to PBDEs has been performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2007). In addition, the report on "Characterizing and

Communicating Uncertainty in Exposure Assessment" has been considered (WHO/IPCS, 2008). According to the guidance provided by the EFSA opinion (EFSA, 2007) the following sources of uncertainties have been considered: assessment objectives, exposure scenario, exposure model, and model input (parameters).

10.1. Assessment objectives

The objectives of the assessment were clearly specified in the terms of reference. The CONTAM Panel assessed the new occurrence data that were collected by EFSA, and carried out an exposure assessment for the general population as well as for specific subgroups. The uncertainty in the assessment objectives is considered to be negligible.

10.2. Exposure scenarios/Exposure model

In response to EFSA's request to submit PBDE occurrence data in food, 11 European countries submitted data on 3,971 samples collected and analysed between 2001 and 2009. Norway submitted 28 % of the samples, followed by Germany (24 %) and Ireland (11 %). The food products for which data were provided varied between submissions from the different European countries, but most samples belonged to the fish and seafood category, followed by products of terrestrial animal origin and only a few samples of plant origin. Moreover, there are considerable differences in the number of PBDE congeners reported. There is uncertainty in possible regional differences in PBDE contamination of food commodities, and the CONTAM Panel recognised that the data set is not fully representative of food on the EU market. Reports on the effects of food processing on the PBDE levels in prepared food commodities are scarce. However, it can be assumed that PBDEs behave similar as PBBs. Taking into account, that the processed foods in general had lower PBB concentrations than the respective raw materials, this could have lead in a similar way to some overestimation of the overall PBDE exposure.

The high proportion of samples having levels below the LOD or LOQ may have introduced uncertainties to the overall estimate. The use of the upper bound in this opinion tends to overestimate the dietary exposure. Because of the high proportion of samples below the LOD or LOQ, all the exposure calculations were based on the mean concentrations. It is generally accepted that the use of the mean contamination to represent the long term dietary exposure is expected to be an overestimation compared with the use of the median. Taken together, the uncertainties regarding the exposure estimates are considered to overestimate the exposure.

10.3. Model input (parameters)

There are no prescribed fixed official methods for the analysis of PBDEs and laboratories can use any method of analysis, provided it can be demonstrated in a traceable manner that they fulfil the requirements according to ISO 17025. This may have added to the uncertainty in the analytical results. The limited number of certified reference materials is a limitation when the method performance for the analytical methods for analysis of PBDEs in food is assessed, and add thereby to the overall uncertainty in the analytical results.

10.4. Other uncertainties

Most of the toxicological data were gained from experiments with technical mixtures rather than purified individual congeners. As only the major constituents of these mixtures are known but not potential impurities, such as PBDDs and PBDFs, this adds a considerable uncertainty to the derivation of a toxicological reference point. Even in cases where levels of an individual contaminant are low, their concentration adds to the total body burden of different contaminants, thereby inducing uncertainty about the specific health impact of the PBDE mixture studied. Moreover, the congener

profile found in foods does neither resemble the profiles found in the individual technical mixtures tested nor in human specimes.

The aformentioned studies by Eriksson et al. and Viberg et al. do not provide information on the levels of dioxin-like impurities in the PBDEs tested except for general information about a purity of > 98 %. This fact is of particular concern since dioxin-like compounds have been reported to elicit neurobehavioural developmental effects in rodents which resemble those reported for PBDEs by Eriksson et al. and Viberg et al. (Thiel et al., 1994; Nishijo et al., 2007). Upon request the authors responded that the PBDE congeners used in the studies were purified from dioxin-like contaminants using activated charcoal and that the remaining 1-2 % are other PBDE congeners.

Regarding the assessment of the toxicological endpoints (effects on neurobehaviour, thyroid hormone regulation and reproductive function) it is of concern that most of the data are generated from experiments based on a single administration during the pre- or postnatal period. Particularly for effects on neurodevelopmental behaviour it is difficult to relate specific periods of neurodevelopment in rodents to an equivalent period in humans. This adds to the uncertainty regarding the interpretation of this specific endpoint. In addition, The CONTAM Panel noted that litter effects were not taken into account appropriately. Uneven distribution of littermates over dose groups without statistical consideration of the litter as the experimental unit may have biased the results of the studies. This provides an additional source of uncertainty. In addition, nearly all experiments with individual PBDE congeners on neurodevelopmental behaviour with single administration have been carried out in the same laboratory. Confirmation of the observations in other laboratories is desirable.

The limited data on the elimination half-life for PBDEs in humans and the relatively large range of reported values is an additional source of uncertainty. By applying the longest reported half-lives for the individual PBDE congeners in the hazard assessment, the CONTAM Panel considered this assumption to be conservative.

10.5. Summary of uncertainties

In Table 42 a summary of the uncertainty evaluation is presented, highlighting the main sources of uncertainty and indicating an estimate whether the respective source of uncertainty might have led to an over- or underestimation of the exposure or the resulting risk.

Table 42: Summary of qualitative evaluation of the impact of uncertainties on the risk assessment of the dietary exposure to PBDEs.

Sources of uncertainty	Direction
Measurement uncertainty of analytical results	+/- [(a)]
Limited number of food categories with varying number of congeners reported	+/-
Extrapolation of occurrence data from a few countries to whole Europe	+/-
Influence of upper-bounds for non-detects on exposure estimate	+
Lack of information on the impact of food processing	+/-
Limited information on the composition and purity of technical mixtures used in animal studies.	+
Congener pattern of technical mixtures used in toxicological studies do not resemble the profiles found in food	+/-
Study design and interpretation of animal experiments on developmental neurobehaviour used to derive the BMDLs.	+
Relevance of the developmental neurobehavioural effects in mice for humans	+/-
Relationship between body burden in young mouse to a pregnant woman	+/-
Relevance of the toxicological effects to humans	+
Possibility of combined effects of different PBDE congeners	-

(a): + = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure/risk.

The CONTAM Panel considered that the impact of the uncertainties on the risk assessment of exposure to PBDEs is considerable and concluded that its assessment of the risk is likely to be conservative – i.e. more likely to overestimate than to underestimate the risk.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

General

- Polybrominated diphenylethers (PBDEs) are a class of brominated aromatic compounds with a basic structure consisting of two phenyl rings linked by an ether bond. The position and number of the bromine atoms results in 209 possible compounds, referred to as PBDE congeners.

- Technical mixtures of PBDEs were used as additive flame retardants and are not chemically bound to the polymers, and therefore they can leach into the environment. They have been widely used in polymers and textiles, applied in construction materials, furniture, and electric and electronic equipment.

- International agreements on ban and regulations for production and use of technical mixtures of PBDEs have been introduced since 2004, leading to declining levels in the environment, i.e. air and dust.

- The chemical stability of the PBDE congeners varies with the individual structure but a general rule is that PBDE congeners with up to three bromine substituents and those with nine

and ten bromine substituents are more susceptible to abiotic transformations. PBDE congeners with four to eight bromine substituents show the highest stability.

- PBDE congeners are susceptible to photolysis, reductive debromination and radical reactions while they are less susceptible to oxidation and hydrolysis.

- In general, PBDE congeners are persistent and bioaccumulative. Bioaccumulation is congener- and species-dependent.

- The technical mixture Decabromodiphenyl ether (DecaBDE), in particular its major constituent, BDE-209, has different physicochemical properties compared to the PBDE congeners making up the Pentabromodiphenyl ether technical mixture (PentaBDE) and the Octabromodiphenyl ether technical mixture (OctaBDE).

- Based on the composition of the technical PBDE mixtures, occurrence in the environment and available data on toxicity, the Panel on Contaminants in the Food Chain (CONTAM Panel) considered the following eight PBDE congeners to be of primary interest: BDE-28, -47, -99, -100, -153, -154, -183 and -209.

- OH-PBDEs can occur from biosynthesis by marine organisms or from metabolic transformation of PBDEs in wildlife and humans. Information on occurrence and toxicity of these is scarce.

Occurrence

- The eight PBDE congeners considered are ubiquitously present in biota and likewise in food and feed.

- Following an EFSA call for data, results from the analysis of 19 PBDE congeners on 3,971 food samples were provided to EFSA by 11 European countries, covering the period from 2001 to 2009.

- 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”, “Milk and dairy products” and “Eggs and egg products”. Less than 80 samples were reported for the remaining food categories.

- The data were characterised by a high proportion of non detects, therefore only those food categories 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 used for the exposure assessment (“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”,“Food for infants and small children”).

- In a specific study on the sub-category of “Fish meat”, the results indicate a relationship between the PBDE levels and the fat content of the different fish.

- The average concentrations of the predominant PBDE congeners in human milk showed a comparable mean contamination across various European countries. BDE-47 was generally the predominant congener with mean concentrations across countries of 0.14-3.0 ng/g fat. The average concentrations across European countries for BDE-99 and BDE-153 were <0.03-1.1 ng/g fat and 0.10-2.4 ng/g fat, respectively. However, the individual contamination may differ considerably as indicated by the wide concentration ranges for several PBDEs from various countries.

- BDE-209 was determined in human milk at mean concentrations between 0.21 and 2.9 ng/g fat. In those studies that measured all eight PBDE congeners considered, BDE-209 amounts to 8-66 % of the sum of the eight PBDEs.

- In human adipose tissue and liver samples reported in the literature from different European countries, BDE-153 was the most predominant congener (1.0-2.5 ng/g fat) followed by BDE-47. In placental tissue, serum or blood BDE-47 was the predominant congener (0.16-7.0 ng/g fat) followed by BDE-153 and BDE-99. When analysed, BDE-209 was reported to be the most predominant congener in serum or blood samples (0.77-37 ng/g fat).

Human exposure

- The highest dietary PBDE exposure is due to BDE-47 and -209. The range of estimated exposure for average consumers across European countries and surveys for BDE-47 is 0.29 and 1.91 ng/kg b.w. per day, and for BDE-209 is 0.35 and 2.82 ng/kg b.w., for minimum lower bound and maximum upper bound, respectively. For BDE-99 and BDE-153, the minimum lower bound and maximum upper bound intakes across European surveys are 0.11 and 0.65 ng/kg b.w. per day and 0.03 and 0.42 ng/kg b.w. per day, respectively.

- The range of estimated dietary exposure for high consumers (95^{th} percentiles) across European surveys of BDE-47 is 1.1 and 4.51 ng/kg b.w. per day, and for BDE-209 is 0.7 and 4.58 ng/kg b.w., for minimum lower bound and maximum upper bound, respectively. In the case of BDE-99 and BDE-153, the minimum lower bound and maximum upper bound intakes for high consumers across European surveys are estimated at 0.30 and 1.07 ng/kg b.w. per day, and 0.07 and 0.67 ng/kg b.w. per day, respectively.

- For a specific population group consisting of high and frequent consumers of fatty fish meat (≥8 % fat) the mean dietary upper bound intake of BDE-47 (maximum upper bound across European surveys) is 7.27 ng/kg b.w. per day.

- Supplements, such as fish oil, e.g. cod liver oil, are another source of PBDE exposure. Assuming a maximum daily intake of 15 mL of oil, the highest estimates of the total average daily exposure to individual PBDE congeners can reach up to 2.53 and 4.27 ng/kg b.w. per day, respectively for BDE-47 and -209 (maximum upper bound across European surveys).

- As contamination of food samples of plant origin is generally lower than that of food samples of animal origin, it can be assumed that the dietary exposure to PBDEs for vegetarians is lower than that for people consuming a mixed diet.

- For children from 1 to 3 years old the dietary intake of BDE-47, -99, -153 and -209, for average and high consumers, is about 3-6 times higher than for adults. The CONTAM Panel noted that exposure to BDE-99 for this age group could be overestimated due to one high sample in the category "Food for infants and small children".

- Due to the limited occurrence data "Food for infants and small children" and the restricted number of consumption surveys for infants below 1 year, this age group could not be further considered in the risk assessment.

- For infants with average human milk consumption the mean daily exposure to BDE-47, -99 and -153 across European countries where data are available on PBDEs in human milk, ranges from 0.64-13.8, <0.14-5.05 and 0.46-11.0 ng/kg b.w., respectively. For BDE-209 the exposure scenario based on average human milk consumption results in a range of 0.96-13.3 ng/kg b.w. per day. For infants with a high human milk consumption the respective daily exposure for BDE-47, -99 and -153 ranges from 0.96-20.6, <0.14-7.57 and 0.69-16.5 ng/kg b.w.,

respectively. For BDE-209 exposure based on a high human milk consumption scenario amounts to 1.4-20 ng/kg b.w. per day.

- PBDEs in house and car dust, particularly BDE-209, can be an important source of exposure for children.

Hazard identification and characterization

- Following oral exposure BDE-209 is absorbed at a limited extent (<25 % of the dose) and residues are mainly distributed to adrenals, kidneys, and liver, whereas absorption of other congeners is typically 50-80 %, with lipophilic tissues as the preferred sites for deposition.

- PBDEs are biotransformed in mammals. Debromination and hydroxylation are the major metabolic pathways.

- The estimated elimination half-life of PBDEs in human serum varies from 1-2 weeks for BDE-209 to 3-7 years for BDE-153 and -154.

- Commercial PBDE mixtures showed low acute toxicity in rats.

- PBDEs cause hepatocellular hypertrophy and induce drug metabolism in the liver of experimental animals.

- Changes in enzymes of hepatic xenobiotic metabolism and transthyretin expression seem to play a key role in the decrease in serum T4 observed in rodents.

- The animal studies showed that exposure to PBDEs during gestation and/or postnatally can cause developmental and reproductive effects, including impaired spermatogenesis and changes in female reproductive organs, and perturbation of thyroid hormone regulation.

- Exposure to PBDE congeners during development can cause neurobehavioural effects. Alterations in the thyroid hormone regulation may play a critical role in the onset of these effects.

- No teratogenic effects have been observed. Fetotoxic effects of PBDEs seem to occur at lower doses than those causing maternal toxicity.

- Activation of nuclear receptors such as the constitutive androstane receptor and the pregnane X receptor appear to underlie changes in biotransformation enzymes, eventually leading to effects on steroid and thyroid hormones levels. Furthermore, antagonism of the androgen receptor and the thyroid hormone receptor β, estrogen receptor activation and disruption of transthyretin binding have also been associated with developmental effects in experimental animals.

- PBDEs themselves do not appear to be relevant AhR agonists. Some of the toxic effects reported with technical PBDE mixtures may be due to dioxin-like contaminants. In some studies with PBDEs of a purity in the range of 98-99 % or less, without detailed information on the identity of the contaminants, a crucial role of 'dioxin-like' contaminants in the effects observed cannot be excluded.

- 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.

- There is some evidence for an increase in liver adenoma in rats and liver adenoma and carcinoma in mice treated with decaBDE, which in the view of the CONTAM Panel might be related to a secondary mode of action.

- Results of most epidemiological studies on thyroid homeostasis suggest an association between exposure to PBDEs and altered thyroid hormone regulation. The CONTAM Panel noted that the observed effects on thyroid hormone levels were not always consistent. An association between neuropsychological functioning (motor, cognitive and behavioural performance and mental and physical development in children) and exposure to PBDEs has been described. Exposure to other halogenated contaminants could have confounded the outcome of these studies.

- Cross sectional studies investigating the excess risk for diabetes and/or metabolic syndrome show inconsistent associations with exposure to PBDEs.

- Epidemiological studies on site-specific cancer, effects on fertility and effects on offspring are limited. The CONTAM Panel noted that most of the associations are either based on one single study or are inconsistent between studies. Furthermore, confounding by other compounds and/or life-style factors, small sample size, multiple comparisons and study design hamper interpretation of results.

- Recognizing some similarities in the effects of the various PBDE congeners the CONTAM Panel considered the potential for additivity. The divergent responses of the different toxicological endpoints, and the limited information available, precluded, however, establishment of a common mode of action. Therefore, the CONTAM Panel decided to perform the risk assessment on the basis of the individual congeners.

- Eight congeners were considered by the CONTAM Panel to be of primary interest, however, relevant toxicity data were only available for BDE-47, -99, -153 and -209.

- Based on the information from animal experiments on neurodevelopmental behavioural changes the CONTAM Panel derived $BMDL_{10}$ values (the lower confidence limit for the benchmark dose of a 10 %) for individual PBDE congeners: 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.

- Elimination kinetics between experimental animals and humans differ considerably for most PBDE congeners, therefore the CONTAM Panel converted the derived $BMDL_{10}$s into estimated human intakes associated with the body burden at the $BMDL_{10}$, as basis for the risk assessment. For BDE-47, -99 and -153 the resulting figures are 172, 4.2 and 9.6 ng/kg b.w. For BDE-209 the estimated human dietary intake associated with the body burden at the $BMDL_{10}$ is 1.7 mg/kg b.w.

- The CONTAM Panel concluded that due to the limitations and uncertainties in the database the derivation of health based guidance values for PBDE congeners was not appropriate. Instead, a margin of exposure (MOE) approach was used for the risk characterization.

Risk characterization

- For BDE-47, -153 and -209 the MOE between the intake associated with the body burden at the $BMDL_{10}$ and the estimated dietary intake for the different population groups indicate that current dietary exposure to these PBDEs is unlikely to raise a health concern.

- The MOEs for BDE-99 for young children (1-3 years) with average and high exposure are 1.4 and 0.7, respectively. These MOEs indicate a potential health concern for dietary exposure to BDE-99.

RECOMMENDATIONS

- As numerous products containing PBDEs are still in use, surveillance of PBDEs should continue.
- There is a need for certified reference materials in food other than fish.
- Any further toxicological studies of PBDEs should be conducted with purified and characterised individual congeners most relevant to human exposure, and should be conducted according to appropriate and relevant study designs for risk characterization. Such studies should also include investigations of the mechanisms involved and the determination of tissue concentrations of PBDEs.
- Further epidemiological studies of PBDEs are required focusing on the relevant endpoints and with suitable estimates of human exposure.

DOCUMENTATION PROVIDED TO EFSA

1. Additional French data for EFSA opinions on brominated flame retardants. Submitted by ANSES (French Agency for food, environmental and occupation health safety). Data from the second French Total Diet Study (TDS2) about Brominated flame retardants. Ref. AQR-PC/JRC/2010-308. Provided on 8 October 2010.

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APPENDICES

A. PREVIOUSLY REPORTED PBDES OCCURRENCE RESULTS / LITERATURE DATA

Table A1: Median PBDE-levels (ng/g wet weight (w.w.) otherwise stated) in a selection of fish samples reported in the literature (with a focus on Europe). ΣPBDE includes BDE-209 in the few studies were it has been measured. If medians were not available means were used (as indicated). p = pools. Table adapted from Frederiksen et al. (2009a).

Country	Year	n[a]	Sample[b]	Fat (%)	PBDE congener							Sum[c]		Range sum	Source
					-28	-47	-99	-100	-153	-154	-183		-209		
Fish															
ES (Catalonia)	2005	3 p	Anchovy	n.r.	n.r.	0.3	0.05	0.1	0.008	0.05	0.001	n.r.	n.r.	n.r.	Domingo et al., 2006
CZ	2005	15	Bream	2.1	0.2	7.1	0.1	1	0.2	0.4	–	9.5[d]	n.r.	3.2-20.8[d]	Hajslova et al., 2007
Baltic	2001-2003	3 p	Bream	2.0-6.0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	2.0-4.1[e]	Isosaari et al., 2006
Baltic	2001-2003	3 p	Burbot	0.3-0.5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.06-0.13[e]	Isosaari et al., 2006
TR	2003	17	Carp	0.34	ND	0.13	0.02	ND	ND	ND	n.r.	0.15[f]		0.02–1.3[f]	Erdogrul et al., 2005
CZ	2005	45	Chub	1.8	0.1	3.5	0.1	0.6	0.2	0.3	0.1	4.9[d]	n.r.	0.9-36[d]	Hajslova et al., 2007
BE	2005	2	Cod	0.3	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.04[g]	ND	n.r.	Voorspoels et al., 2007
NL (North Sea)	2003	2 p	Cod	0.8	0.2	0.4	<0.1	0.2	n.r.	<0.1	<0.1	n.r.	<0.1	n.r.	van Leeuwen et al., 2008
DK (Skagerak)	1996	3	Cod liver	50	n.r.	43	3.4	11	0.4	n.r.	n.r.	-	n.r.	n.r.	DVFA, 2003
DK (W. Baltic)	1996	3	Cod liver	66	n.r.	39	2.4	8.6	0.3	n.r.	n.r.	-	n.r.	n.r.	DVFA, 2003
NL[h]	2007	1	Cod (F)	1.5	<0.002	0.02	<0.002	0.005	<0.002	<0.002	<0.002	0.03[i]	<0.004	0.03[i]	van Leeuwen et al., 2009

Table A1: Continued.

Country	Year	n[a]	Sample[b]	Fat (%)	PBDE congener							Sum[c]		Range sum	Source
					-28	-47	-99	-100	-153	-154	-183		-209		
Fish															
ES (Catalonia)	2005	3 p	Cuttlefish	n.r	n.r.	0.004	0.001	0.002	0.0006	0.0005	0.001	n.r.	n.r.	n.r.	Domingo et al., 2006
DK (W. Baltic)	1996	2	Eel	22	n.r.	1.6	0.1	0.7	0.1	n.r.	n.r.	2.5[h]	n.r.	n.r.	DVFA, 2003
NL	2003	14 p	Eel	15.9	0.4	20	0.9	7.6	n.r.	2.1	0.1	n.r.	<0.5	n.r.	van Leeuwen et al., 2008
NL, It	2003	2 p	Eel (F)	28.9	<0.1	1.2	0.3	0.2	n.r.	0.2	0.2	n.r.	<0.5	n.r.	van Leeuwen et al., 2008
NL (Western Scheldt)	2003	2 p	Flounder	1.4	0.3	7.7	0.7	1.6	n.r.	0.6	<0.1	n.r.	<0.1	n.r.	van Leeuwen et al., 2008
Baltic	2001-2003	4 p	Flounder	4.9-10	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.4-1.2[e]	Isosaari et al., 2006
ES (Catalonia)	2005	3 p	Hake	n.r.	n.r.	0.1	0.006	0.03	0.002	0.01	0.005	n.r.	n.r.	n.r.	Domingo et al 2006
DK (W. Baltic)	1998	32	Herring	9.6	n.r.	1.7	0.4	0.3	0.06	n.r.	n.r.	2.5[h]	n.r.	n.r.	DVFA, 2003
DK (North Sea)	1998	8	Herring	5.0	n.r.	4.3	1.0	0.8	0.1	n.r.	n.r.	6.2[h]	n.r.	n.r.	DVFA, 2003
NL (North Sea, Atlantic)	2003	4 p	Herring	17	0.2	3.0	0.9	1.0	n.r.	0.2	<0.1	n.r.	<0.5	n.r.	van Leeuwen et al., 2008
PL	2006	10 p	Herring (smoked)	9.0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.7[j]	n.r.	n.r.	Usydus et al., 2009
PL	2006	30 p	Herring (salted)	6.1	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.8[j]	n.r.	n.r.	Usydus et al., 2009
PL	2006	20 p	Herring (marinated)	14.4	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.5[j]	n.r.	n.r.	Usydus et al., 2009
TR	2003	24	Kalashpa	1.6	ND	0.54	ND	0.04	0.04	0.03	n.r.	0.65[f]		0.2-1.6[f]	Erdogrul et al., 2005
BE	2005	2	Mackerel	16	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.2[g]	ND	n.r.	Voorspoels et al., 2007

Table A1: Continued.

Country	Year	n[a]	Sample[b]	Fat (%)	PBDE congener							Sum[c]	-209	Range sum	Source
					-28	-47	-99	-100	-153	-154	-183				
Fish															
DK (North Sea)	1996	2	Mackerel	22	n.r.	0.9	0.4	0.2	0.08	n.r.	n.r.	1.6[h]	n.r.	n.r.	DVFA, 2003
ES (Catalonia)	2005	3 p	Mackerel	n.r.	n.r.	0.4	0.2	0.1	0.03	0.08	0.009	n.r.	n.r.	n.r.	Domingo et al 2006
PL	2006	10 p	Mackerel (smoked)	20.8	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.8[j]	n.r.	n.r.	Usydus et al., 2009
PL	2006	10 p	Mackerel (fried, vinegar)	15.2	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.4[j]	n.r.	n.r.	Usydus et al., 2009
TR	2003	17	Nose carp	1.6	ND	0.07	ND	ND	ND	ND	n.r.	0.08[f]	n.r.	ND–1.5[f]	Erdogrul et al., 2005
NL[h]	2007	7 p	Pangasius (F)	1.5	<0.002	0.002	0.006	0.01	0.007	0.004	0.006	0.02[i]	0.02	0.007-0.2[i]	van Leeuwen et al., 2009
CZ	2005	20	Perch	1.7	0.2	2.5	0.2	0.5	0.1	0.2	0.1	3.9[d]	n.r.	0.9-6.8[d]	Hajslova et al 2007
Baltic	2001-2003	11 p	Perch	0.8-4.2	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.3-2.8[e]	Isosaari et al., 2006
NL	2003	2 p	Pike Perch	1.0	<0.1	0.04	0.02	0.08	n.r.	0.07	<0.1	n.r.	<0.1	n.r.	van Leeuwen et al., 2008
Baltic	2001-2003	4 p	Pike Perch	0.9-1.7	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.5-0.7[e]	Isosaari et al., 2006
Baltic	2001-2003	6 p	Pike	0.4-0.7	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.2-0.9[e]	Isosaari et al., 2006
ES (Catalonia)	2005	3 p	Red mullet	n.r.	n.r.	0.1	0.08	0.04	0.03	0.1	0.003	n.r.	n.r.	n.r.	Domingo et al., 2006
Baltic	2001-2003	3 p	River Lamprey	15-21	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	3.6-4.3[e]	Isosaari et al., 2006
Baltic	2001-2003	3 p	Roach	1.1-1.7	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.3-0.7[e]	Isosaari et al., 2006
DK, W. Baltic	1996	2	Salmon	6.7	n.r.	2.9	0.3	0.5	0.06	n.r.	n.r.	3.8[h]	n.r.	n.r.	DVFA, 2003

Table A1: Continued.

Country	Year	n[a]	Sample[b]	Fat (%)	PBDE congener							Sum[c]		Range sum	Source
					-28	-47	-99	-100	-153	-154	-183		-209		
Fish															
BE	2005	3	Salmon, smoked	13	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.0[g]	ND	n.r.	Voorspoels et al., 2007
BE	2005	2	Salmon, fresh	13	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.6[g]	ND	n.r.	Voorspoels et al., 2007
NL[h]	2007	7 p	Salmon (F)	14.5	0.03	0.6	0.1	0.2	0.03	0.07	<0.3	1.2[i]	0.05	0.08-1.8[i]	van Leeuwen et al., 2009
ES (Catalonia)	2005	3 p	Salmon	n.r.	n.r.	1.1	0.2	0.2	0.03	0.08	0.007	n.r.	n.r.	n.r.	Domingo et al., 2006
UK	2003	1 p	Salmon	11.9	0.1	1.6	0.7	0.3	n.r.	0.1	<0.1	n.r.	<0.2	n.r.	van Leeuwen et al., 2008
PL (Baltic)	2006	10 p	Salmon (smoked)	11.5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	4.0[j]	n.r.	n.r.	Usydus et al., 2009
NO	2006	10 p	Salmon (smoked)	15.5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	2.2[j]	n.r.	n.r.	Usydus et al., 2009
Baltic	2001-2003	10 p	Salmon	5.3-21	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	2.7-8.1[e]	Isosaari et al., 2006
ES (Catalonia)	2005	3 p	Sardine	n.r.	n.r.	0.3	0.02	0.2	0.01	0.01	0.001	n.r	n.r.	n.r.	Domingo et al., 2006
BE	2005	1	Sardines	7.2	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.001[g]	ND	n.r.	Voorspoels et al., 2007
FR, West coast	n.r.	2 p	Seabass		0.04	1.2	0.009	0.2	0.06	0.06	0.0006	1.6[k]		0.4-2.7[k]	Bodin et al., 2007[l]
ES (Catalonia)	2005	3 p	Sole	n.r.	n.r.	0.1	0.004	0.06	0.005	0.04	0.001	n.r.	n.r.	n.r.	Domingo et al., 2006
PL	2006	10 p	Sprat (smoked)	13.8	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	2.1[j]	n.r.	n.r.	Usydus et al., 2009
Baltic	2001-2003	3 p	Sprat	8.4-14	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.4-1.4[e]	Isosaari et al., 2006
ES (Catalonia)	2005	3 p	Swordfish	n.r.	n.r.	0.3	0.01	0.2	0.02	0.07	0.003	n.r.	n.r.	n.r.	Domingo et al., 2006

Table A1: Continued.

Country	Year	n[a]	Sample[b]	Fat (%)	PBDE congener							Sum[c]		Range sum	Source
					-28	-47	-99	-100	-153	-154	-183		-209		
Fish															
IT (Mediterranean)	2005	17	Swordfish	8.8-9.5	<0.004	0.4	0.03	0.08	N.D.	0.04	N.D.	0.4[n]	n.r.	<0.004-1.9	Corsolini et al., 2008
NL[h]	2007	7 p	Tilapia (F)	3.3	0.003	0.02	0.002	0.003	0.002	0.003	<0.005	0.0[h]	<0.007	0.007-0.04[h]	van Leeuwen et al., 2009
NL[h]	2007	5 p	Trout (F)	6.6	0.008	0.2	0.05	0.04	0.005	0.02	<0.01	0.40[h]	1.8[o]	0.3-3.8[h]	van Leeuwen et al., 2009
BE	2005	2	Trout	3.1	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.3	ND		Voorspoels et al., 2007
CZ	2004	9	Lake trout	6.4	0.2	6.6	3.9	1.0	0.2	0.3	ND	13[o]	0.6	5.8-25	Cheaib et al., 2009
NO	2004	8	Brown trout	10	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	407[p]	nr	n.r.	Mariussen et al., 2008
ES (Catalonia)	2005	3 p	Tuna	n.r.	n.r.	0.03	0.008	0.02	0.004	0.01	0.001	n.r.	n.r.	n.r.	Domingo et al., 2006
Baltic	2001-2003	3 p	Vendace	4.3-5.5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.7-1.3[e]	Isosaari et al., 2006
TR	2003	22	Wels	0.95	ND	0.3	0.03	0.04	0.02	0.03	n.r.	0.5[f]	n.r.	0.06–6.7[f]	Erdogrul et al., 2005
Baltic	2001-2003	3 p	Whitefish	2.1-5.0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.3-2.5[e]	Isosaari et al., 2006
Crustacea															
BE	2005	3	Shrimp	1.3	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.05[g]	ND	n.r.	Voorspoels et al., 2007
NL[h]	2007	6 p	Tropical shrimp (F)	1.25	0.02	0.005	<0.001	0.002	0.002	0.003	<0.002	0.02[i]	0.02	0.008-0.06(i)	van Leeuwen et al., 2009
ES (Catalonia)	2005	3 p	Shrimp	n.r.	n.r.	0.006	0.001	0.001	0.001	0.001	0.001	n.r.	n.r.	n.r.	Domingo et al., 2006
NL (North Sea)	2003	1 p	Shrimp	2.2	<0.1	0.7	0.8	<0.1	ND	0.2	<0.1	n.r.	<0.3	n.r.	van Leeuwen et al., 2008
FR, West coast	n.r.	10 p	Crab		0.001	0.01	0.003	0.002	0.000	0.0002	0.0003	0.02[k]	n.r.	0.007-0.04[k]	Bodin et al., 2007[l]

Table A1: Continued.

Country	Year	n[(a)]	Sample[(b)]	Fat (%)	PBDE congener							Sum[(c)]		Range sum	Source
					-28	-47	-99	-100	-153	-154	-183		-209		
Cephalopods															
ES (Catalonia)	2005	3 p	Squid	n.r.	n.r.	0.06	0.01	0.03	0.007	0.009	0.003	n.r.	n.r.	n.r.	Domingo et al., 2006
Bivalves															
DK	2000	15	Blue mussels	0.7-2.4	n.r.	0.1	0.05	0.01	0.01	n.r.	n.r.	0.17	n.r.	0.08-0.8	Christensen and Platz, 2001
ES (Catalonia)	2005	3 p	Mussel	n.r.	n.r.	0.1	0.06	0.06	0.004	0.005	0.006	n.r.	n.r.	n.r.	Domingo et al., 2006
France, West coast	n.r.	2 p	Mussel		0.002	0.03	0.01	0.0004	0.001	0.001	0.0006	0.06[(k)]	n.r.	0.05-0.07[(k)]	Bodin et al., 2007[(l)]
ES (Catalonia)	2005	3 p	Clam	n.r.	n.r.	0.02	0.02	0.006	0.003	0.004	0.003	n.r.	n.r.	n.r.	Domingo et al., 2006

ES: Spain; CZ: Czech Republic; TR: Turkey; BE: Belgium; NL: The Netherlands; DK: Denmark; PL: Poland; NO: Norway; FR: France; IT: Italy.
(a): P indicates if a sample consisted of pooled individuals (or multiple samples each consisted of pooled individuals)
(b): F indicates that the sample consisted of farmed fish
(c): Sum of BDE-28, -47, -99, -153, -154 and -183. BDE-209 is not included unless otherwise specified.
(d): Sum of BDE-28, -47, -49, -66, -85, -99, -100, -153, -154 and -183.
(e): Upperbound values, Sum of,28, 47, 66, 71, 75, 77, 85, 99, 100, 119, 138, 153, 154, 183, and 190
(f): Sum of BDE-28, -47, -99, -100, -153 and -154.
(g): Median value not available, mean value included instead, Lower bound: <LOQ =zero
(h): Median value not available, mean value included instead
(j): Country where fish was purchased, not necessarily farmed. Sum of BDE-17, -28, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -153, -154, -156, -183, -184, -191, -196, -197 and -209.
(j): Average value: Sum of: 28, 47, 99, 100, 153, 154 and 183
(k): Sum of BDE -17, -28, -47, -66, -71, -85,- 99, -100, -138, -153, -154, -183 and -190.
(l): Calculated from the pg/g dry weight concentrations reported
(m): Sum of BDE-3, -5, -7, -17, -28, -47, -49, -66, -71, -77, -85, -99, -100, -119, -126, -138, -153, -154 and -156.
(n): Outlying value in one sample
(o): Sum of BDE-28, -47, -49, -66, -99, -100, -119, -153, -154 and -209. Calculated from average fat weight values and average fat content.
(p): Sum of BDE-28, -47, -49, -66, -99, -100, -119, -153 and -154.

Table A2: PBDE-levels (median concentration and [range]) (ng/g fat) in **meat samples** reported in the literature carried out in European countries.

Country, Year	*n*	Sample	PBDE congeners								Reference
			BDE-28	**BDE-47**	**BDE-99**	**BDE-100**	**BDE-153**	**BDE-154**	**BDE-183**	**Sum 7 PBDEs**	**BDE-209**	
DE, 2006	4	Meat	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.066 (c)	n.a.	Kotz et al., 2006[(a)(b)(g)]
DE, 2007-2009	12	Liver, lamb	0.0145 [<0.010-0.0233]	0.142 [0.0357-0.348]	0.120 [0.0238-0.571]	0.0484 [<0.020-0.112]	0.0969 [<0.030-0.286]	0.0394 [<0.030-0.0394]	<0.150	n.r.	<0.500	Päpke et al., 2009[(a)]
EE, 2007	3	Meat, pork	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	[0.48-3.90][(d)]	n.a.	Roots et al., 2007[(f)]
ES, 2003-2005	10	Meat, pork	< 0.0004	0.00873 [0.00232-0.0623]	0.00941 [0.00156-0.030]	0.00131 [<0.00020-21.5]	0.00276 [<0.00015-0.0112]	0.0005 [0.00009-0.00333]	0.00153 [<0.00001-0.138]	n.r.	0.00794 [<0.0001-2.066]	Gómara et al., 2006[(a)(b)]
	10	Meat, chicken	<0.00097	0.013 [0.0096-0.0546]	0.0093 [0.00122-0.0234]	0.00199 [<0.00027-0.0137]	0.00515 [0.00078-0.00828]	<0.00048	0.00113 [0.00019-0.326]	n.r.	0.0116 [<0.00024-0.416]	
	10	Transformed meat and cured ham	<0.00065	0.0227 [0.00474-0.0813]	0.025 [<0.00042-0.0681]	0.00003 [<0.00030-0.019]	0.00550 [<0.00063-0.0351]	0.00125 [<0.00035-0.00714]	0.00070 [<0.00009-0.0999]	n.r.	0.0113 [<0.00048-0.495]	
FI, 2003-2005	3	Meat, pork	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.77 [(e)] [0.61-1.43]	n.r.	Kiviranta et al., 2006[(f)]
	3	Meat, bovine	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.60 [(e)] [0.59-0.68]	n.r.	
	9	Meat, chicken	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	2.58 [(e)] [0.93-4.04]	n.r.	
	3	Meat, sheep	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.092 [0.065-0.13] [(e)]	n.r.	

Table A2: Continued.

Country, Year	*n*	Sample	PBDE congeners								Reference
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	Sum 7 PBDEs	BDE-209	
FI, 2003-2005	3	Meat, elk	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.53 (e) [0.40-2.79]	n.r.	
	4	Meat, reindeer	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.72 (e) [1.26-2.19]	n.r.	
	4	Meat, calf	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	1.52 (e) [1.35-1.57]	n.r.	
	3	Liver, bovine	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.14 (e) [0.11-0.37]	n.r.	
	3	Liver, pork	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.47 (e) [0.20-0.73]	n.r.	

n.a: not analysed; n.r.: not reported in the original publication; DE: Germany; EE; Estonia; ES: Spain; FI: Finland.
(a): Original values expressed in pg/g.
(b): fresh weight
(c): Sum PBDEs: BDE-15,-17, **-28**, **-47**, -66, -71, -75, -77, -85, **-99**, **-100**, -119, -126, -138, **-153**, **-154**, **-183**, -190.
(d): Sum PBDEs: BDE-**47**, **-99**, **-100**, **-153**, **-154**.
(e): Sum PBDEs: BDE-**28**, **-47**, -66, -71, -75, -77, -85, **-99**, **-100**, -119, -138, **-153**, **-154**, **-183**, **-209**.
(f): Upper-bound levels.
(g): Mean values.

Table A3: PBDE-levels (median concentration and [range]) (ng/g fat) in eggs, dairy products, oils and vegetables reported in the literature carried out in European countries.

Country, year	*n*	Sample	PBDE congeners									References
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	Sum 7 PBDEs	BDE-209	
Eggs												
BE, 2006 (Autumn) (Spring)	 10 10	Eggs, home-produced	 < 0.15 < 0.15	 0.28 < 0.15	 0.33 < 0.15	 0.15 < 0.15	 0.19 < 0.15	 < 0.15 < 0.15	 < 0.15 < 0.15	 n.r. n.r.		Covaci et al., 2009
ES, 2003-2005	5	Eggs	0.00027 [<0.00017-0.00125]	0.00825 [0.00216-0.0416]	0.00794 [<0.00186-0.0539]	<0.00135	0.00691 [<0.0005-0.01567]	0.00037 [<0.00024-0.00246]	0.00191 [0.00031-0.0143]	n.r.	0.0369 [0.00171-0.446]	Gómara et al., 2006[(a)(b)]
DE, 2006	4	Eggs	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.470[(e)]	n.a.	Kotz et al., 2006[(a)(b)(j)]
FI, 2003-2005	16	Eggs	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	1.42 [0.82-8.18][(d)]	n.r.	Kiviranta et al., 2006[(h)]
Milk												
CH, 2004	55	Milk	n.r.	n.r.	n.r.	n.r.	[0.005-0.017]	n.a.	[0.013-0.045]	0.203[(g)]	n.a.	Grümping et al., 2006[(i)]
DE, 2006	4	Milk	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.005[(e)]	n.a.	Kotz et al., 2006[(a)(b)(j)]
DE, 2007-09	22	Milk	0.0028 [0.002.7-0.003]	0.0347 [0.0084-0.105]	0.0198 [0.0016-0.089]	0.0069 [0.0021-0.018]	0.0087 [0.0011-0.075]	0.0045 [0.0035-0.024]	<0.020	n.r.	<0.500	Päpke et al., 2009[(a)]
EE, 2007	3	Milk	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	[0.93-1.40][(f)]	n.a.	Roots et al., 2007[(h)]
ES, 2003-2005	7	Milk	0.00007 [<0.00002-0.00031]	0.00421 [0.00108-0.00956]	0.00303 [0.00076-0.00845]	0.00077 [0.00011-0.00238]	0.00038 [0.0001-0.00177]	0.00026 [<0.00004-0.00068]	0.00023 [0.00008-0.00761]	n.r.	0.00051 [<0.00006-0.126]	Gómara et al., 2006[(b)]
FI, 2003-2005	13	Milk	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	1.51 [0.40-1.66][(d)]	n.r.	Kiviranta et al., 2006[(h)]
IR, 2004	12	Milk	[0.016-0.035]	n.r.	n.r.	n.r.	[0.018-0.075]	n.a.	[0.031-0.098]	0.407[(g)]	n.a.	Grumping et al., 2006[(i)]

Table A3: Continued.

Country, year	*n*	Sample	PBDE congeners									References
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	Sum 7 PBDEs	BDE-209	
Butter												
DE, 2006	4	Butter	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.210[(e)]	n.a.	
EE, 2007	2	Butter	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	[1.40-1.80][(f)]	n.a.	
ES, 2003-2005	4	Butter	<0.00416	0.0509 [0.0131-0.0676]	0.0223 [0.00921-0.0554]	0.00247 [<0.00126-0.0125]	0.00357 [<0.00046-0.0124]	0.00379 [0.00164-0.00395]	0.029.8 [0.00231-0.0427]	n.r.	0.428 [0.011.9-0.554]	
Cheese and cream												
DE, 2007-2009	12	Cheese	<0.005	0.0430 [0.0272-0.146]	0.0168 [0.0122-0.113]	0.0241 [0.0207-0.027]	0.0266 [0.0252-0.028]	<0.015	<0.020	n.r.	<0.500	Päpke et al., 2009[(a)]
ES, 2003-2005	5	Cheese	0.00146 [0.00020-0.00555]	0.0314 [0.00556-0.0623]	0.0181 [0.00517-0.0336]	0.00367 [<0.00014-0.00532]	0.0079 [0.00126-0.0207]	0.00224 [0.00025-0.00294]	0.00129 [0.00010-0.00221]	n.r.	0.00464 [<0.00015-0.0217]	Gómara et al., 2006[(b)]
ES, 2003-2005	2	Cream	0.00047 [<0.00014-0.0008]	0.01504 [0.00382-0.0263]	0.00823 [0.00296-0.0149]	0.00136 [0.001-0.00.71]	0.00168 [0.00082-0.00254]	<0.00043	0.00087 [0.00065-0.00109]	n.r.	0.00275 [<0.00055-.00494]	Gómara et al., 2006[(a)(b)]
FI, 2003-2005	5	Cheese	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	0.39[(d)] [0.27-0.85]	n.r.	Kiviranta et al., 2006[(h)]
Oil												
BE, 2006	69	Fish oil supplements	n.a.	0.42	< 0.1	< 0.1	n.r.	n.r.	n.r.	0.59 [<0.2-44]	n.a.	Covaci et al., 2006[(k)]
ES, 2003-05	16	Oil	0.00085 [<0.00024-0.00137]	0.0216 [0.00665-0.0553]	0.0139 [<0.00108-0.0545]	0.00412 [<0.00032-0.0195]	0.00538 [<0.00063-0.0159]	0.00182 [<0.00054-0.0107]	0.00097 [<0.00005-0.160]	n.r.	0.0249 [<0.0004-2.482]	Gómara et al., 2006[(a)(b)]
CH, 2006	6	Fish oil supplements	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.069-3.8	0.12-1.5 [(c)]	Zennegg and Schmid, 2006

Table A3: Continued.

Country, year	*n*	Sample	PBDE congeners									References
			BDE-28	BDE-47	BDE-99	BDE-100	BDE-153	BDE-154	BDE-183	Sum 7 PBDEs	BDE-209	
UK, 2001-2002	7	Dietary oil supplements (cod liver oil)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	14.6-34.2	n.a.	Jacobs et al., 2004
	6	Dietary oil supplements (fish oil)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.8-2.7	n.a.	
	4	Dietary oil supplements (fish and vegetable oil)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	nd-1.9	n.a.	
	4	Dietary oil supplements	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	nd	n.a.	
Vegetables												
DE, 2006	12	Kale	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	0.066[(e)]	n.a.	Kotz et al., 2006[(a)(b)(j)]

n.a: not analysed; n.r.: not reported in the original publication; nd: not detected; BE: Belgium; ES: Spain; DE: Germany; FI: Finalnd: CH: Switzerland; EE: Estonia; IR: Ireland; UK: United Kingdom.
(a): Original values expressed in pg/g.
(b): Fresh weight.
(c): values reported to be very close or even below the method blank.
(d): Sum PBDEs: BDE-**47**, **-99**, -66, -71, -75, -77, -85, **-99**, **-100**, -119, -138, **-153**, **-154**, **-209**.
(e): Sum PBDEs: BDE-15, -17, **-28**, **-47**, -66, -71, -75, -77, -85, **-99**, **-100**, -119, -126, -138, **-153**, **-154**, **-183**, -190.
(f): Sum PBDEs: BDE-**47**, **-99**, **-100**, **-153**, **-154**.
(g): Sum PBDEs: BDE-**28**, **-47**, **-99**, **-100**, **-153**, **-183**.
(h): Upper-bound levels.
(i): Original values expressed in ng/kg.
(j): Mean values.
(k): ng/g oil.

B. CURRENT OCCURRENCE DATA ON PBDEs (TABLES)

Table B1: Statistical description of concentrations of BDE-28, -47, -99, -100, -153, -154 and -183 and the sum of these seven congeners (number of analysed samples, mean and percentage of not detected), calculated on 18,410 analytical records (2,630 samples) across the food categories defined by Commission Regulation (EC) No 1881/2006, Annex, Section 5. PBDE levels (mean concentration) are reported on fat (ng/g fat) or wet weight basis (ng/g w.w.) according to the different food categories as requested by the above mentioned legislation. The mean fat content calculated from the original samples is also reported (%).

Food categories	N	TYPE	Individual PBDE congeners and sum of seven PBDE congeners															Mean % fat in original sample
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		Sum 7 PBDEs	
			MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	
Meat and meat products ruminants – ng/g fat	71	LB	0.00	76%	0.08	17%	0.07	11%	0.02	44%	0.04	41%	0.01	62%	0.02	69%	0.24	8.97
	71	UB	0.02	76%	0.10	17%	0.08	11%	0.03	44%	0.06	41%	0.02	62%	0.05	69%	0.36	8.97
Meat and meat products poultry – ng/g fat	58	LB	0.01	84%	0.09	40%	0.11	22%	0.03	45%	0.02	47%	0.02	52%	0.02	60%	0.30	8.02
	58	UB	0.08	84%	0.16	40%	0.17	22%	0.10	45%	0.12	47%	0.11	52%	0.13	60%	0.87	8.02
Meat and meat products pigs – ng/g fat	40	LB	0.00	93%	0.14	33%	0.12	15%	0.02	40%	0.03	25%	0.01	50%	0.03	60%	0.35	10.32
	40	UB	0.03	93%	0.18	33%	0.15	15%	0.04	40%	0.06	25%	0.04	50%	0.06	60%	0.56	10.32
Liver and products terrestrial animals – ng/g fat	35	LB	0.00	83%	0.19	5.7%	0.19	5.7%	0.04	37%	0.05	26%	0.02	60%	0.03	40%	0.52	7.32
	35	UB	0.02	83%	0.20	5.7%	0.20	5.7%	0.05	37%	0.06	26%	0.03	60%	0.05	40%	0.61	7.32
Muscle meat fish and fish products excl. eel – ng/g w.w.	1419	LB	0.03	23%	0.40	7.6%	0.09	17%	0.09	14%	0.02	39%	0.04	24%	0.02	68%	0.67	4.67
	1419	UB	0.03	23%	0.40	7.6%	0.09	17%	0.09	14%	0.02	39%	0.04	24%	0.03	68%	0.71	4.67
Muscle meat eel – ng/g w.w.	54	LB	0.08	7.4%	8.65	5.6%	0.38	11%	4.67	5.6%	0.47	5.6%	0.56	5.6%	0.03	37%	14.85	14.93
	54	UB	0.08	7.4%	8.65	5.6%	0.39	11%	4.68	5.6%	0.47	5.6%	0.56	5.6%	0.04	37%	14.87	14.93
Raw milk and dairy products incl. butter – ng/g fat	195	LB	0.00	91%	0.10	39%	0.08	39%	0.01	59%	0.02	57%	0.00	76%	0.01	90%	0.22	30.51
	195	UB	0.07	91%	0.17	39%	0.14	39%	0.07	59%	0.11	57%	0.10	76%	0.11	90%	0.76	30.51
Hen eggs and egg products – ng/g fat	51	LB	0.00	88%	0.09	37%	0.13	12%	0.04	16%	0.05	18%	0.02	35%	0.04	49%	0.36	21.20
	51	UB	0.03	88%	0.13	37%	0.15	12%	0.06	16%	0.07	18%	0.04	35%	0.06	49%	0.54	21.20
Fat ruminants – ng/g fat	19	LB	0.00	100%	0.10	16%	0.11	16%	0.02	47%	0.06	42%	0.01	53%	0.11	74%	0.41	87.88
	19	UB	0.08	100%	0.16	16%	0.17	16%	0.10	47%	0.19	42%	0.14	53%	0.26	74%	1.09	87.88

Table B1: Continued.

Food categories	N	TYPE	Individual PBDE congeners and sum of seven PBDE congeners														Mean % fat in original sample
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		Sum 7 PBDEs	
			MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	ND	MEAN	
Fat poultry – ng/g fat	21	LB	0.00	100%	0.16	4.8%	0.22	0%	0.04	29%	0.06	4.8%	0.02	48%	0.01	67%	0.51	82.05
	21	UB	0.03	100%	0.17	4.8%	0.22	0%	0.06	29%	0.06	4.8%	0.04	48%	0.05	67%	0.62	82.05
Fat pigs – ng/g fat	25	LB	0.00	88%	0.13	24%	0.17	24%	0.02	56%	0.05	36%	0.01	60%	0.01	64%	0.39	86.74
	25	UB	0.05	88%	0.16	24%	0.20	24%	0.06	56%	0.08	36%	0.06	60%	0.08	64%	0.69	86.74
Mixed animal fats – ng/g fat	19	LB	0.00	95%	0.08	16%	0.12	5.3%	0.04	32%	0.14	5.3%	0.02	42%	0.02	47%	0.43	87.05
	19	UB	0.05	95%	0.11	16%	0.14	5.3%	0.08	32%	0.20	5.3%	0.09	42%	0.12	47%	0.80	87.05
Vegetable oils and fats – ng/g fat	42	LB	0.00	100%	0.02	69%	0.02	74%	0.00	95%	0.00	90%	0.00	95%	0.01	95%	0.05	96.53
	42	UB	0.11	100%	0.13	69%	0.13	74%	0.11	95%	0.16	90%	0.16	95%	0.17	95%	0.97	96.53
Marine oils – ng/g fat	3	LB	0.08	33%	0.47	0%	0.11	0%	0.07	0%	0.01	.00%	0.04	0%	0.00	100%	0.79	100.00
	3	UB	0.08	33%	0.47	0%	0.11	0%	0.07	.0%	0.01	.00%	0.04	0%	0.01	100%	0.80	100.00
Fish liver and products – ng/g fat	211	LB	0.32	1.4%	6.02	0%	0.21	.95%	1.02	.47%	0.03	45%	0.58	1.4%	0.01	70%	8.19	48.20
	211	UB	0.32	1.4%	6.02	0%	0.21	.95%	1.02	.47%	0.04	45%	0.59	1.4%	0.03	70%	8.23	48.20
Fruits, vegetables and cereals – ng/g w.w.	16	LB	0.00	69%	0.00	69%	0.00	75%	0.00	75%	0.00	69%	0.00	81%	0.00	56%	1.14	0.32
	16	UB	0.00	69%	0.01	69%	0.01	75%	0.00	75%	0.00	69%	0.00	81%	0.00	56%	1.51	0.32
Other products – ng/g w.w.	317	LB	0.04	49%	1.07	11%	0.25	17%	0.23	23%	0.07	40%	0.11	34%	0.01	64%	0.88	22.81
	317	UB	0.06	49%	1.08	11%	0.27	17%	0.25	23%	0.10	40%	0.13	34%	0.05	64%	0.94	22.81
Infant and baby food – ng/g w.w.	34	LB	0.01	74%	0.50	32%	0.26	38%	0.04	59%	0.01	79%	0.01	74%	0.00	94%	0.82	2.73
	34	UB	0.11	74%	0.56	32%	0.32	38%	0.14	59%	0.15	79%	0.16	74%	0.15	94%	1.59	2.73

N: number of samples; LB: lower bound; UB: upper bound. The number of figures after the decimal point is the same for all food categories and does not reflect precision. (ND (%): indicates the percentage of results below the LOD or the limit of quantification.

Table B2: Percentiles values (90th, 95th and 99th percentiles) of concentrations of BDE-28, -47, -99, -100, -153, -154, -183 calculated on 18,410 analytical records (2,630 samples) across the food categories defined by Commission Regulation (EC) No 1881/2006, Annex, Section 5.

			Individual congeners																				
			BDE-28			BDE-47			BDE-99			BDE-100			BDE-153			BDE-154			BDE-183		
			P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99
Food categories	N	TYPE	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
Meat and meat products ruminants – ng/g fat	71	LB	0.01	0.01	0.05	0.19	0.30	0.60	0.15	0.18	0.75	0.04	0.10	0.14	0.15	0.18	0.42	0.02	0.05	0.06	0.04	0.07	0.79
	71	UB	0.01	0.20	0.20	0.20	0.30	0.60	0.18	0.20	0.75	0.10	0.20	0.20	0.18	0.20	0.42	0.05	0.20	0.20	0.07	0.20	0.79
Meat and meat products poultry – ng/g fat	58	LB	0.01	0.06	0.13	0.24	0.35	0.55	0.26	0.46	0.79	0.08	0.13	0.16	0.08	0.12	0.19	0.06	0.08	0.13	0.06	0.13	0.35
	58	UB	0.20	0.50	0.92	0.35	0.50	0.92	0.50	0.51	0.92	0.20	0.50	0.92	0.20	1.00	1.00	0.20	1.00	1.00	0.26	1.00	1.00
Meat and meat products pigs – ng/g fat	40	LB	0.00	0.02	0.02	0.41	0.55	0.76	0.27	0.42	0.57	0.04	0.06	0.07	0.09	0.11	0.15	0.04	0.05	0.06	0.11	0.15	0.29
	40	UB	0.20	0.20	0.20	0.41	0.55	0.76	0.27	0.42	0.57	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.29
Liver and products terrestrial animals – ng/g fat	35	LB	0.01	0.01	0.02	0.40	0.62	0.77	0.34	0.88	1.12	0.09	0.16	0.21	0.13	0.16	0.23	0.05	0.07	0.10	0.08	0.11	0.30
	35	UB	0.05	0.05	0.05	0.40	0.62	0.77	0.34	0.88	1.12	0.09	0.16	0.21	0.13	0.16	0.23	0.05	0.07	0.10	0.10	0.11	0.30
Muscle meat fish and fish products excl. eel – ng/g w.w.	1419	LB	0.07	0.09	0.24	1.15	1.59	2.42	0.24	0.34	0.65	0.24	0.34	0.67	0.04	0.06	0.12	0.11	0.15	0.25	0.01	0.03	0.15
	1419	UB	0.07	0.10	0.24	1.15	1.59	2.42	0.24	0.34	0.65	0.24	0.34	0.67	0.05	0.07	0.20	0.11	0.15	0.25	0.05	0.05	0.20
Muscle meat eel – ng/g w.w.	54	LB	0.18	0.25	0.57	22.56	31.25	56.57	1.21	1.48	2.29	12.06	15.10	31.10	1.34	1.51	2.43	1.42	2.31	3.76	0.08	0.09	0.31
	54	UB	0.18	0.25	0.57	22.56	31.25	56.57	1.21	1.48	2.29	12.06	15.10	31.10	1.34	1.51	2.43	1.42	2.31	3.76	0.09	0.10	0.31
Raw milk and dairy products incl. butter – ng/g fat	195	LB	0.00	0.02	0.03	0.25	0.42	0.94	0.20	0.29	0.77	0.03	0.04	0.20	0.05	0.08	0.33	0.01	0.02	0.07	0.01	0.04	0.10
	195	UB	0.20	0.50	0.50	0.42	0.50	0.94	0.32	0.50	0.77	0.20	0.50	0.50	0.20	1.00	1.00	0.20	1.00	1.00	0.20	1.00	1.00
Hen eggs and egg products – ng/g fat	51	LB	0.00	0.01	0.02	0.22	0.30	0.56	0.21	0.27	2.05	0.04	0.07	0.85	0.07	0.13	0.74	0.02	0.04	0.42	0.07	0.09	0.86
	51	UB	0.11	0.20	0.20	0.22	0.30	0.56	0.21	0.27	2.05	0.11	0.20	0.85	0.20	0.20	0.74	0.11	0.20	0.42	0.17	0.20	0.86
Fat ruminants – ng/g fat	19	LB	0.00	0.00	0.00	0.18	0.23	0.23	0.28	0.36	0.36	0.07	0.15	0.15	0.19	0.45	0.45	0.06	0.06	0.06	0.07	1.89	1.89
	19	UB	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.89	1.89
Fat poultry – ng/g fat	21	LB	0.00	0.00	0.00	0.28	0.29	0.35	0.36	0.37	0.50	0.11	0.12	0.15	0.08	0.08	0.12	0.05	0.06	0.06	0.03	0.03	0.04
	21	UB	0.05	0.05	0.05	0.28	0.29	0.35	0.36	0.37	0.50	0.11	0.12	0.15	0.08	0.08	0.12	0.05	0.06	0.06	0.10	0.10	0.10
Fat pigs – ng/g fat	25	LB	0.00	0.00	0.00	0.24	0.34	0.37	0.29	0.44	0.74	0.04	0.07	0.09	0.10	0.14	0.27	0.04	0.04	0.12	0.05	0.05	0.08
	25	UB	0.13	0.13	0.13	0.24	0.34	0.37	0.29	0.44	0.74	0.13	0.13	0.13	0.13	0.14	0.27	0.13	0.13	0.13	0.13	0.13	0.13
Mixed animal fats – ng/g fat	19	LB	0.00	0.03	0.03	0.11	0.36	0.36	0.17	0.18	0.18	0.12	0.15	0.15	0.20	0.81	0.81	0.07	0.10	0.10	0.09	0.09	0.09
	19	UB	0.05	0.50	0.50	0.36	0.50	0.50	0.18	0.50	0.50	0.15	0.50	0.50	0.81	1.00	1.00	0.10	1.00	1.00	0.10	1.00	1.00

Table B2: Continued.

			Individual congeners																				
			BDE-28			BDE-47			BDE-99			BDE-100			BDE-153			BDE-154			BDE-183		
			P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99	P90	P95	P99
Food categories	**N**	**TYPE**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**	**VAL**
Vegetable oils and fats – ng/g fat	42	LB	0.00	0.00	0.00	0.06	0.09	0.15	0.06	0.11	0.13	0.00	0.00	0.02	0.00	0.02	0.05	0.00	0.00	0.03	0.00	0.00	0.23
	42	UB	0.13	0.50	0.50	0.15	0.50	0.50	0.13	0.50	0.50	0.13	0.50	0.50	0.13	1.00	1.00	0.13	1.00	1.00	0.23	1.00	1.00
Marine oils – ng/g fat	3	LB	0.20	0.20	0.20	0.83	0.83	0.83	0.15	0.15	0.15	0.10	0.10	0.10	0.02	0.02	0.02	0.05	0.05	0.05	0.00	0.00	0.00
	3	UB	0.20	0.20	0.20	0.83	0.83	0.83	0.15	0.15	0.15	0.10	0.10	0.10	0.02	0.02	0.02	0.05	0.05	0.05	0.03	0.03	0.03
Fish liver and products – ng/g fat	211	LB	0.65	0.87	1.62	16.41	21.98	34.09	0.53	1.14	2.10	2.42	5.54	7.44	0.08	0.20	0.36	1.44	2.45	5.48	0.02	0.03	0.43
	211	UB	0.65	0.87	1.62	16.41	21.98	34.09	0.53	1.14	2.10	2.42	5.54	7.44	0.12	0.22	0.36	1.44	2.45	5.48	0.02	0.07	0.43
Fruits, vegetables and cereals – ng/g w.w.	16	LB	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	16	UB	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Other products – ng/g w.w.	317	LB	0.08	0.19	0.56	2.02	6.71	9.90	0.48	1.24	2.79	0.48	1.13	2.01	0.16	0.31	0.97	0.25	0.57	1.37	0.04	0.06	0.23
	317	UB	0.11	0.29	0.56	2.02	6.71	9.90	0.50	1.24	2.79	0.50	1.13	2.01	0.19	0.61	1.00	0.34	0.73	1.37	0.10	0.12	1.00
Infant and baby food – ng/g w.w.	34	LB	0.00	0.09	0.40	0.91	3.80	8.80	0.39	3.20	3.20	0.02	0.29	0.82	0.01	0.07	0.10	0.01	0.15	0.20	0.00	0.02	0.07
	34	UB	0.50	0.50	0.74	0.91	3.80	8.80	0.50	3.20	3.20	0.50	0.74	0.82	0.74	1.00	1.00	0.74	1.00	1.00	0.74	1.00	1.00

N: number of samples; LB: lower bound; UB: upper bound; P90: 90th percentile; P95: 95th percentile; P99: 99th percentile.
The number of figures after the decimal point is the same for all food categories and does not reflect precision. If N<130 then the calculated percentiles should be considered only as an indicative value due to limited number of data (EFSA, 2008).

Table B3: Percentiles values (90th, 95th and 99th percentiles) of the concentrations of the sum of seven congeners (BDE-28, -47, -99, -100, -153, -154 and -183) calculated on 18,410 analytical records (2,630 samples) across the food categories defined by Commission Regulation (EC) No 1881/2006, Annex, Section 5. Concentration levels are reported on fat (ng/g fat) or wet weight basis (ng/g w.w.) according to the different food categories as requested by the above mentioned legislation.

			Sum of 7 selected congeners		
			P90	P95	P99
Food categories	N	TYPE	VAL	VAL	VAL
Meat and meat products ruminants – ng/g fat	71	LB	0.60	0.73	1.69
	71	UB	0.73	1.40	1.69
Meat and meat products poultry – ng/g fat	58	LB	0.78	0.91	1.85
	58	UB	1.40	5.00	6.43
Meat and meat products pigs – ng/g fat	40	LB	0.83	1.07	1.45
	40	UB	1.40	1.40	1.46
Liver and products terrestrial animals – ng/g fat	35	LB	1.20	1.97	2.29
	35	UB	1.26	1.98	2.30
Muscle meat fish and fish products excl. eel – ng/g w.w.	1419	LB	1.86	2.50	4.23
	1419	UB	1.88	2.59	4.25
Muscle meat eel – ng/g w.w.	54	LB	37.89	51.24	95.44
	54	UB	37.89	51.24	95.44
Raw milk and dairy products incl. butter – ng/g fat	195	LB	0.55	0.77	2.04
	195	UB	1.40	5.00	5.00
Hen eggs and egg products – ng/g fat	51	LB	0.60	0.72	4.68
	51	UB	1.32	1.40	4.69
Fat ruminants – ng/g fat	19	LB	0.85	2.77	2.77
	19	UB	5.00	5.00	5.00
Fat poultry – ng/g fat	21	LB	0.71	0.84	1.05
	21	UB	0.90	0.91	1.07
Fat pigs – ng/g fat	25	LB	0.72	0.95	1.59
	25	UB	1.09	1.15	1.74
Mixed animal fats – ng/g fat	19	LB	0.88	1.42	1.42
	19	UB	1.43	5.00	5.00
Vegetable oils and fats – ng/g fat	42	LB	0.13	0.23	0.61
	42	UB	0.91	5.00	5.00
Marine oils – ng/g fat	3	LB	1.34	1.34	1.34
	3	UB	1.37	1.37	1.37
Fish liver and products – ng/g fat	211	LB	20.47	33.68	45.80
	211	UB	20.48	33.69	45.81
Fruits, vegetables and cereals – ng/g w.w.	16	LB	4.56	10.28	10.28
	16	UB	4.56	10.28	10.28
Other products – ng/g w.w.	317	LB	1.42	6.19	13.10
	317	UB	1.57	6.21	13.12
Infant and baby food – ng/g w.w.	34	LB	1.30	7.00	13.54
	34	UB	5.00	10.70	13.54

N: number of samples; LB: lower bound; UB: upper bound; P90: 90th percentile; P95: 95th percentile; P99: 99th percentile. The number of figures after the decimal point is the same for all food categories and does not reflect precision. If N<130 then the calculated percentiles should be considered only as an indicative value due to limited number of data (EFSA, 2008).

Table B4: Statistical description of BDE-209, including number of analysed samples, mean concentration, percentage of not detected and percentiles values (90th, 95th and 99th percentiles). The reported values are calculated across the food categories defined by Commission Regulation (EC) No 1881/2006, Annex, Section 5. Concentration levels are reported on fat (ng/g fat) or wet weight basis (ng/g w.w.) according to the different food categories as requested by the avobe mentioned legislation.

		BDE-209					
Food categories	**TYPE**	**n**	**ND (%)**	**MEAN**	**P90**	**P95**	**P99**
Meat and meat products ruminants	LB	46	0.64	0.54	1.36	2.06	7.44
	UB	46	3.83	0.54	7.44	23.68	54.09
Meat and meat products poultry	LB	41	1.88	0.54	5.30	11.00	22.00
	UB	41	4.36	0.54	11.00	18.37	47.98
Meat and meat products pigs	LB	17	0.24	0.59	0.83	0.94	0.94
	UB	17	5.30	0.59	23.78	42.12	42.12
Liver and products terrestrial animals	LB	37	0.44	0.57	1.32	3.12	5.11
	UB	37	1.37	0.57	3.82	5.11	7.97
Muscle meat fish and fish products excl. eel	LB	409	0.03	0.69	0.07	0.12	0.36
	UB	409	0.38	0.69	1.26	1.63	2.02
Muscle meat eel	LB	37	0.06	0.86	0.12	0.49	0.98
	UB	37	0.91	0.86	3.39	4.56	4.78
Raw milk and dairy products incl. butter	LB	196	0.39	0.79	0.37	1.30	13.68
	UB	196	1.80	0.79	3.04	5.67	14.72
Hen eggs and egg products	LB	11	0.76	0.18	1.45	2.26	2.26
	UB	11	1.17	0.18	2.26	2.30	2.30

		BDE-209					
Food categories	**TYPE**	**n**	**ND (%)**	**MEAN**	**P90**	**P95**	**P99**
Fat ruminants	LB	22	0.04	0.82	0.15	0.29	0.30
	UB	22	1.07	0.82	2.55	2.60	2.60
Fat poultry	LB	26	0.05	0.88	0.13	0.43	0.83
	UB	26	1.26	0.88	2.59	2.65	2.73
Fat pigs	LB	24	0.01	0.96	0.00	0.00	0.17
	UB	24	1.41	0.96	2.50	2.70	2.70
Mixed animal fats	LB	20	0.07	0.80	0.33	0.56	0.65
	UB	20	0.88	0.80	1.63	1.65	1.65
Vegetable oils and fats	LB	41	0.08	0.85	0.10	0.20	2.40
	UB	41	1.56	0.85	2.60	2.60	2.60
Fish liver and products	LB	1	0.90	0.00	0.90	0.90	0.90
	UB	1	0.90	0.00	0.90	0.90	0.90
Fruits, vegetables and cereals	LB	44	0.12	0.77	0.12	0.15	4.67
	UB	44	0.15	0.77	0.12	0.15	4.67
Other products	LB	264	3.29	0.38	2.70	5.15	52.54
	UB	264	3.69	0.38	3.45	6.10	52.54
Infant and baby food	LB	36	1.66	0.44	3.70	7.79	17.00
	UB	36	1.95	0.44	3.70	7.79	17.00

N: number of samples; LB: lower bound; UB: upper bound; P90: 90th percentile; P95: 95th percentile; P99: 99th percentile. (ND (%): indicates the percentage of results below the LOD or the limit of quantification.The number of figures after the decimal point is the same for all food categories and does not reflect significant figures for each reported value. If N<130 then the calculated percentiles should be considered only as an indicative value due to limited number of data (EFSA, 2008).

Table B5: Statistical description of concentrations of BDE-28, -47, -99, -100, -153, -154 and -183 and the sum of these seven congeners (number of analysed samples, mean and percentage of not dectected), calculated on 18,410 analytical records (2,630 samples) across eight broad food categories of the FoodEx food classification system. PBDE levels (mean concentration) are reported on fat (ng/g fat) or wet weight basis (ng/g w.w.) according to the different food categories. The mean fat content calculated from the original samples is also reported (%).

		Individual PBDE congeners and sum of seven PBDE congeners																								
		BDE-28			BDE-47			BDE-99			BDE-100			BDE-153			BDE-154			BDE-183			Sum 7 PBDEs			Mean (%)
Food categories (FoodEx_Level 1)	**TYPE**	**N**	**MEAN**	**ND (%)**	**N**	**MEAN**	**ND (%)**	**N**	**MEAN**	**ND (%)**	**N**	**MEAN**	**ND (%)**	**N**	**MEAN**	**ND (%)**	**N**	**MEAN**	**ND (%)**	**N**	**MEAN**	**ND (%)**	**N**	**MEAN**	**ND (%)**	**fat in original sample**
Results expressed on fat basis (ng/g fat)																										
Eggs and egg products	LB	105	0.01	84%	105	0.14	24%	105	0.21	12%	105	0.07	19%	105	0.07	19%	105	0.03	41%	105	0.03	47%	105	0.56	-	15.57
	UB	105	0.04	84%	105	0.18	24%	105	0.25	12%	105	0.10	19%	105	0.12	19%	105	0.08	41%	105	0.08	47%	105	0.84	-	15.57
Milk and dairy products	LB	143	0.00	89%	143	0.12	37%	143	0.09	39%	143	0.01	57%	143	0.02	55%	143	0.00	79%	143	0.01	90%	143	0.25	-	11.58
	UB	143	0.06	89%	143	0.18	37%	143	0.15	39%	143	0.07	57%	143	0.10	55%	143	0.09	79%	143	0.10	90%	143	0.74	-	11.58
Meat and meat products (including edible offal)	LB	255	0.00	78%	255	0.17	20%	255	0.14	11%	255	0.03	38%	255	0.05	32%	255	0.01	53%	255	0.02	56%	255	0.42	-	9.36
	UB	255	0.03	78%	255	0.19	20%	255	0.16	11%	255	0.05	38%	255	0.08	32%	255	0.05	53%	255	0.07	56%	255	0.64	-	9.36
Animal and vegetable fats and oils	LB	182	0.00	96%	185	0.08	36%	185	0.09	34%	185	0.02	60%	185	0.04	49%	185	0.01	65%	185	0.02	79%	185	0.26	-	87.69
	UB	182	0.08	96%	185	0.15	36%	185	0.15	34%	185	0.09	60%	185	0.13	49%	185	0.11	65%	185	0.13	79%	185	0.83	-	87.69
Results expressed on wet weight basis (ng/g w.w.)																										
Fish and other seafood (including amphibians, reptiles, snails and insects)	LB	1825	0.06	21%	1825	1.28	7.1%	1825	0.11	15%	1825	0.33	13%	1825	0.03	40%	1825	0.12	21%	1825	0.02	67%	1825	1.95	-	9.96
	UB	1825	0.06	21%	1825	1.29	7.1%	1825	0.11	15%	1825	0.33	13%	1825	0.04	40%	1825	0.12	21%	1825	0.03	67%	1825	1.98	-	9.96
Products for special nutritional use	LB	70	0.06	54%	70	1.79	17%	70	0.33	26%	70	0.32	39%	70	0.05	50%	70	0.16	47%	70	0.00	93%	70	2.71	-	78.03
	UB	70	0.09	54%	70	1.79	17%	70	0.35	26%	70	0.34	39%	70	0.09	50%	70	0.20	47%	70	0.05	93%	70	2.91	-	78.03
Food for infants and small children	LB	34	0.00	74%	34	0.01	32%	34	0.00	38%	34	0.00	59%	34	0.00	79%	34	0.00	74%	34	0.00	94%	34	0.02	-	2.73
	UB	34	0.00	74%	34	0.02	32%	34	0.01	38%	34	0.00	59%	34	0.00	79%	34	0.00	74%	34	0.00	94%	34	0.04	-	2.73

N: number of samples; LB: lower bound; UB: upper bound. The number of figures after the decimal point is the same for all food categories and does not reflect precision. (ND (%): indicates the percentage of results below the LOD or the limit of quantification.

C. CONSUMPTION DATA

Table C1: Basic information on the dietary surveys included in the "Comprehensive European Food Consumption Database" considered for the chronic dietary exposure assessment.

Country	Name of the dietary survey (Acronym)	Abbreviation	Survey period	Geographical level	Age range (years old)	Number of subjects	Method	Replicates	Reference
Belgium	Diet National 2004	BE/1	2004 – 05	National	> 15	3,245	24-hour recall	2	de Vriese et al., 2005
	Regional Flanders	BE/2	2002 – 03	Regional	2.5 to 6.5	661	Food record	3	Huybrechts et al., in press
Bulgaria	NUTRICHILD	BG	2007	National	< 5	1,723	24-hour recall	2	Petrova et al., 2009
Cyprus	Childhealth	CY	2003	National	11 to 18	303	Food record	3	Not available
Czech Republic	SISP04	CZ/1	2003 – 04	National	> 4	1,666	24-hour recall	2	Ruprich et al., 2006
	SISP04_expochi	CZ/2	2003 – 04	National	10 to 18	85	24-hour recall	2	Ruprich et al., 2006
Denmark	Danish Dietary Survey	DK	2000 – 02	National	4 to 75	4,118	Food record	7	Lyhne et al.2005
Finland	DIPP	FI/1	2003 – 06	Regional	1, 3 and 6	1,448	Food record	3	Räsänen et al., 2006
	STRIP	FI/2	2000	Regional	7 to 8	250	Food record	4	Simell et al., 2009
France	INCA2	FR	2005 – 07	National	3 to79	4,079	Food record	7	AFSSA, 2009; Lioret et al. 2010; Dubuisson et al. 2010
Germany	DONALD_2006	DE/1	2006	Regional	1 to 10	303	Food record	3	Kroke et al., 2004; Sichert-Hellert and Kersting, 2004
	DONALD_2007	DE/2	2007	Regional	1 to 10	311	Food record	3	Kroke et al., 2004; Sichert-Hellert and Kersting, 2004
	DONALD_2008	DE/3	2008	Regional	1 to 10	307	Food record	3	Kroke et al., 2004; Sichert-Hellert and Kersting, 2004
	National Nutrition Survey II	DE/4	2005 – 07	National	14 to 80	13,926	24-hour recall	2	MRI, 2008; Krems et al., 2006

Table C1: Continued.

Country	Name of the dietary survey (Acronym)	Abbreviation	Survey period	Geographical level	Age range (years old)	Number of subjects	Method	Replicates	Reference
Greece	Regional Crete	GR	2004 – 05	Regional	4 to 6	874	Food record	3	Linardakis et al., 2008
Hungary	National Repr Surv	HU	2003	National	> 18	1,360	Food record	3	Rodler et al., 2005
Ireland	NSIFCS	IE	1997 – 99	National	18 to 64	958	Food record	7	Kiely et al., 2001; Harrington et al., 2001
Italy	INRAN-SCAI 2005–06	IT	2005 – 06	National	> 0.1	3,323	Food record	3	Leclercq et al., 2009
Latvia	EFSA_TEST	LT	2008	National	7 to 66	2,070	24-hour recall	2	Šantare et al., 2008
The Netherlands	VCP_kids	NL/1	2005 – 06	National	2 to 6	1,279	Food record	3	Ocké et al., 2008
	DNFCS-2003	NL/2	2003	National	19 to 30	750	24-hour recall	2	Ocké et al., 2005
Spain	enKid	ES/4	1998 – 00	National	1 to 14	382	24-hour recall	2	Serra-Majem et al., 2001
	NUT-INK05	ES/3	2004 – 05	Regional	4 to 18	1,050	24-hour recall	2	Larrañaga Larrañaga et al., 2006
	AESAN-FIAB	ES/1	1999–2001	National	17 to 60	1,068	Food record	3	Requejo et al., 2002
	AESAN	ES/2	2009	National	18 to 60	418	24-hour recall	2	Ortega et al., 2011
Sweden	NFA	SE/2	2003	National	3 to 18	2,495	24-hour recall	4	Enghardt-Barbieri et al., 2006
	RIKSMATEN 1997-98	SE/1	1997 – 98	National	18 to 74	1,210	Food record	7	Becker and Pearson, 2002
United Kingdom	NDNS	UK	2000 – 01	National	19 to 64	1,724	Food record	7	Henderson et al 2002

(a): More information on the dietary surveys is given in the Guidance of EFSA "Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment" (EFSA, 2011); (b): Abbreviations to be used consistently in all tables on exposure assessment; (c): 95th percentile calculated over a number of observations lower than 60 require cautious interpretation us the results may not be statistically robust (EFSA, 2011). Therefore, for these dietary surveys/age classes the 95th percentile estimates will not be presented in the exposure assessment.

D. DIETARY EXPOSURE

Table D1: Total dietary exposure (ng/kg b.w. per day) to the eight PBDE congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) for average and 95th percentiles children consumers between 1 to 3 years old across a number of subjects (N subjects) in European surveys (N surveys).

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (1-3 years old) with average consumption																		
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		BDE-209	
Age class	**N surveys**	**N Subjects**	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
1 - 3 years	BE/2	36	0.03	0.51	1.43	2.08	0.58	1.24	0.24	0.93	0.09	1.10	0.08	1.21	0.03	1.11	1.65	5.72
	BG	428	0.03	0.59	1.43	2.12	0.83	1.49	0.32	1.01	0.17	1.09	0.11	1.13	0.06	0.96	2.61	7.18
	FI/1	500	0.06	0.68	5.57	6.40	2.15	2.99	0.72	1.60	0.17	1.47	0.20	1.62	0.08	1.44	4.38	9.69
	DE/1	92	0.03	0.39	3.58	4.05	1.47	1.93	0.49	0.97	0.13	0.84	0.14	0.91	0.05	0.80	2.86	5.92
	DE/2	85	0.03	0.41	2.91	3.41	1.18	1.69	0.40	0.93	0.11	0.88	0.11	0.97	0.05	0.87	2.57	5.82
	DE/3	84	0.03	0.38	3.55	4.02	1.46	1.93	0.47	0.96	0.12	0.85	0.13	0.93	0.05	0.83	2.93	6.02
	IT	36	0.15	0.69	5.37	6.09	1.47	2.20	1.10	1.86	0.21	1.27	0.37	1.52	0.09	1.23	2.89	8.11
	NL/2	322	0.02	0.49	1.04	1.68	0.59	1.22	0.19	0.85	0.11	1.08	0.07	1.14	0.04	1.07	1.55	5.76
	ES/4	17	0.11	0.87	3.50	4.46	0.98	1.96	0.73	1.76	0.19	1.62	0.25	1.81	0.09	1.56	2.39	9.53
Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (1-3 years old) with high consumption (95th percentiles)																		
Age class	**N surveys**	**N Subjects**	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
1 - 3 years	BE/2	36[(b)]	0.10	1.03	5.61	6.05	1.67	2.37	1.19	1.81	0.16	2.16	0.32	2.30	0.07	2.07	2.70	9.56
	BG	428	0.18	0.93	6.50	7.23	1.97	2.96	1.20	2.07	0.33	1.95	0.42	2.08	0.11	1.87	4.98	11.29
	FI/1	500	0.18	1.40	14.69	15.57	5.31	6.16	1.80	3.09	0.36	3.18	0.50	3.45	0.16	3.24	9.55	17.63
	DE/1	92	0.15	0.65	11.07	11.52	4.23	4.64	1.22	1.89	0.29	1.53	0.37	1.65	0.11	1.53	6.51	10.44
	DE/2	85	0.10	0.72	8.99	9.35	3.42	3.80	1.12	1.84	0.20	1.53	0.29	1.74	0.09	1.66	5.89	10.64
	DE/3	84	0.12	0.66	11.25	11.42	4.18	4.48	1.28	1.78	0.24	1.64	0.33	1.79	0.11	1.69	6.66	10.00
	IT	*36[(b)]*	*0.38*	*1.17*	*13.00*	*13.51*	*3.27*	*4.51*	*2.35*	*3.31*	*0.40*	*2.20*	*0.81*	*2.56*	*0.16*	*2.23*	*6.29*	*15.02*
	NL/2	322	0.12	0.85	4.44	5.09	1.36	2.24	0.76	1.69	0.22	1.87	0.26	2.02	0.07	1.90	2.90	9.76
	ES/4	*17[(b)]*	*1.02*	*3.80*	*27.36*	*28.51*	*4.12*	*6.31*	*6.26*	*7.69*	*0.98*	*5.74*	*2.13*	*5.54*	*0.51*	*4.93*	*6.84*	*46.75*

(a): Original acronyms of the dietary surveys and the number of subjects is given in Table C1 in Appendix C b): P95 estimates for dietary surveys/age classes with less than 60 observations may not be statistically robust (EFSA, 2011) and therefore they should not be considered in the risk characterisation.

Table D2: Total dietary exposure (ng/kg b.w. per day) to eight the PBDE congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) for average and 95th percentiles children consumers between 3 to 6 years old across a number of subjects (N subjects) in European surveys (N surveys).

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (3-6 years old) with average consumption																		
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BDE-154		BDE-183		BDE-209	
Age class	**N surveys**	**N Subjects**	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
3- 6 years	BE/2	608	0.03	0.41	1.17	1.68	0.42	0.94	0.23	0.77	0.07	0.87	0.08	0.96	0.03	0.88	1.27	4.53
	BG	434	0.03	0.52	0.93	1.51	0.57	1.13	0.26	0.82	0.14	0.87	0.10	0.89	0.05	0.73	2.24	6.13
	CZ	113	0.05	0.49	1.35	1.89	0.59	1.12	0.35	0.90	0.14	0.88	0.12	0.93	0.05	0.77	1.52	5.36
	DK	159	0.04	0.53	1.15	1.78	0.56	1.18	0.29	0.93	0.13	1.02	0.10	1.08	0.05	0.95	1.80	6.01
	FI/1	464	0.04	0.67	1.35	2.20	0.72	1.56	0.32	1.20	0.15	1.42	0.11	1.52	0.05	1.37	1.98	7.41
	FR	163	0.07	0.51	1.97	2.53	0.65	1.22	0.47	1.05	0.14	0.93	0.16	1.04	0.05	0.86	1.60	5.42
	DE/1	95	0.02	0.30	0.92	1.30	0.52	0.88	0.21	0.58	0.09	0.62	0.07	0.65	0.03	0.57	1.38	3.72
	DE/2	97	0.03	0.32	0.95	1.35	0.50	0.89	0.23	0.63	0.10	0.67	0.08	0.71	0.03	0.63	1.34	3.85
	DE/3	92	0.03	0.32	0.99	1.38	0.48	0.86	0.24	0.63	0.09	0.65	0.08	0.69	0.03	0.60	1.35	3.81
	UK	696	0.04	0.30	1.11	1.48	0.39	0.75	0.27	0.65	0.08	0.63	0.09	0.71	0.02	0.62	0.86	3.20
	IT	67	0.11	0.59	3.01	3.61	0.87	1.46	0.77	1.37	0.19	0.97	0.27	1.11	0.07	0.85	2.19	6.52
	NL/2	738	0.02	0.41	0.82	1.34	0.45	0.96	0.17	0.71	0.09	0.87	0.06	0.92	0.03	0.85	1.16	4.64
	ES/3	93	0.11	0.57	2.73	3.36	0.56	1.20	0.65	1.32	0.12	1.05	0.23	1.24	0.05	1.03	1.27	5.48
	ES/4	57	0.08	0.58	2.24	2.89	0.54	1.21	0.52	1.21	0.12	1.07	0.18	1.23	0.05	1.03	1.51	5.81
	SE/2	590	0.06	0.43	1.67	2.18	0.52	1.04	0.36	0.90	0.10	0.87	0.13	0.99	0.03	0.85	1.33	4.62
Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (3-6 years old) with high consumption (95th percentiles)																		
Age class	**N surveys**	**N Subjects**	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
3- 6 years	BE/2	608	0.15	0.70	4.18	4.80	0.85	1.71	0.86	1.64	0.15	1.57	0.31	1.75	0.06	1.64	2.31	8.01
	BG	434	0.19	0.84	4.71	5.21	1.30	2.03	1.19	1.81	0.30	1.49	0.42	1.59	0.09	1.32	4.02	10.22
	CZ	113	0.27	0.84	6.35	6.97	1.32	2.06	1.59	2.32	0.29	1.57	0.56	1.75	0.11	1.37	2.67	9.60
	DK	159	0.12	0.87	2.92	3.62	0.98	1.87	0.71	1.57	0.22	1.68	0.25	1.77	0.08	1.63	2.93	9.62
	FI/1	464	0.14	1.08	3.72	4.79	1.32	2.54	0.92	2.11	0.28	2.30	0.32	2.49	0.09	2.33	3.36	11.89
	FR	163	0.15	0.79	4.73	5.47	1.28	2.10	0.93	1.80	0.24	1.56	0.33	1.74	0.08	1.49	2.89	8.65
	DE/1	95	0.08	0.43	3.01	3.41	1.16	1.59	0.64	1.09	0.21	1.06	0.22	1.08	0.05	1.05	2.29	6.28
	DE/2	97	0.11	0.58	3.40	3.86	1.15	1.77	0.75	1.26	0.24	1.31	0.26	1.40	0.06	1.35	2.55	6.97
	DE/3	92	0.11	0.51	3.14	3.69	1.14	1.71	0.68	1.22	0.21	1.11	0.24	1.25	0.05	1.08	2.39	5.96
	UK	696	0.18	0.56	4.35	4.91	0.91	1.47	1.10	1.67	0.19	1.15	0.38	1.34	0.06	1.17	1.69	5.79
	IT	67	0.32	0.97	7.89	8.63	1.96	3.11	1.96	2.82	0.37	1.36	0.69	1.82	0.14	1.23	4.10	9.47
	NL/2	738	0.13	0.67	3.36	3.94	0.96	1.71	0.76	1.43	0.19	1.51	0.27	1.62	0.06	1.53	2.13	7.79
	ES/3	93	0.30	0.94	7.40	8.08	1.04	1.97	1.79	2.59	0.23	1.72	0.63	2.05	0.10	1.68	2.04	9.29
	ES/4	*57*[(b)]	*0.37*	*1.12*	*9.15*	*9.95*	*1.21*	*2.38*	*2.23*	*3.11*	*0.25*	*2.04*	*0.78*	*2.46*	*0.11*	*2.04*	*3.35*	*11.11*
	SE/2	590	0.15	0.69	4.39	4.98	1.07	1.93	0.97	1.70	0.18	1.55	0.33	1.72	0.07	1.58	2.19	7.62

(a): Original acronyms of the dietary surveys and the number of subjects is given in Table C1 in Appendix C b): P95 estimates for dietary surveys/age classes with less than 60 observations may not be statistically robust (EFSA, 2011) and therefore they should not be considered in the risk characterisation.

Table D3: Total dietary exposure (ng/kg b.w. per day) to eight the PBDE congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) for average and 95th percentiles children consumers between 6 to 10 years old across a number of subjects (N subjects) in European surveys (N surveys).

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (6-10 years old) with average consumption																		
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BD-154		BDE-183		BDE-209	
Age class	**N surveys**	**N subjects**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
6-10 years	BE/2	17	0.03	0.37	1.03	1.49	0.35	0.81	0.21	0.70	0.07	0.77	0.08	0.85	0.03	0.77	1.14	4.11
	CZ	276	0.03	0.36	0.79	1.19	0.42	0.81	0.22	0.62	0.10	0.62	0.08	0.64	0.04	0.52	1.19	3.91
	DK	331	0.03	0.44	0.90	1.43	0.46	0.98	0.22	0.76	0.11	0.85	0.08	0.90	0.04	0.79	1.49	4.98
	FI/1	484	0.04	0.54	1.15	1.83	0.58	1.24	0.28	0.97	0.13	1.12	0.10	1.20	0.04	1.07	1.55	5.91
	FI/3	250	0.02	0.32	0.71	1.13	0.32	0.73	0.15	0.58	0.06	0.69	0.06	0.75	0.02	0.69	0.96	3.56
	FR	319	0.05	0.37	1.35	1.76	0.44	0.84	0.35	0.76	0.10	0.65	0.12	0.72	0.04	0.57	1.18	3.87
	DE/1	98	0.03	0.23	0.72	0.99	0.30	0.56	0.19	0.46	0.07	0.44	0.07	0.48	0.02	0.40	0.89	2.65
	DE/2	105	0.02	0.24	0.64	0.93	0.32	0.60	0.17	0.46	0.07	0.48	0.06	0.51	0.02	0.44	0.97	2.83
	DE/3	104	0.02	0.24	0.66	0.95	0.31	0.59	0.18	0.46	0.07	0.46	0.06	0.49	0.02	0.41	1.01	2.81
	UK	151	0.03	0.25	0.78	1.09	0.29	0.61	0.19	0.51	0.06	0.54	0.07	0.59	0.02	0.53	0.76	2.75
	IT	126	0.09	0.43	2.20	2.61	0.59	1.00	0.58	1.00	0.14	0.67	0.20	0.78	0.05	0.57	1.48	4.56
	LT	190	0.01	0.17	0.38	0.57	0.17	0.36	0.10	0.29	0.04	0.29	0.04	0.31	0.02	0.24	0.54	1.68
	NL/2	219	0.02	0.33	0.59	1.02	0.34	0.76	0.13	0.57	0.07	0.71	0.05	0.76	0.02	0.70	0.95	3.77
	ES/3	306	0.08	0.43	1.93	2.40	0.41	0.88	0.46	0.95	0.09	0.76	0.16	0.90	0.04	0.73	0.96	4.05
	ES/4	99	0.06	0.47	1.59	2.09	0.41	0.92	0.37	0.90	0.10	0.80	0.13	0.90	0.05	0.74	1.13	4.69
	SE/2	883	0.03	0.30	0.98	1.34	0.31	0.68	0.22	0.61	0.06	0.62	0.08	0.70	0.02	0.61	0.78	3.10
Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (6-10 years old) with high consumption (95th percentiles)																		
Age class	**N surveys**	**N subjects**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
6-10 years	*BE/2*	*17[(b)]*	*0.11*	*0.58*	*2.97*	*3.40*	*0.62*	*1.31*	*0.69*	*1.24*	*0.12*	*1.30*	*0.24*	*1.39*	*0.05*	*1.36*	*2.44*	*6.70*
	CZ	276	0.16	0.67	3.94	4.28	0.97	1.59	0.99	1.59	0.22	1.11	0.35	1.25	0.08	0.97	2.25	7.26
	DK	331	0.08	0.69	2.13	2.88	0.79	1.57	0.53	1.31	0.18	1.41	0.19	1.50	0.06	1.38	2.59	7.92
	FI/1	484	0.14	0.81	3.46	4.21	0.97	1.84	0.89	1.72	0.21	1.70	0.31	1.85	0.07	1.66	2.33	8.78
	FI/3	250	0.09	0.52	2.16	2.83	0.65	1.25	0.50	1.04	0.13	1.12	0.19	1.23	0.04	1.10	2.01	5.95
	FR	319	0.12	0.63	3.10	3.76	0.85	1.48	0.76	1.38	0.18	1.14	0.27	1.25	0.07	1.07	2.06	6.83
	DE/1	98	0.11	0.39	2.63	2.95	0.66	0.95	0.67	1.01	0.15	0.77	0.23	0.89	0.04	0.70	1.71	4.15
	DE/2	105	0.08	0.41	1.96	2.34	0.70	1.21	0.49	1.03	0.15	0.99	0.17	0.99	0.04	0.92	1.78	4.98
	DE/3	104	0.10	0.40	2.55	2.93	0.66	0.98	0.71	0.98	0.14	0.84	0.25	0.92	0.04	0.79	1.84	4.79
	UK	151	0.14	0.46	3.41	3.84	0.68	1.16	0.84	1.29	0.14	1.07	0.29	1.13	0.05	1.08	1.57	4.98
	IT	126	0.27	0.71	6.46	6.98	1.10	1.72	1.61	2.20	0.27	1.06	0.56	1.39	0.10	0.95	2.79	7.10
	LT	190	0.08	0.37	1.98	2.22	0.51	0.76	0.49	0.78	0.11	0.57	0.17	0.64	0.04	0.52	1.32	3.87
	NL/2	219	0.10	0.61	2.60	2.92	0.80	1.45	0.62	1.18	0.18	1.39	0.21	1.49	0.05	1.41	1.75	7.07

Table D3: Continued.

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (6-10 years old) with high consumption (95th percentiles)																		
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BD-154		BDE-183		BDE-209	
Age class	**N surveys**	**N subjects**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
	ES/3	306	0.22	0.71	5.47	6.09	0.83	1.51	1.32	2.07	0.18	1.27	0.46	1.57	0.08	1.28	1.63	6.59
	ES/4	99	0.22	1.03	5.29	5.76	0.95	1.67	1.30	1.90	0.25	1.58	0.45	1.62	0.13	1.32	2.46	11.90
	SE/2	883	0.11	0.51	2.80	3.27	0.59	1.20	0.67	1.20	0.12	1.08	0.24	1.24	0.04	1.10	1.38	5.36

(a): Original acronyms of the dietary surveys and the number of subjects is given in Table C1 in Appendix C b): P95 estimates for dietary surveys/age classes with less than 60 observations may not be statistically robust (EFSA, 2011) and therefore they should not be considered in the risk characterisation.

Table D4: Total dietary exposure (ng/kg b.w. per day) to eight PBDE congeners considered (BDE-28, -47, -99, -100, -153, -154, -183 and -209) for average and 95th percentiles children consumers between 10 to 18 years old across a number of subjects (N subjects) in European surveys (N surveys).

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (10-18 years old) with average consumption																		
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BD-154		BDE-183		BDE-209	
Age class	**N surveys**	**N subjects**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
10-18 years	BE/2	611	0.03	0.17	0.73	0.91	0.22	0.40	0.16	0.34	0.05	0.29	0.07	0.33	0.02	0.25	0.90	2.10
	BG	162	0.02	0.19	0.52	0.71	0.24	0.42	0.15	0.34	0.06	0.29	0.05	0.30	0.02	0.22	0.75	2.14
	CY	303	0.02	0.13	0.56	0.69	0.13	0.26	0.14	0.27	0.03	0.21	0.05	0.25	0.01	0.19	0.45	1.28
	CZ/2	85	0.02	0.23	0.49	0.73	0.26	0.49	0.14	0.38	0.07	0.36	0.05	0.37	0.03	0.29	0.73	2.40
	CZ/1	213	0.03	0.30	0.75	1.07	0.35	0.66	0.21	0.52	0.09	0.49	0.07	0.51	0.03	0.40	0.94	3.17
	DK	479	0.02	0.24	0.50	0.80	0.26	0.54	0.13	0.42	0.06	0.46	0.05	0.49	0.02	0.42	0.83	2.70
	FR	973	0.03	0.20	0.70	0.91	0.23	0.43	0.18	0.39	0.05	0.32	0.06	0.36	0.02	0.27	0.63	1.97
	FI/3	1011	0.01	0.11	0.21	0.33	0.09	0.21	0.05	0.17	0.02	0.18	0.02	0.19	0.01	0.15	0.34	1.12
	FR	18	0.03	0.20	0.74	0.97	0.24	0.46	0.18	0.41	0.05	0.36	0.06	0.40	0.02	0.33	0.78	2.20
	DE/4	24	0.02	0.20	0.55	0.77	0.22	0.44	0.14	0.37	0.05	0.35	0.05	0.39	0.02	0.32	0.79	2.22
	DE/1	27	0.02	0.18	0.47	0.68	0.25	0.46	0.13	0.34	0.06	0.35	0.05	0.37	0.02	0.30	0.68	1.98
	DE/2	247	0.06	0.27	1.42	1.68	0.36	0.61	0.37	0.63	0.09	0.40	0.13	0.47	0.03	0.34	1.00	2.91
	DE/3	496	0.01	0.12	0.26	0.39	0.13	0.26	0.07	0.20	0.03	0.20	0.03	0.21	0.01	0.16	0.42	1.22
	IT	86	0.04	0.26	1.14	1.40	0.33	0.60	0.30	0.57	0.08	0.42	0.11	0.48	0.03	0.35	0.80	2.56
	LT	590	0.05	0.28	1.27	1.55	0.25	0.54	0.30	0.60	0.06	0.45	0.11	0.54	0.03	0.42	0.65	2.56
	ES/2	209	0.05	0.28	1.23	1.51	0.25	0.54	0.30	0.59	0.06	0.44	0.10	0.52	0.03	0.40	0.67	2.56
	ES/3	7	0.02	0.16	0.59	0.77	0.17	0.35	0.14	0.33	0.04	0.30	0.05	0.34	0.02	0.29	0.40	1.69
	ES/4	1018	0.03	0.21	0.71	0.96	0.21	0.46	0.16	0.42	0.04	0.41	0.06	0.47	0.02	0.40	0.53	2.07
	SE/1	611	0.03	0.17	0.73	0.91	0.22	0.40	0.16	0.34	0.05	0.29	0.07	0.33	0.02	0.25	0.90	2.10
	SE/2	162	0.02	0.19	0.52	0.71	0.24	0.42	0.15	0.34	0.06	0.29	0.05	0.30	0.02	0.22	0.75	2.14
Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children 10-18 years old) with high consumption (95th percentiles)																		
Age class	**N surveys**	**N subjects**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
10-18 years	BE/2	611	0.11	0.35	2.49	2.72	0.63	0.92	0.61	0.89	0.13	0.56	0.23	0.70	0.03	0.47	1.39	4.18
	BG	162	0.12	0.39	3.10	3.32	0.77	1.09	0.80	1.00	0.19	0.65	0.28	0.71	0.05	0.56	1.62	4.98
	CY	303	0.08	0.24	2.09	2.28	0.30	0.55	0.52	0.72	0.07	0.45	0.18	0.53	0.03	0.44	0.92	2.56
	CZ/2	85	0.11	0.43	2.62	2.84	0.54	0.99	0.67	0.90	0.13	0.72	0.23	0.80	0.05	0.67	1.44	4.23
	CZ/1	213	0.14	0.52	3.50	3.91	0.78	1.28	0.88	1.34	0.19	0.89	0.31	0.92	0.07	0.78	1.67	5.92
	DK	479	0.05	0.45	1.34	1.73	0.54	1.03	0.34	0.83	0.12	0.90	0.12	0.96	0.04	0.86	1.54	4.99
	FR	973	0.08	0.36	1.95	2.23	0.48	0.82	0.49	0.83	0.11	0.61	0.17	0.70	0.04	0.55	1.23	3.68
	DE/4	1011	0.05	0.23	1.24	1.41	0.26	0.51	0.31	0.49	0.06	0.40	0.11	0.43	0.03	0.37	0.74	2.44
	DE/1	18	0.15	0.31	3.60	3.81	0.51	0.82	0.90	1.14	0.11	0.59	0.31	0.71	0.05	0.60	1.35	3.20
	DE/2	24	0.07	0.30	1.65	1.89	0.41	0.70	0.40	0.75	0.09	0.59	0.14	0.64	0.03	0.54	1.48	3.68

Table D4: Continued.

Dietary exposure to eight PBDE congeners (ng/kg b.w. per day) for children (10-18 years old) with high consumption (95th percentiles)																		
			BDE-28		BDE-47		BDE-99		BDE-100		BDE-153		BD-154		BDE-183		BDE-209	
Age class	**N surveys**	**N subjects**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
	DE/3	27	0.06	0.31	1.44	1.68	0.51	0.78	0.43	0.65	0.11	0.68	0.15	0.71	0.03	0.65	1.13	3.24
	IT	247	0.18	0.49	4.21	4.47	0.76	1.13	1.07	1.44	0.18	0.68	0.37	0.91	0.07	0.61	1.80	4.79
	LT	496	0.06	0.28	1.31	1.42	0.40	0.64	0.33	0.52	0.09	0.45	0.12	0.49	0.03	0.39	0.98	2.66
	ES/2	86	0.12	0.46	2.92	3.38	0.59	0.97	0.76	1.15	0.14	0.70	0.27	0.83	0.05	0.62	1.38	4.26
	ES/3	590	0.16	0.47	3.78	4.07	0.52	0.96	0.93	1.32	0.12	0.76	0.32	0.93	0.05	0.75	1.12	4.31
	ES/4	209	0.18	0.51	4.18	4.60	0.58	1.07	1.04	1.49	0.13	0.79	0.36	1.01	0.07	0.74	1.37	4.81
	SE/1	7	0.03	0.31	0.89	1.04	0.34	0.62	0.26	0.52	0.07	0.63	0.09	0.67	0.03	0.63	0.66	3.53
	SE/2	1018	0.09	0.37	2.30	2.66	0.43	0.87	0.55	0.92	0.09	0.79	0.19	0.91	0.03	0.81	0.95	3.86
	DE/3	27	0.06	0.31	1.44	1.68	0.51	0.78	0.43	0.65	0.11	0.68	0.15	0.71	0.03	0.65	1.13	3.24
	IT	247	0.18	0.49	4.21	4.47	0.76	1.13	1.07	1.44	0.18	0.68	0.37	0.91	0.07	0.61	1.80	4.79

(a): Original acronyms of the dietary surveys and the number of subjects is given in Table C1 in Appendix C b): P95 estimates for dietary surveys/age classes with less than 60 observations may not be statistically robust (EFSA, 2011) and therefore they should not be considered in the risk characterisation.

E. OBSERVATIONS IN HUMANS (TABLES)

Table E1: Epidemiological studies on effects on thyroid and endocrine disruption.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Menorca (Spain) Prospective cohort 1997 - 2001	Thyroid hormone levels	To study the association between pre and postnatal PBDE exposure and thyroid hormone levels in children at age 4 years and isolate the effects of PBDEs from those of PCBs, DDT, DDE and HCB.	Prospective birth cohort of 482 pregnant mothers. N = 88 cord blood N = 244 children 4 years old	PBDE (-12–13, -32, -17, -28–33, -47, -100, -119, -99, -116, -85, -126, -155, -153, -183, -66, -71, -154, -138, -190) concentrations were measured in 88 cord blood samples and 244 serum samples of 4 year old children. Levels of TSH, Total T3 and free T4 were measured from the serum samples obtained at age 4 by chemiluminescence assay.	Levels of thyroid hormones were not associated to PBDE exposure.	This study does not report any association between thyroid hormones and PBDE exposure in 4-year-old children pre and postnatally exposed.	Gascón et al., 2011.
Quebec, Canada	Thyroid hormones levels	To study serum thyroid hormones in relation to serum PBDE	N = 50 adult men recruited in a fertility clinic	Plasma PBDE congeners (BDE-47, -99, -100, -153). TSH, free T3, free T4 were determined on 50 serum samples. Multiple regression analysis was performed controlling for age and other covariates.	T4 levels were negatively associated to serum BDE-47 ($p < 0.05$), BDE-99 ($p < 0.05$), Sum of PBDEs ($p < 0.05$) No relations were observed between T3, TSH and any of the chemicals measured.	PBDEs might interfere with thyroid status in general population.	Abdelouahab et al., 2011

Table E1: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Salinas Valley (agricultural region of California). Time period not specified	Free T4, total T4 and TSH	To determine whether PBDE serum concentrations are associated with thyroid hormone levels in pregnant women.	CHAMACOS cohort of low-income, predominantly Mexican women. 270 pregnant women	The study measured the concentration of 10 PBDE congeners (BDE-17, - 28, -47, -66, -85, -99, -100, -153, -154 and -183), free T4, total T4 and TSH in pregnant women around the 27th week of gestation.	Serum concentrations of individual PBDE congeners with detection frequencies >50 % (BDE-28, -47, -99, -100 and -153) and their sum were inversely associated with TSH levels. Decreases in TSH ranged between 10.9-% (95-%CI= -20.6, 0.0) and 18.7-% (-29.2, -4.5) for every 10-fold increase in individual congeners. Odds of subclinical hyperthyroidism (low TSH (second (TSH<0.5 mlU/l) or third (TSH<0.8 mlU/l) trimester of pregnancy) but normal T4) were also significantly elevated in participants in the highest quartile of the sum of PBDEs, and BDE-100 and -153 relative to those in the first quartile. Associations between PBDEs and free and total T4 were not statistically significant.	The study reports an inverse association between the sum of PBDEs and BDE-28, -47, -99, -100 and -153, and TSH serum concentrations in pregnant women around the 27th week of gestations. Exposure to PBDEs is associated with lower TSH during pregnancy. No association was found between PBDEs and free and total T4.	Chevrier et al., 2010
South-eastern China 2008	Serum THs and TSH	Impact of e-waste exposure during recycling and dismantling activities on thyroid hormone levels	236 occupational-exposed people, 89 non-occupational-exposed people in e-waste recycling sites; 117 subjects in the control group	BDE-209, -77, -85, -126, -205 and -203.	People having worked on an e-waste recycling and dismantling had significantly lower TSH compared to the control group ($p<0.01$). A positive relation was also found between the levels of BDE-126 and T4	Exposure to BFRs released from primitive e-waste handling may contribute to the changes of THs and TSH.	Wang et al., 2010

Table E1: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Massachusetts USA 2002-03	Serum hormone level including free T4	PBDE serum concentrations and hormone levels	24 men recruited through a US infertility clinic	Preliminary study within an ongoing study on the impact of environmental exposure on male reproductive health. Measures of serum hormone levels and BDE-47, -99 and -100 concentrations		PBDEs were positively associated with free T4	Meeker et al., 2009
Nunavik (Quebec, Canada) 2004	Thyroid function	To study the relationship between exposure to several PHCs and thyroid hormone homeostasis in Inuit adults from Nunavik.	Permanents Inuit residents of Nunavik > 18years old (n = 623)	The cross-sectional study measured TSH, free T4, total T3, TBG and concentrations of 41 contaminants, including BDE-47 and -153.	Percent detected of BDE-47 and -153 were 57.3 and 73.8, respectively. Geometric means were 2.16 (95 % CI: 1.84-2.54) and 2.05 (1.85-2.27), respectively. Range <LOD-343.45 and <LOD-75.74, respectively. Exposure to BDE-47 was positively related to total T3. The association weakened after controlling for food consumption.	Exposure to BDE-47 was positively related to total T3	Dallaire et al., 2009
New York State Angler Cohort Study (NYSACS): a prospective investigation of health effects in consumers of Great Lakes sportfish among licensed anglers residing in 16 New York State counties contiguous to Lakes Erie and Ontario enrolled in 1996. 2006	Thyroid function	The aim of this preliminary study was to generate hypotheses regarding associations between body burdens of PBDE from environmental sources, and biomarkers of thyroid function.	n = 36 licensed anglers	Anglers donated blood and completed questionnaires regarding demographic, clinical and sportfish consumption information. Archived blood specimens were analyzed for thyroid stimulating hormone, total and free thyroxine, total triiodothyronine, total serum lipids and nine PBDE congeners (BDE-28, -47, -66, -85, -99, -100, -138, -153 and -154).	PBDE congener profiles were dominated by BDE-47 (median = 7.9 ng/g fat), BDE-153 and -99 (medians = 1.8 ng/g fat).	No significant associations were observed between congeners, or their sum (ΣPBDEs), and thyroid function. The study had very low power. The possibility of a positive association between BBDEs and free T4 could be detected with an approximate nine-fold increase in sample size.	Bloom et al., 2008

Table E1: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Wisconsin Great Lakes (USA) cohort (4,206 men) frequent and infrequent consumers of Great Lake fish. Established in early 1990s. 2003-04	Thyroid disease, steroid hormone level, thyroid antibodies	To study the relationships between PBDE body burdens and thyroid and steroid hormone levels, thyroid antibodies and thyroid disease	405 adult males	Longitudinal study in a subset of the Wisconsin Great Lakes cohort. 10yrs of data. Serum tested for PBDEs (BDE-47, -99, -100, -153), PCBs, testosterone, SHBG, thyreoglobuline antibodies, T3, T4, TSH	Median sum of PBDEs was 38 ng/g fat. Sum of PBDEs positively related to T4 and reverse T3 and inversely related to total T3 and TSH. Participants with PBDE 95th percentile were more likely to have thyreoglobuline antibodies. PBDE effects were independent of PCB exposure and sport fish consumption.	PBDE exposure at levels comparable with those of the general US population was associated with increased thyroglobulin antibodies and increased T4 and free T4 in adult males. PBDE exposure was not associated with thyroid disease.	Turyk et al., 2008
John Hopkins Hospital DC, USA. 2004 - 2005	Thyroid hormone levels	Relationships between cord serum levels of PBDEs (and PCBs) and thyroid hormones measured in cord blood serum and neonatal blood spots.	Cord blood serum from 297 infants who were delivered at the Johns Hopkins Hospital in 2004–2005.	Measures of PBDEs, (congeners BDE-47, -100 and -153), PCBs, TSH, T4 and free T4 in cord blood serum. Delivery mode (augmented vaginal deliveries and nonelective cesarean deliveries) was used as a surrogate for intrapartum stress, which is known to alter cord blood thyroid hormones.	In the full study population, no compounds were associated with a change in average TSH, free T4, or total T4. BDE-100 was associated with increased odds of low cord total T4, BDE-153 with increased odds of low cord total T4 and free T4, and no compounds were associated with increased odds of high TSH. For infants born by spontaneous, vaginal, deliveries, PBDEs showed consistent but mainly non-significant negative associations with total T4 and free T4 measurements.	Prenatal PBDE exposures were associated (mainly with no statistical significance) with reduced total T4 and free T4 levels among infants born by spontaneous, vaginal delivery.	Herbstman et al., 2008

Table E1: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Southeast China Time period not specified	Thyroid function	Impact of e-waste exposure during recycling and dismantling activities on thyroid hormone levels.	23 workers dismantling and recycling electronic goods in a village close to an e-waste site were the exposed group. Controls were 26 farmers located 50 km away from the e-waste.	Serum total PBDEs was measured	Serum levels of PBDEs (median PBDEs, 382 ng/g fat; range, 77-8452 ng/g fat) and TSH (median TSH, 1.79 microIU/mL; range, 0.38-9.03 microIU/mL) were significantly higher in the exposed group than in the control group (158 ng/g, range of 18-436 ng/g, and $p < 0.05$; 1.15 microIU/mL, range of 0.48-2.09, and $p < 0.01$; and 0% per hundred, range of 0-5% per hundred, and $p < 0.01$, respectively). There was no association between PBDEs exposure and oxidative DNA damage.	The exposure to PBDEs at the e-waste site may have an effect on the levels of TSH.	Yuan et al., 2008
Salinas Valley, an agricultural region of California. Time period not specified	Neonatal TSH level	To examine whether prenatal exposure to PBDEs is associated to neonatal TSH levels.	CHAMACOS cohort of low-income, predominantly Mexican women. 228 mother-infant pairs.	The study measured the concentration of 7 PBDEs (BDE-47, -85, -99, -100, -153, -154 and -183) in serum samples collected at 26 weeks gestation. Data on TSH levels at birth were obtained.	TSH levels were normal (<25 mIU/L) for all neonates (GM = 5.7, GSD = 1.8 mIU/L). There was negative association between all PBDE congeners and TSH levels but BDE-99.		Chevrier et al., 2005
Oerebro, Sweden 2001-2002	thyroid function	The aim of this longitudinal study was to measure plasma level of PBDEs in workers at an electronic recycling facility and to relate these to the workers thyroid status.	n = 11 workers	7 PBDE congeners (BDE-28, -47, -100, -99, -154, -153 and -183) and three thyroid hormones: T3, T4 and TSH were repeatedly analysed in plasma from 11 workers during a period of 1.5 years.	Plasma levels of PBDEs at start of employment were <0.5–9.1 pmol/g fat. The most common congener was BDE-47 (median 2.8 pmol/g fat), followed by BDE-153 (median 1.7 pmol/g fat), and BDE-183 had a median value of <0.19 pmol/g fat. After dismantling the corresponding median concentrations were: 3.7, 1.7 and 1.2 pmol/g fat, respectively. All measured levels of thyroid hormones (T3, T4 and TSH) were within the normal physiological range.	The workers plasma levels of PBDEs fluctuated during the study period. No relevant changes were present in relation to PBDE exposure within the workers participating in this study.	Julander et al., 2005

Table E1: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Central Indiana, USA August-December 2001	Total and free T3 and T4	To determine the human fetal and maternal serum concentrations of PBDEs in Central Indiana.	12 paired samples of maternal and cord blood	BDE-47, -99, -100, -153, -154 and -183. Total and free T3 and T4	No correlation between serum PBDEs and thyroid hormone concentrations	No correlation between serum PBDEs and thyroid hormone concentrations	Mazdai et al., 2003
Sweden 1991	Hormone levels	The authors assessed the possible relationship between high dietary exposure to persistent organohalogens (OHS) through fatty fish from the Baltic Sea and hormone levels in adult men	N = 110 men who consumed varying amounts of fish	Plasma levels of some OHS including BDE-47 and of follicle-stimulating hormone, luteinizing hormone, prolactin, thyrotropin, free and total T3, free and total T4, and free testosterone were analyzed.	The authors found a negative correlations between BDE-47 and plasma thyrotropin ($p < .001$),	High consumption of organohalogen-polluted fish did not appear to affect plasma concentrations of pituitary, thyroid, or testosterone hormone levels in male adults.	Hagmar et al, 2001

Table E2: Epidemiological studies on neurodevelopmental effects.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Menorca (Spain) Prospective cohort 1997 - 2001	Child neurodevelopment	To study the association between pre and postnatal PBDE concentrations in children at age 4 years controlling for the effects of PCBs, DDT, DDE and HCB.	Prospective birth cohort of 482 pregnant mothers. N = 88 cord blood N = 244 children 4 years old	PBDEs (BDE-12–13, 32, 17, 28–33, 47, 100, 119, 99, 116, 85, 126, 155, 153, 183, 66, 71, 154, 138, 190) concentrations were measured in 88 cord blood samples and 244 serum samples of 4 year old children. At 4 years, children were assessed for motor and cognitive function (McCarthy Scales of Children's Abilities), attention-deficit, hyperactivity and impulsivity (ADHD-DSM-IV) and social competence (California Preschool Social Competence Scale).	Scores for cognitive and motor functions were always lower in children pre and postnatally exposed to PBDE47 than in referents, but none of these associations was statistically significant (β coefficient (95%CI) of the total cognition score:−2.7 (−7.0, 1.6) for postnatal exposure, and−1.4 (−9.2, 6.5) for prenatal exposure). Postnatal exposure to PBDE 47 was statistically significantly related to an increased risk of symptoms on the attention deficit subscale of ADHD symptoms (RR (95%CI)=1.8 (1.0, 3.2)) but not to hyperactivity symptoms. A statistically significant higher risk of poor social competence symptoms was observed as a consequence of postnatal PBDE 47 exposure (RR (95%CI)=2.6 (1.2, 5.9)). Adjustment for other organochlorine compounds did not influence the results.	This study highlights the importance of assessing the effects of PBDE exposure not just prenatally but also during the early years of life. In the light of current evidence a precautionary approach towards PBDE exposure of both mothers and children seems warranted.	Gascón et al., 2011

Table E2: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Manhattan (USA) Prospective cohort 2001-2007	Child neurodevelopment	To study prenatal PBDE exposure and neurodevelopment at ages 1-4 and 6 years.	Longitudinal cohort of 329 women who were pregnant on September 2001. 210 cord blood were analysed.	210 cord blood specimens were analyzed for selected PBDE congeners. A subset of 152 children with cord BDE measurements participated in the tests. Multivariate regression analyses were used to evaluate the associations between concentrations of individual PBDE congeners and neurodevelopmental indices.	Prenatal exposure to BDE-47 was negatively associated with neurodevelopmental indices with statistical significance for 12-month Psychomotor Development Index, 24-month Mental Development Index, 48-month full and verbal IQ scores. For BDE-99, a significant negative association was detected for 24-month Mental Development Index. Exposure to BDE-100 was negatively associated with neurodevelopment for 24-month Mental Development Index, 48-month full verbal and performance IQ scores and for 72-month performance IQ scores. BDE-153 showed significant negative effects on 48- and 72-month full and performance IQ scores. A comparison in developmental scores between the highest 20% and lower 80% prenatal exposure groups showed that children with higher prenatal concentrations of BDE-47, -99 and -100 scored lower than the rest of the population for nearly all neurodevelopmental indices at all time points. Median cord blood concentrations of PBDE congeners BDE-47, -99, and -100 were 11.2, 3.2, and 1.4 ng/g lipid, respectively. After adjustment for potential confounders, including Cord blood total mercury and lead concentrations, children with higher concentrations of BDE-47, -99, or -100 scored lower on tests of mental and physical development at 1-4 and 6 years.	This study reports that children who had a higher cord blood concentration of BDE-47, -99 and -100 scored lower on tests for mental and physical development at ages between 1 and 4 and 6 years	Herbstman et al., 2010

Table E2: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
The Netherlands, Prospective Groningen infant COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens) study October 2001-November 2002	Child motor, cognitive and behavioural outcome	To investigate the influence of prenatal exposure to organohalogen compounds (OHCs), including brominated flame retardants, on motor, cognitive and behavioural outcome in healthy children of school age	N = 62	Children in whose mothers the following compounds had been determined in the 35th week of pregnancy: BDE-47, -99, -100, -153, -154. When the children were 5–6 years of age, their neuropsychological functioning was assessed: motor performance (coordination, fine motor skills), cognition (intelligence, visual perception, visuomotor integration, inhibitory control, verbal memory, and attention), and behavior.	PBDEs correlated positively and negatively with neurodevelopmental outcome in Dutch children at 5 – 6 years: worse fine manipulative abilities, worse attention, better coordination, better visual perception, and better behavior. In detail, BDE-47 was significantly correlated with alterations in sustained attention, internalized behavior (including emotional reactivity, anxiety/depression, somatic complains, withdrawn behavior), total behavioral outcome (no further details are given) and coordination. For BDE-99, significant changes in internalizing behavior and total behavioral outcome were detected. BDE-100 significantly correlated with coordination, internalizing behavior, externalizing behavior (attention, aggression) and total behavioral outcome alterations. BDE-153 was significantly correlated to visual perception changes assessed using the "geometric puzzles" subtest, in which the child is asked to match two shapes outside a grid with shapes inside the grid. BDE-154 induced changes in fine manipulative abilities.	Transplacental transfer of polybrominated flame retardants is associated with the development of children at school age	Roze et al., 2009

Table E3. Epidemiological studies on cancer.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Sweden 2000-2002	non-Hodgkin lymphoma (NHL)	To determine lipid-based plasma concentrations of organochlorine compounds and PBDE. To correlate the concentration of these substances to titres of antibodies to EBV EA	Case-control study: 99 cases with NHL and 99 population based controls.	Measurements of lipid adjusted plasma concentrations of one PBDE congener (no. 47) in people with NHL and controls	For BDE-47 mean and median concentrations (ng/g lipid) were 2.8, 2.7 and 1,5, 1.8 in cases and controls respectively (p=0.3). An association was found between the organohalogen and titres of EA IgA for the diffuse large B-cell type.	No association was found between concentrations of PBDE and non-Hodgkin lymphoma risk. There was no interaction of PBDE with titre of IGG antibody to EBV EA.	Hardell et al., 2009
Sweden 1996-99	Exocrine pancreatic cancer	Association of adipose tissue concentrations of POPs, including PBDEs, with exocrine pancreatic cancer risk and survival.	Case-control study: 21 consecutive cases with exocrine pancreatic cancer; 59 controls	Tests on abdominal adipose tissue; anamnestic questionnaire	Significantly increased concentrations of PBDEs were found in cases. Sum of PDBEs: mean and median: 5.1, 3.1 and 2.3 and 1.6 (ng/g fat) in cases and controls respectively, P=.0004. The OR was not significantly increased for PBDEs concentrations in adipose tissue and pancreatic cancer risk (3.9; 95 % CI, 0.93-16.3). Adjusting for differences in body mass index (BMI) between cases and controls did not affect this result. Survival of cases was not significantly affected by levels of PBDEs present in the adipose tissue (P = 0.09). It should be noted that the number of cases in this study was low, with corresponding effects on study power.	No association between high tissue concentration of PBDE and decreased survival. No statistically significant association between tissue concentration of PBDE and pancreatic cancer risk.	Hardell et al., 2007

Table E3. Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Sweden 1997-2000	Testicular cancer Prenatal exposure	Possible associations between the concentrations of a number of persistent halogenated compounds, including PBDEs, in blood and the risk of testicular cancer.	Case-control study 58 cases with testicular cancer 61 age-matched controls. 44 case mothers 45 control mothers	Tests on blood ; Anamnestic questionnaire	No significant differences were found between cases and controls. Case mothers had in general higher concentrations of persistent halogenated compounds. There was a statistically elevated risk of testicular cancer in association with blood levels of PBDEs in case mothers, OR = 2.5, 95 % CI = 1.02-6.0. The OR was somewhat higher for non-seminoma than seminoma, and was significant only for the non-seminoma (high BPDE v low BPDE OR for seminoma: 2.1 (0.5-9.2); non-seminoma: 3.2 (1.1-8.9).	The authors suggest their results provide evidence that in utero exposure to BPDEs may be a risk factor for testicular cancer. However, in view of the temporal trends in BPDEs, it is also possible that the association could be due to more general differences in diet.	Hardell et al., 2006
Wisconsin Great Lakes USA 1998-2000	Breast cancer	Association between recent consumption of sport-caught fish, a source of BPDEs amongst other organic contaminants and breast cancer	Population-based case-control study Cases: 1,481 women from Wisconsin Cancer Reporting System, age 20-69 years, Controls: 1,301 women of similar age, randomly selected from population lists	Telephone interviews	Women who recently consumed sport-caught fish vs women who had never eaten it: RR = 1.00. 95 % CI = 0.86-1.17. Recent consumption and postmenopausal breast cancer: RR = 0-78. 95 % CI = 0.57-1.07. Recent consumption and premenopausal breast cancer: OR = 1.70 (95 % CI: 1.16-2.50).	No overall association between recent consumption of sport-caught fish, and breast cancer. There may be an increased breast cancer risk for subgroups of women who are young and/or premenopausal.	McElroy et al., 2004
San Francisco Bay Area, California, USA Late 1990s	Breast cancer	PBDE levels in breast adipose tissue of 23 Californian women	11 breast cancer cases, 3 ductal carcinoma *in situ* , 7 controls	Concentrations of the ΣPBDE, BDE-47, 99,100,153, 154 in the adipose tissue were determined	See conclusions	There was no correlation between disease status and total PBDE concentrations	She et al., 2002

Table E3. Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Sweden 1995-97	Non-Hodgkin's lymphoma	Association between non-Hodgkin's lymphoma and adipose tissue levels of BDE-47.	77 subjects, age 28 to 85 years. 19 patients had non-Hodgkin's lymphoma, 23 had malignant melanoma, 8 had other cancers or in situ changes, and 27 had no cancer diagnosis.	Concentrations of the flame retardant 2,2',4,4'-TeBDE in the adipose tissue were determined.	Adipose tissue levels of BDE-47 were used as a biomarker for total PBDE exposure. The mean concentration of 2,2',4,4'-TetraBDE was 5.1 ng/g fat (range 0.6-27.5) for the 27 persons without malignancies. For NHL patients the mean concentration was 13.0 ng/g fat (range 1.0-98.2). A non significantly elevated risk with dose response was found for NHL when the cases and controls were compared in the two highest concentration groups (2.05-< 5.43 ng/g fat and > or = 5.43 ng/g fat) with the lowest group (< 2.05 ng/g fat) yielding odds ratio (OR) 1.9 with 95 % confidence interval 0.3-14 and OR 3.8, CI 0.7-26, respectively. The results for the patients with malignant melanoma did not differ from the controls.	There was no clear association between non-Hodgkin's lymphoma and exposure to BDE-47.	Hardell et al., 1998

NHL: non-Hodgkin's lymphoma; IgA: immunoglobulin A; EA: early antigen; EBV: Epstein Barr virus; POP: persistent organic pollutant; OR: odds ratio; BMI: body mass index; CI: confidence interval; RR: relative risk.

Table E4: Epidemiological studies on diabetes and metabolic syndrome.

Reference, Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Wisconsin Great Lakes (USA) cohort (4,206 men) frequent and infrequent consumers of Great Lake fish. Established in early 1990s 2004-2005	Diabetes	To determine whether POP (including PBDE) body burdens are related to diabetes in a cross section of Great Lake sport fish consumers.	N = 503	Cross- sectional study. Serum was collected and tested for DDE, PCBs, sum of 8 PBDEs, BDE-47, -153, hemoglobin A1c and lipids. Diabetes diagnosis, demographics and fish consumption were assessed by self-report.	The odds of diabetes with above 66th percentile PBDEs was 13.5 (95 % CI: 0.7 251.2) in 38 persons with hypothyroid disease and 0.9 (95 % CI = 0.5, 1.7, p = 0.84) in 465 persons without hypo-thyroid disease.	Non-significant association of PBDEs, BDE-47 and -153 with diabetes was found only in subjects with hypothyroid disease.	Turyk et al., 2009
NHANES established 1999 2003-2004	Diabetes and metabolic syndrome	To study serum concentrations of BFRs in relation to diabetes and metabolic syndrome	N diabetes=1,367. N metabolic syndrome=637.	Cross-sectional study. ORs adjusted for relevant confounders (gender, age, ethnic group, socio-economic status, BMI).	Adjusted odds ratios across quartiles of serum concentrations for BDE-153 and diabetes were 1.0, 1.6, 2.6, 2.7 snf 1.8 (*P* for quadratic term < 0.01). Corresponding figures for metabolic syndrome were 2.1, 2.4, 1.7 (*P* for quadratic term = 0.02).	Most chemicals belonging to PBDEs, except BDE-153 were not clearly associated with diabetes and metabolic syndrome.	Lim et al., 2008

Table E5: Epidemiological studies on effects on fertility and offspring.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Quebec, Canada	Sperm quality	To study semen parameters in relation to serum PBDE.	N = 52 adult men recruited in a fertility clinic	Plasma PBDE congeners (BDE-47, BDE-99, BDE-100, BDE-153) were measured. Sperm analyses were performed. Multiple regression analysis was performed controlling for age and other covariates.	Semen mobility was negatively related to BDE-47 ($p < 0.05$), BDE-100 ($p < 0.05$), Sum of PBDE ($p < 0.01$). No relations were observed with other semen parameters.	PBDE might interfere with semen mobility in general population.	Abdelouahab et al., 2011
Salinas Valley (agricultural region of California). April 2007-2008	Menstruation characteristics.	Whether high human milk PBDE levels in reproductive-age females lead to interference with menstruation characteristics.	CHAMACOS cohort of low-income, predominantly Mexican women. n = 46	BDE-15, -28, -47, -49, -99, -100, -153, -154, --183, -196, -197, -203, -207, -208 and -209	Women's age at menarche was not correlated with human milk PBDE levels. Increased BDE-208 and -209 levels were associated with the prolonged length of average and the longest menstrual cycle. Higher concentrations of the sum of PBDEs and the higher brominated diphenyl ethers from BDE-183 to -209, except -197, were linked to women whose menstruation periods were still coming irregularly at the sampling time. Age-adjusted odds ratios (ORs) of BDE-153, -183, -207, -208, and sum of PBDEs were higher in women with length of average menstrual cycle N32 days, compared to the control. Women whose menstruation periods still came irregularly when they were 18 years old had higher age-adjusted ORs of BDE-207, -208, -209, and sum of PBDEs than those whose periods came regularly at the same age.	Sum of PBDEs and certain individual PBDEs appear to have potential to prolong length of average menstrual cycle and delay the age when menstruation periods begin coming regularly. Findings are of difficult interpretation because of small sample size.	Chao et al., 2010

Table E5: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Salinas Valley (agricultural region of California). 1999-2000	Time to pregnancy (TTP), menstrual cycle characteristics	Association of maternal concentrations of PBDEs in serum during pregnancy with TTP and menstrual cycle characteristics.	CHAMACOS cohort of low-income, predominantly Mexican women. *n* = 223 pregnant women	BDE-47, -99, -100, -153, sum of the 4 congeners	Increasing levels of BDE-47, -99, -100, -153 and the sum of the four congeners were all associated with longer TTP: BDE-47 (OR:0.7, 95%CI 0.5-1.0), BDE-99 (OR:0.7, 0.5-1.0), BDE-100 [OR: 0.6, 0.4–0.9], BDE-153 (OR : 0.5;,0.3–0.8), sum of four congeners (OR: 0.7, 0.5–1.0). PBDEs were not associated with menstrual cycle characteristics.	Increasing levels of PBDE were associated to longer TTP, but not with menstrual cycle characteristics.	Harley et al., 2010
Singapore 2006	Birth outcomes	To correlate birth outcomes with the levels of persistent organic pollutants (including PBDEs)	41 cord blood samples	Effects were explored using multivariate data analysis. No correction was made for multiple comparisons	Relatively few PBDE congeners (BDE-28, -47, -99) were detected in more than half of the samples. BDE-47 and -99 were positively associated with Apgar score at 1 minute	BDE-47 and -99 exhibited as positive factors on neonatal performance at birth. Results defy interpretation multiple comparisons	Tan et al., 2009
Salinas Valley (agricultural region of California). Time period not specified	Shortened gestation duration Lower birth weight	To determine whether maternal PBDE serum concentrations during pregnancy were associated with shortened gestation duration and lower birth weight	CHAMACOS cohort of low-income, predominantly Mexican women. Women who delivered a live birth and had enough stored serum for PBDE (n = 413)	The concentration of 10 PBDE congeners in serum samples collected at 26 weeks gestation (n = 316) and shortly before delivery (n = 97) were measured	Preliminary analyses suggest that serum concentrations of BDE-28, -47, -99, -100 and -153 measured at 26 weeks gestation, but not before delivery, were inversely associated with birth weight (β= 93–145 grams for every 10-fold increase in exposure; $P < 0.05$) after controlling for potential confounders including gestational duration. Every 10-fold increase in ΣPBDE was associated with a 148 grams (95 % CI = -260, -36) reduction in birth weight Gestational duration was not associated with PBDE exposure	Results suggest that maternal PBDE serum concentrations at the beginning of the third trimester of pregnancy is inversely associated with birth weight Gestational duration was not associated with PBDE exposure	Chevrier et al., 2009

Table E5: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Osaka (Japan) 2003	Sperm quality Testis size	Pilot study on the relationship between human serum PBDEs and sperm quality and testis size	10 randomly selected samples from 45 samples of 45 young Japanese males	Blood serum and sperm samples were collected on a monthly basis during 2003. 29 PBDE congeners were monitored	The sperm concentration of these participants ranged from 25-115 million/mL. No participant had a sperm concentration below 20 million/mL, the minimum fertility standard established by the WHO. Inverse correlations were observed between the serum BDE-153 concentration and sperm concentration ($r = -0.841$, $p = 0.002$) and testis size ($r = -0.764$, $p = 0.01$). However, no significant relationships were observed between the serum concentrations of the other congeners and the sperm concentration (r ranged from -0.187 to -0.099, $p = 0.605$-0.786) or testis size (r ranged from -0.216 to -0.054, $p = 0.548$– 0.883).	Inverse correlations were observed between the serum concentration of BDE-153 and sperm concentration. No significant relationships were observed between serum concentrations of the other congeners and sperm concentration	Akutsu et al., 2008

Table E5: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Denmark-Finland. 1997–2001	Cryptorchidism	To study the association of exposure to PBDEs with testicular maldescent	Cases: 95 cryptorchid boys Controls: 185 healthy boys from a prospective cohort study.	Analyses of whole placentas and individual human milk samples for 14 PBDEs and infant serum samples for gonadotropins, sex-hormone binding globulin, testosterone, and inhibin B	In 86 placenta-milk pairs, placenta PBDE concentrations in fat were lower than in human milk, and a larger number of congeners were nondetectable. There was no significant difference between boys with and without cryptorchidism for individual congeners, the sum of 5 most prevalent, or all 14 congeners The concentration of PBDEs in human milk was significantly higher in boys with cryptorchidism than in controls (sum of BDE-47, -153, -99, -100, -28, -66 and -154: median, 4.16 vs. 3.16 ng/g fat; $p < 0.007$) There was a positive correlation between the sum of PBDEs and serum luteinizing hormone ($p < 0.033$) The sum of PBDEs in human milk did not differ between Denmark and Finland (median, 3.52 vs. 3.44 ng/g fat), but significant differences in some individual congeners were found	Prenatal PBDEs levels in human milk, but not in placenta, showed an association with congenital cryptorchidism	Main et al., 2007

Table E5: Continued.

Location, Time period	Outcome	Aim	Study population	Methods	Results	Conclusions	References
Taiwan 2000 - 2001.	Birth outcome Maternal menstruation characteristics.	To examine how PBDEs in human milk are associated with infant birth outcome and maternal menstruation characteristics.	Human milk samples from 20 healthy women	Twelve PBDE congener levels (BDE-17, -28, -47, -66, -85, -99, -100, -138, -153, -154, -183, -209) were measured in human milk samples. Participants answered a detailed questionnaire concerning maternal age, maternal weight before pregnancy, maternal height, smoking and dietary habits, drinking alcohol, medical and pregnancy history, and menstruation characteristics. The demographic characteristics of newborns were measured after delivery, including birth weight, birth length, gestational age, head and chest circumference, and the assessment of Apgar score at 1 and 5 min.	The mean level of PBDEs in human milk was 3.93±1.74 ng/g fat. The estimated PBDE daily intake for a breast fed infant was 20.6 ng/kg b.w. per day after delivery. After adjustment for maternal age, pre-pregnant BMI, and parity, increased PBDEs in human milk was related with decreased birth outcome, particularly for birth weight and length, chest circumference, and Quetelet's index of infants No significant differences in PBDEs were found between the two groups of menstrual cycle length higher and lower than 30 days after adjustment for maternal age, pre-pregnant BMI, and parity.	*In utero* exposure to low doses of PBDEs may result in lower birth weight and short birth length Interpretation of results is hampered by the small sample size and multiple comparisons	Chao et al., 2007

F. BODY BURDEN AS DOSE METRIC FOR PBDE TOXICITY

The body burden (BB, amount/kg b.w.) reflects the accumulation of a chemical at the level of the total body. Assuming toxicity in the i^{th} organ to be directly related to a chemical's organ concentration the time course of the organ concentration $C_i(t)$ can be related to the $BB_{(t)}$, with "t" being the time since the start of exposure to the chemical. The most straightforward way of modeling is to relate $C_i(t)$ to the concentration in blood $C_{bl}(t)$ by means of a partition coefficient p_i:

$$C_i(t) = p_i \cdot C_{bl}(t) \qquad \text{(A.1)}$$

with:

p_i	the organ-blood partition coefficient
$C_{bl}(t)$	the concentration in the blood (amount/kg)

$C_i(t)$ can also be expressed using the total amount of the chemical in a specific organ and the organ volume:

$$C_i(t) = \frac{A_i(t)}{V_i} \qquad \text{(A.2)}$$

with:

$A(t)$	total amount in the organ (amount)
Vi	organ volume (l)

Consequently $BB_{(t)}$ is:

$$BB(t) = \frac{\sum_i A_i(t)}{\sum_i V_i} \qquad \text{(A.3)}$$

Substituting A.1 and A.2 into A.3 then gives:

$$BB(t) = C_{bl}(t) \cdot \frac{\sum_i p_i V_i}{\sum_i V_i} \qquad \text{(A.4)}$$

Denoting the ratio $\frac{V_i}{\sum_i V_i}$ as f_i , i.e. the fraction of the i^{th} organ compartment of the total body weight, in equation A.4 then relates $BB(t)$, via $C_{bl}(t)$ and f_i , to the organ specific exposure $p_i C_{bl}(t)$:

$$BB(t) = C_{bl}(t) \cdot \sum_i p_i f_i \qquad \text{(A.5)}$$

Basically equation A.5 states that *BB(t)* can be obtained by multiplying the concentration in blood with the organ specific exposure, determined by the product of an organ's affinity for a chemical relative to the blood (as reflected by the organ's partition coefficient p_i) and the organ's fraction of the total body weight (as reflected by f_i). Consequently, the concentration in the blood is determined by the combined effect of these two parameters over all *i* organs.

Regarding PBDEs, the partition coefficients p_i are in general determined by the organ lipid content. Assuming this content to be constant within a species the partition coefficients likely have a constant value too, with interspecies differences being caused by differences in organ lipid content. An exception may be the partition coefficient p_l in the rodent liver. Whether or not lipid partitioning suffices as the starting point for the *BB(t)* as the dose metric for PBDE organ concentration, induced PBDE organ toxicity depends on the AhR binding affinity, efficiency of the PBDE-AhR complex to induce P450 proteins and the P450 binding affinity. In the case of PBDEs the affinity for the AhR is low, and kinetic experiments have not given indication for the hepatic sequestration (Staskal et al., 2005, 2006a,b). Therefore equation A.5 is considered valid in relating the *BB(t)* to organ exposure after repeated exposure. It should be noted that in the statistical analysis, interspecies differences in p_i and f_i are considered as "residual uncertainty" when using the *BB(t)* as dose metric for organ exposure.

The adipose tissue concentration as dose metric for extrahepatic toxicity

In practice, due to the absence of suitable information on the organ specific concentrations as calculated from the *BB(t)* may be available only for a limited number of organs, whereas toxicity data may be available for more organs. In these cases the adipose tissue concentration instead of the BB can be used as a dose surrogate for the concentration in the extrahepatic organs, in particular when the BB does not reflect hepatic sequestration. In the case of thyroid toxicity, for instance, the adipose tissue concentration can be used as a dose surrogate for the thyroid concentration. Assuming (for the sake of simplicity) "steady state" conditions with respect to PBDE exposure and thyroid toxicity (E_{thy}) to be induced this toxicity depends on the total "steady state" thyroid concentration ($C_{thy,ss}$), or:

$$E_{thy} = f(C_{thy,ss}) \qquad \text{(A.6)}$$

where *f* denotes the relation (function) in a generic manner.

Furthermore, assuming $C_{thy.ss}$ to be a function of the total "steady state" adipose tissue concentration $C_{f.ss}$, the following equation holds:

$$C_{thy,ss} = f'(C_{f,ss}) \qquad \text{(A.7)}$$

and thus:

$$E_{thy} = f(f'(C_{f,ss})) \qquad \text{(A.8)}$$

Assuming the lipid content of the thyroid and the adipose tissue to be constant the "steady state" distribution between these organs is characterized by the ratio of their lipid partition coefficients the following relationship holds:

$$\frac{C_{thy,ss}}{C_{f,ss}} = \frac{p_{thy}}{p_f} \tag{A.9}$$

So, in the case of a linear relationship between thyroid toxicity and the total thyroid concentration the induction of thyroid toxicity (E_{thy}) can be expressed as a linear function of the concentration in the adipose tissue:

$$E_{thy} = \alpha \cdot \frac{p_{thy}}{p_f} \cdot C_{f,ss} \tag{A.10}$$

A more complicated situation occurs when the relationship between thyroid toxicity and the thyroid concentration is non-linear. In such a case a convenient, non-linear dose response relation would be of the form:

$$E_{thy} = a \cdot [c - (c-1) \cdot \exp(-b \cdot C_{thy,ss})] \tag{A.11}$$

which then leads to the following relation between induced thyroid toxicity and the concentration in the adipose tissue:

$$E_{thy} = a \cdot [c - (c-1) \cdot \exp(-b \cdot \frac{p_{thy}}{p_f} C_{f,ss})] \tag{A.12}$$

G. DOSE RESPONSE MODELING

PBDEs are characterized by their slow removal from the body and, consequently, their bioaccumulating properties after repeated exposure. As a result the dose metric associated with the risk of PBDEs gradually changes from the daily (external) intake to its accumulated amount in the body. Regarding the latter, the body burden (BB, total amount in the body divided by body weight) provides a generic dose metric for a chemical's accumulation in the body. The BB was used as the dose metric for the risk characterization as follows:

Step 1: The determination of the acute/chronic BMDL in the animal and its corresponding BB in the average animal (*BMDL* and BB_a, dimension: amount/kg b.w.)).

In the case of a single oral dose the BB_a is:

$$BB_a = F_{abs,a} \cdot BMDL$$

with:

$F_{abs,a}$	Fraction of the chemical in food which is absorbed into the animal body (dimensionless)
BMDL	Bench Mark Dose Lower Limit for animal toxicity (amount/kg b.w.)
BB_a	Body burden in the experimental animal at the BMDL (amount/kg b.w.)

Step 2: The interspecies extrapolation of the BMDL BB in the animal to man. Assuming PBDE exposure to occur mainly via the food the chronic human (external) exposure ($D_{r,h}$) is calculated which leads to this BB in the (average) human corresponding to the BMDL BB in the animal. As PBDEs are expected to distribute solely in the adipose tissue in humans one compartmental modeling may suffice here. Assuming the chronic human exposure to lead to a "steady state" situation $D_{r,h}$ can be calculated by:

$$D_{r,h} = \frac{BB_a \cdot k_{el,h}}{F_{abs,h}} \quad (1)$$

with:

BB_a	Body burden in the experimental animal at the BMDL (amount/kg b.w.)
$k_{el,h}$	Rate constant[28] for the removal from the human body (dimension: day^{-1})
$F_{abs,h}$	Fraction of the chemical in food which is absorbed into the body (dimensionless)
$D_{r,h}$	Chronic human daily dietary intake (amount/kg b.w. per day)

The calculated human dietary intake, i.e. $D_{r,h}$ can then be compared with the estimated human dietary intake (see Chapter 9).

[28] Note that for one-compartmental modeling the relationship $\ln 2 = k_{el} \cdot t_{1/2}$ holds, with $t_{1/2}$ the half-life in the body, i.e. the time needed for half of the amount of a chemical to be removed from the body once the exposure has stopped.

BMD analysis

The dose-response analysis and the calculation of the BMD and the BMDL, i.e. its 95 % lower confidence limit was performed using the PROAST software (Slob, 2002). This results in a BMD and its associated uncertainty distribution (confidence interval, CI), related to a predefined benchmark response (BMR). Two families of nested dose response models, the Exponential and Hill models, present in PROAST were fitted to the (continuous) toxicity data. This procedure accounts for the incorporation of model uncertainty in the dose-response analysis. For the evaluated endpoints both model families resulted in acceptable fits (based on the log-likelihood criteria, see Slob, 2002). The bootstrap technique (1000 runs) was used to generate a BMD distribution for each model (Moerbeek et al., 2004). Both BMD distributions were subsequently combined to generate an overall BMD distribution. In the applied probabilistic risk assessment approach the whole uncertainty distribution around the BMD is used as an input (Bokkers, 2009; Slob and Pieters, 1998). All BMD/BMDL calculations were performed for BMR=5 % and BMR=10 %. As explained in Section 8.5 a BMR=10 % was used for risk characterization.

The quality of the dose-response data was checked by applying the criteria for the application of dose - response modeling in risk characterization as developed by EFSA (2009). Dose-response data are considered poor, and therefore not informative, when one (or more) of the following criteria are met:

1) the confidence interval around the BMD is wide
2) different models result in widely different BMDL values
3) the BMD is estimated by extrapolation outside the range of observation, such that the BMD(L) would then depend heavily on the model used.

Criteria to judge the adequacy of the dose-response data on the basis of the range of BMDL values obtained (criterion no. 2) have so far not been established. EFSA (2009) proposes that, as a general rule, dose-response data should not result in a range of BMDL values from different accepted models that substantially exceeds one order of magnitude. The other two criteria are not quantified either. For consistency reasons, we propose that criteria no. 1 and 3 should meet this requirement too. Thus, the upper and lower limits of the 90 % CI should not exceed one order of magnitude. Furthermore, the BMD should not be 10 times higher than the highest applied dose level, or 10 times lower than the lowest applied dose level.

BDE-47

Selected toxicity studies

Eriksson et al. (2001)

The Eriksson et al. (2001) study identified neurotoxicity on the developing brain of neonatal male mice as a sensitive toxic effect of BDE-47. In this study neonatal mice were exposed by gavage to a single dose (0, 0.7 and 10.5 mg/kg b.w.) at PND10. BDE-47 was administered in a 20 % weight:water peanut oil emulsion. At the age of 2 and 4 months the mice were tested on their spontaneous motor behavior and habituation capability, i.e. the ability to explore a new environment (total activity, locomotion, rearing).

Using equation (1) for the extrapolation of the BB at PND10 to man basically assumes that in humans this BB is reached after prolonged exposure, i.e. after a time period long enough to reach a “steady state”. Given an expected human BDE-47 half-life of just over 2 years (see below) such a situation may be expected around 10-12 years. Now, assuming the sensitive time window for the induction of neurodevelopmental toxicity in humans to lie before this age, the application of a “steady state” BB as a dose metric for the induction of this effect on the period between birth and 10-12 years of age overestimates toxic risk. Nevertheless, using a “steady state” BB for the calculation of $D_{r,h}$ guarantees

that up to the age of 10-12 years the human BB will stay below the BB in mice which is associated with neurodevelopmental toxicity. In case sensitivity for neurodevelopmental toxicity even extends beyond this age the calculated $D_{r,h}$ guarantees that even during adolescence the human BB will stay just at the level of the BB in mice which is associated with the onset of neurodevelopmental toxicity.

The outcome of the dose-response analyses, i.e. BMD distributions of the various studies and their CIs, is presented in detail in Tables G1 and G2 and in Figure G1.

Locomotion was selected as a more reliable parameter than rearing and therefore the BMD of 0.338 mg/kg b.w. and its $BMDL_{10}$ of 0.309 mg/kg b.w. are the endpoints to be used for BDE-47 in the hazard assessment.

Table G1: Overview of BMDs and 90 % CIs (benchmark dose lower limit: BMDL, benchmark dose upper limit: BMDU) for neurobehavioural toxicity of BDE-47 in mice (Erikson et al., 2001). BMR: 5 %.

Endpoint	Model [a]	BMR (%)	BMD	90 % CI	
				BMDL	BMDU
Locomotion[c]	E	+5	0.173	0.158	0.191
(40-60 min)	H	+5	0.530	0.265	0.541
Rearing	E	-5	0.278	0.251	0.312
(0-20 min)	H	-5	0.087	0.067	0.114
Rearing	E	+5	4.93	0.512 [b]	8.58 [b]
(40-60 min)	H	+5	0.576	0.290	0.589
Total activity	E	-5	0.772	0.659	0.934
(0-20 min)	H	-5	0.531	0.422	0.688
Total activity	E	+5	0.732	0.566	1.04
(40-60 min, age: 2 months)	H	+5	1.00	0.698	1.306
Total activity	E	+5	0.470	0.395	0.579
(40-60 min, age: 4 months)	H	+5	0.757	0.410	0.892

(a): E = exponential model, H = Hill model.
(b): BMDL is more than 10 times smaller than the BMDU, quality criterion 1.
(c): See Figure G1for BMD analysis.

Table G2: Overview of BMDs and 90 % CIs (benchmark dose lower limit: BMDL, benchmark dose upper limit: BMDU) for neurobehavioural toxicity of BDE-47 in mice (Erikson et al., 2001). BMR: 10 %. Bold BMDs are used for further hazard characterization.

Endpoint	Model [(a)]	BMR (%)	BMD	90 % CI	
				BMDL	BMDU
Locomotion (40-60 min)	E	+10	**0.338**	**0.309**	0.373
	H	+10	1.028	0.519	1.061
Rearing (0-20 min)	E	-10	0.572	0.516	0.640
	H	-10	0.184	0.142	0.240
Rearing (40-60 min)	E	+10	6.604	0.885 [(b)]	9.28 [(b)]
	H	+10	1.114	1.098	1.131
Total activity (0-20 min)	E	-10	1.585	1.353	1.918
	H	-10	1.121	0.892	1.453
Total activity (40-60 min, age: 2 months)	E	+10	1.429	1.105	2.022
	H	+10	1.911	1.365	2.490
Total activity (40-60 min, age: 4 months)	E	+10	0.917	0.772	1.13
	H	+10	1.446	0.805	1.704

(a): E = exponential model, H = Hill model,
(b): BMDL is more than 10 times smaller than the BMDU, quality criterion 1.

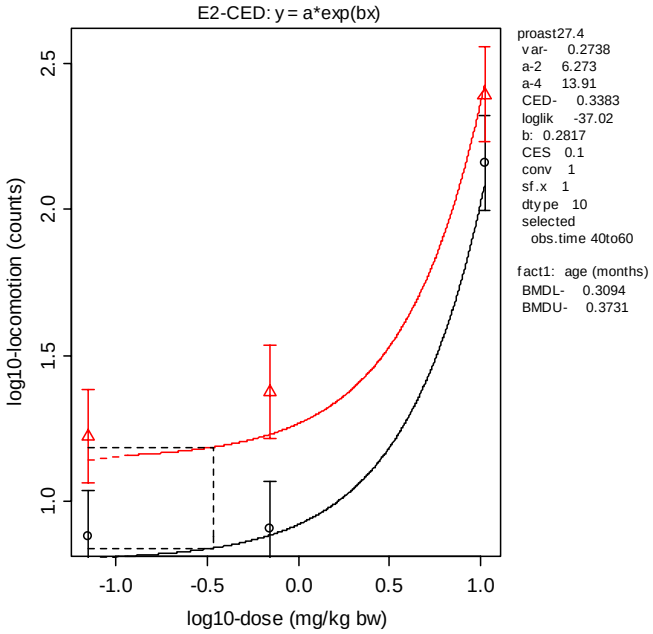

Figure G1: Dose-response analysis of locomotion (counts) against BDE-47 dose for the 40-60 minute observation interval in 2 (circles) and 4 (triangles) month old mice Model fit: Exponential, BMR: 10%. Data, mean, SDs, n/dose group = 8, are from Eriksson et al. (2001). Obtained BMDs are reported in Table G1. The curves indicate sustained exploratory activity in the Eriksson et al. (2001) study protocol of treated mice during the observation period, indicating a delayed habituation response in exploring a new environment.

BDE-99

Selected toxicity studies

Eriksson et al. (2001)

Neonatal male mice received a single dose by gavage of 0, 0.8 or 12.0 mg BDE-99/kg b.w. on PND10. At the age of 2 and 4 months mice were tested for spontaneous motor behaviour (total activity, locomotion, rearing and habituation).

Starting point for the interspecies extrapolation of toxicity is the BB in neonatal mice at PND10. The extrapolation then further proceeds in analogy with the Eriksson et al. (2001) study for BDE-47.

Viberg et al. (2004a)

Neonatal mice (males and females) received a single dose by gavage of 0, 0.4, 0.8, 4.0, 8.0 or 16 mg BDE-99/kg b.w. at PND10. At the age of 2, 5 and 8 months mice were tested for spontaneous motor behaviour (total activity, locomotion, rearing and habituation).

Starting point for the interspecies extrapolation of toxicity is the BB in neonatal mice at PND10. The extrapolation then further proceeds in analogy with the Eriksson et al. (2001) study for BDE-47.

Viberg et al. (2004b)

Neonatal male mice received a single dose by gavage of 0, 0.2, 0.4 or 12.0 mg BDE-99/kg b.w. on PND10. At the age of 2 and 4 months mice were tested for spontaneous motor behaviour (total activity, locomotion, rearing and habituation).

Starting point for the interspecies extrapolation of toxicity is the BB in neonatal mice at PND10. The extrapolation then further proceeds in analogy with the Eriksson et al. (2001) study for BDE-47.

Kuriyama et al. (2005)

Pregnant rats were treated orally (gavage) with a single dose of 0, 60 or 300 µg BDE-99/kg b.w. on GD6. Locomotor activity of offspring was assessed at PND36 and PND71. Effects on sperm quality and reproductive performance were assessed in male offspring at PND140.

The outcome of the dose-response analyses, i.e. BMD distributions of the various studies and their CIs, is presented in detail in Table G3 and Figures G2 and G3.

Table G3: Overview of BMDs (µg/kg b.w.) and 90 % CIs (benchmark dose lower limit: BMDL, benchmark dose upper limit: BMDU) for neurobehavioral toxicity of BDE-99 in mice (Viberg et al., 2004a, b; Eriksson et al., 2001) or the rat (Kuriyama et al., 2005). BMR: 5 % and 10%. Bold BMD/BMDLs are used for further hazard characterization. Shaded grey: does not meet EFSA criteria for BMD modeling.

Viberg et al. (2004a, b), Eriksson et al. (2001)									
Species: mice									
Observation period: 0-20 min			**BMR: 5 %**				**BMR: 10 %**		
Endpoint	**Age (month)**	**Reference**	**Model**	**BMD**	**BMDL**	**BMDU**	**BMD**	**BMDL**	**BMDU**
Locomotion	2	Eriksson et al. (2001)	E	37	21	66	153	93	247
	2	Eriksson et al. (2001)	H	152	89	257	396	244	640
	4	Eriksson et al. (2001)	E	31	17	58	128	75	217
	4	Eriksson et al. (2001)	H	125	70	226	326	191	566
	2	Viberg et al. (2004a)	E	22	12	38	88	55	137
	2	Viberg et al. (2004a)	H	78	50	120	204	140	293
	5	Viberg et al. (2004a)	E	21	11	36	84	53	132
	5	Viberg et al. (2004a)	H	75	48	116	196	135	280
	8	Viberg et al. (2004a)	E	13	7	24	54	33	87
	8	Viberg et al. (2004b)	H	44	27	69	114	76	168
	4	Viberg et al. (2004b)	E	57	32	98	232	144	368
	4	Viberg et al. (2004b)	H	225	142	351	586	389	874
Total activity	2,4	Eriksson et al. (2001)	E	38	21	70	161	96	269
	2,4	Eriksson et al. (2001)	H	102	57	180	295	175	494
	2,5,8 [(a)]	Viberg et al. (2004a)	E	25	14	42	104	66	159
	2 5,8 [(a)]	Viberg et al. (2004a)	H	64	41	99	186	128	265
	4	Viberg et al. (2004b)	E	65	36	112	273	169	436
	4	Viberg et al. (2004b)	H	189	116	300	546	357	826

Table G3: Continued.

Viberg et al. (2004a, b), Eriksson et al. (2001)									
Species: mice									
Observation period: 40-60 min									
Locomotion	2,4	Eriksson et al. (2001)	E	173	115	260	208	145	299
	2,4	Eriksson et al. (2001)	H	133	65	220	164	86	257
	2,5,8	Viberg et al. (2004a)	E	236	173	330	285	219	379
	2,5,8	Viberg et al. (2004a)	H	199	122	293	245	163	342
	4	Viberg et al. (2004b)	E	268	137	2382	323	168	2765
	4	Viberg et al. (2004b)	H	234	102	1366	289	133	1623
Total activity	2	Eriksson et al. (2001)	E	55	35	110	111	70	222
	2	Eriksson et al. (2001)	H	57	32	116	116	66	234
	4	Eriksson et al. (2001)	E	15	10	23	31	20	46
	4	Eriksson et al. (2001)	H	11	6	18	**22**	**12**	36
	2,5,8	Viberg et al. (2004a)	E	91	76	108	183	153	218
	2,5,8	Viberg et al. (2004a)	H	74	61	89	149	124	181
	4	Viberg et al. (2004b)	E	176	107	258	356	216	520
	4	Viberg et al. (2004b)	H	144	86	219	291	175	445
Kuriyama et al. (2005)									
Species: rat									
Locomotion [(b)]			E	60	42	101	**116**	**82**	198
			H	67	50	108	127	95	207

(a): See Figure G2 for BMD analysis.
(b): See Figure G3 for BMD analysis.

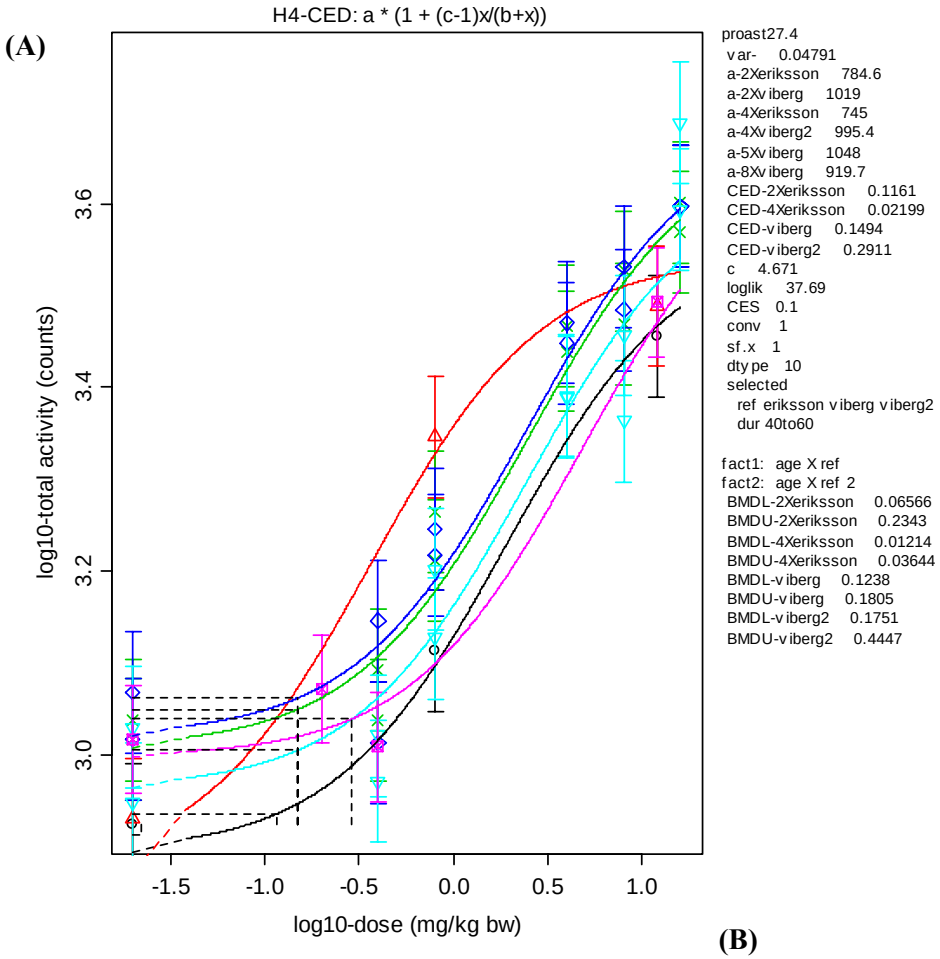

Figure G2: **(A)**: Dose-response analysis of total activity (counts) against BDE-99 dose for the 40-60 minute observation interval in 2, 4, 5 and 8 month old mice. Model fit: Hill model, BMR: 10%. Data, mean, SDs, n/dose group = 8, are from Viberg et al. (2004a,b) and Eriksson et al. (2001). Obtained BMDs are reported in Table G3.

The curves indicate sustained exploratory activity in the Eriksson study protocol of treated mice during the observation period, indicating a delayed habituation response in exploring a new environment. **(B)**: The dose-response relationship for 4 month old mice as reproduced from (A).

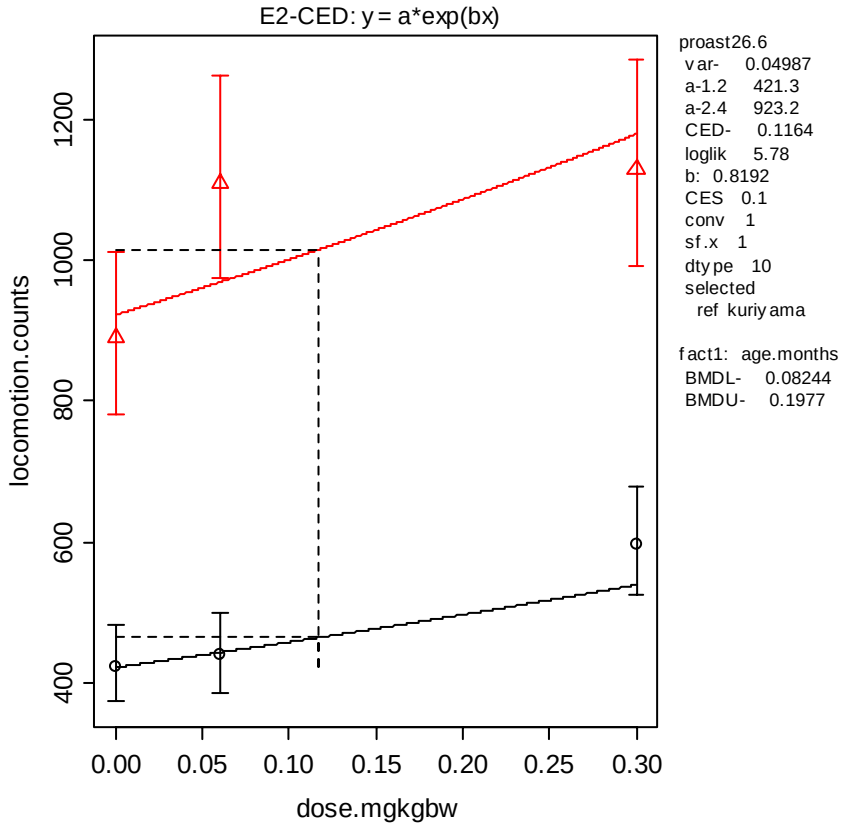

Figure G3: Dose-response analysis of locomotion (counts) against BDE-99 dose. Model fit: Exponential model, BMR: 10 %. Data are from Kuriyama et al. (2005). Upper curve: PND 71, lower curve: PBD36. Obtained BMDs are reported in Table G3. Note that, because of the equal potency parameter b, both dose-response relationships result in the same BMD.

BDE-153

Selected toxicity study

Viberg et al. (2003a)

In Viberg et al. (2003a) neonatal male mice received a single dose by gavage of 0, 0.45, 0.9 or 9 mg BDE-153/kg b.w. on PND10. At the age of 2, 4 and 6 months mice were tested for spontaneous motor behaviour (total activity, locomotion, rearing and habituation).

The outcome of the dose-response analyses, i.e. BMD distributions of the various studies and their CIs, is presented in detail in Table G4 and Figure G4.

Table G4: Overview of BMDs (µg/kg b.w.) and 90 % CIs (benchmark dose lower limit: BMDL, benchmark dose upper limit: BMDU) for neurobehavioral toxicity of BDE-153 in mice (Viberg et al., 2003a). BMR: 5 % and 10 %. Bold BMD/BMDLs are used for further hazard characterization. Shaded grey: does not meet EFSA criteria for BMD modeling.

Viberg et al. (2003a)	**Species: mice**							
Observation period: 0-20 min			**BMR: 5 %**			**BMR: 10 %**		
Endpoint	**Age (month)**	**Model**	**BMD**	**BMDL**	**BMDU**	**BMD**	**BMDL**	**BMDU**
Locomotion	2	E	79	16	324	332	99	954
	2	H	113	28	394	389	132	1028
	4	E	53	10	236	226	63	695
	4	H	75	17	279	258	82	730
	6	E	40	7	177	168	48	516
	6	H	55	13	202	101	63	522
Rearing	2,4,6	E	764	336	783	792	409	808
	2,4,6	H	746	333	765	771	392	788
Total activity	2	E	74	57	97	157	122	208
	2	H	53	37	78	120	83	175
	4	E	250	156	466	533	331	993
	4	H	192	124	304	429	278	681
	6	E	187	127	315	399	271	673
	6	H	141	93	223	317	208	500
Observation period: 40-60 min								
Locomotion	2,4,6	E	725	706	743	744	726	761
	2,4,6	H	731	702	748	749	722	765
Rearing	2	E	1920	861	3407	559	422	773
	2	H	490	357	671	575	439	779
	4	E	349	218	502	392	279	521
	4	H	349	233	477	410	290	536
	6	E	246	142	393	275	188	395
	6	H	241	155	354	283	193	397
Total activity	2[(a)]	E	316	229	435	639	463	879
	4[(a)]	E	119	78	174	241	159	351
	6[(a)]	E	53	41	71	**107**	**83**	144
	2,4,8	H	435	295	806	521	387	829

(a): see Figure G4 for BMD analysis.

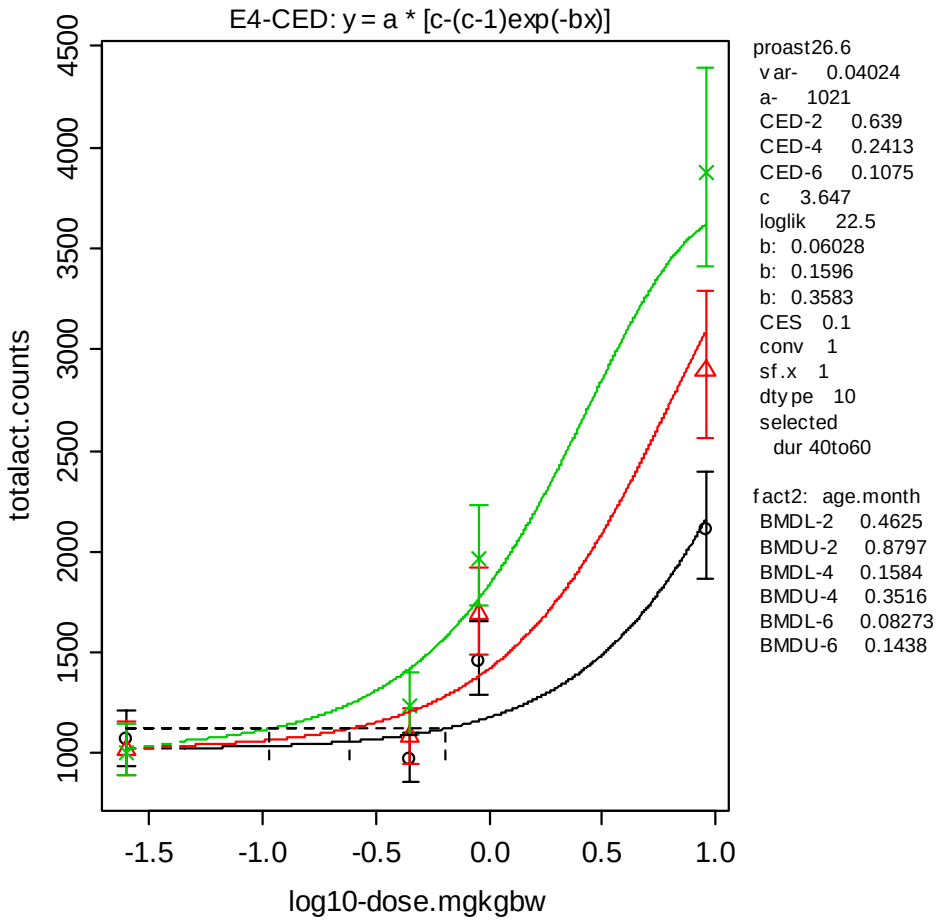

Figure G4: Dose-response analysis of total activity (counts) against BDE-153 dose for the 40-60 minute observation interval in 2, 4 and 6 month old mice. Model fit: Exponential model, BMR: 10 %. Data from Viberg et al. (2003a). Obtained BMDs are reported in Table G4.

The curves indicate sustained exploratory activity in the Eriksson study protocol of treated mice during the observation period, indicating a delayed habituation response in exploring a new environment.

BDE-209

Selected toxicity studies

Viberg et al. (2003b)

Neonatal male mice were exposed orally (gavage) on PND3 to a single dose of 0, 2.22 or 20.1 mg BDE-209/kg b.w. At the age of 2, 4 and 6 months mice were tested for spontaneous motor behaviour (total activity, locomotion, rearing and habituation). Mice exposed on PND10 or 19 did not show any effect of treatment.

Viberg et al. (2007)

Neonatal male rats received a single oral dose (gavage) of 0, 6.7 or 20.1 mg BDE-209/kg b.w. on PND3. Spontaneous motor behaviour (total activity, locomotion, rearing and habituation) was tested at the age of 2 months.

Tseng et al. (2006)

Neonatal male mice were administered by gavage a dose of 0, 10, 100, 500, or 1,500 mg BDE-209 from PND21 to PND70. Effects on sperm function and testes morphology were studied on PND71. Neonatal exposure reduced sperm epididymal sperm mitochondrial membrane potential (MMP), reduced the amplitude of the lateral head displacement (ALH) and induced the generation of hydrogen peroxide in the sperm of sexually mature mice (H_2O_2). The results further allowed for a dose-response analysis of the curvilinear sperm velocity (VCL), angular progressive sperm velocity (VAP) or straight–line sperm velocity (VSL).

Rice et al. (2007)

Neonatal mice (males and females) were exposed to a daily oral dose (gavage) of 0, 6 or 20 mg purified BDE-209/kg b.w. from PND2 to PND15. A functional observational battery was conducted from PND2-20. Locomotor activity was measured for one male and female per litter on PND70 and serum T4 was measured on PND21.

The outcome of the dose-response analyses, i.e. BMD distributions of the various studies and their CIs, is presented in detail in Table G5 and Figures G5 and G6.

Table G5: Overview of BMDs and 90 % CIs (benchmark dose lower limit: BMDL, benchmark dose upper limit: BMDU) for neurobehavioral toxicity (Viberg et al., 2003b, mg/kg b.w.), thyroid toxicity (Rice et al., 2007, mg/kg b.w. per day) and reproductive toxicity (Tseng et al., 2006) of BDE-209 in mice. BMR: 5 and 10%. Bold BMD/BMDLs are used for further hazard characterization.

Viberg et al. (2003, 2007)	**Species: mice**								
Observation period: 0-20 min			**BMR: 5%**				**BMR: 10%**		
Endpoint	**Age (month)**	**Reference**	**Model**	**BMD**	**BMDL**	**BMDU**	**BMD**	**BMDL**	**BMDU**
Locomotion	2,4,6	Viberg et al. (2003b)	E	15.4	6.5	16.4	16.8	9.4	17.6
	2,4,6	Viberg et al. (2003b)	H	17.2	17.2	17.6	18.2	18.0	18.4
	2	Viberg et al. (2007)	E	14.6	5.0	15.6	15.9	7.2	16.8
	2	Viberg et al. (2007)	H	16.8	16.6	17.0	17.6	17.4	17.7
Total activity	2,4,6	Viberg et al. (2007)	E	12.9	8.5	14.4	15.1	11.5	16.4
	2,4,6	Viberg et al. (2007)	H	17.8	17.5	18.0	18.6	18.3	18.8
	2	Viberg et al. (2007)	E	11.7	7.2	13.2	13.8	9.7	15.0
	2	Viberg et al. (2007)	H	17.2	17.0	17.4	18.0	17.8	18.1
Observation period: 40-60 min									
Locomotion	2,4,6	Viberg et al. (2003b)	E	6.4	2.8	9.0	7.7	3.9	10.3
	2,4,6	Viberg et al. (2003b)	H				No acceptable fit		
	2	Viberg et al. (2007)	E	6.0	2.5	8.6	7.2	3.4	9.8
	2	Viberg et al. (2007)	H				No acceptable fit		
Total activity	2,4,6[(a)]	Viberg et al. (2003b)	E	3.9	2.7	5.9	5.8	4.3	7.9
	2,4,6[(a)]	Viberg et al. (2003b)	H	2.7	1.4	5.0	4.6	2.5	7.4
	2[(a)]	Viberg et al. (2007)	E	2.9	1.8	4.6	4.2	2.9	6.2
	2[(a)]	Viberg et al. (2007)	H	1.8	0.9	4.1	**3.2**	**1.7**	6.0
Rice et al. (2007)	Sex: m/f								
Serum T4[(b)]			E	5.9	3.7	15.0	12.1	7.6	30.8
			H	5.4	3.2	14.5	**11.5**	**6.8**	30.6

Table G5: Continued.

Observation period 40-60 min			BMR: 5%				BMR: 10%		
Endpoint	**Age (month)**	**Reference**	**Model**	**BMD**	**BMDL**	**BMDU**	**BMD**	**BMDL**	**BMDU**
Tseng et al (2006)									
Sperm motility			E			No dose response information			
			H			No dose response information			
VCL[(c)]			E	367.0	223.2	1025.0	753.0	458.5	2106.0
			H	328.0	186.8	959.1	692.0	394.4	2025.0
VAP[(c)]			E	450.0	252.7	2070.0	925.0	519.0	4253.0
			H	413.0	217.3	1954.0	873.0	458.8	4126.0
VSL[(c)]			E	391.0	225.5	1476.0	804.0	463.3	3032.0
			H	353.0	189.6	1377.0	745.0	400.3	2908.0
ALH[(c)]			E	340.0	218.7	763.7	698.0	449.2	1569.0
			H	303.0	183.2	712.6	639.0	386.9	1504/0
H_2O_2[(c)]			E	119.0	83.4	205.5	232.0	163.0	401.4
			H	159.9	125.1	250.3	305.0	238.8	477.6

b.w.: body weight; E: exponential model; H: Hill model; VCL: curvilinear sperm velocity; VAP: angular progressive sperm velocity; VSL: straight–line sperm velocity; ALH: amplitude of the lateral head displacement; H_2O_2: hydrogen peroxide.
(a): see Figure G5 for BMD analysis.
(b): see Figure G6 for BMD analysis.
(c): see text study description above.

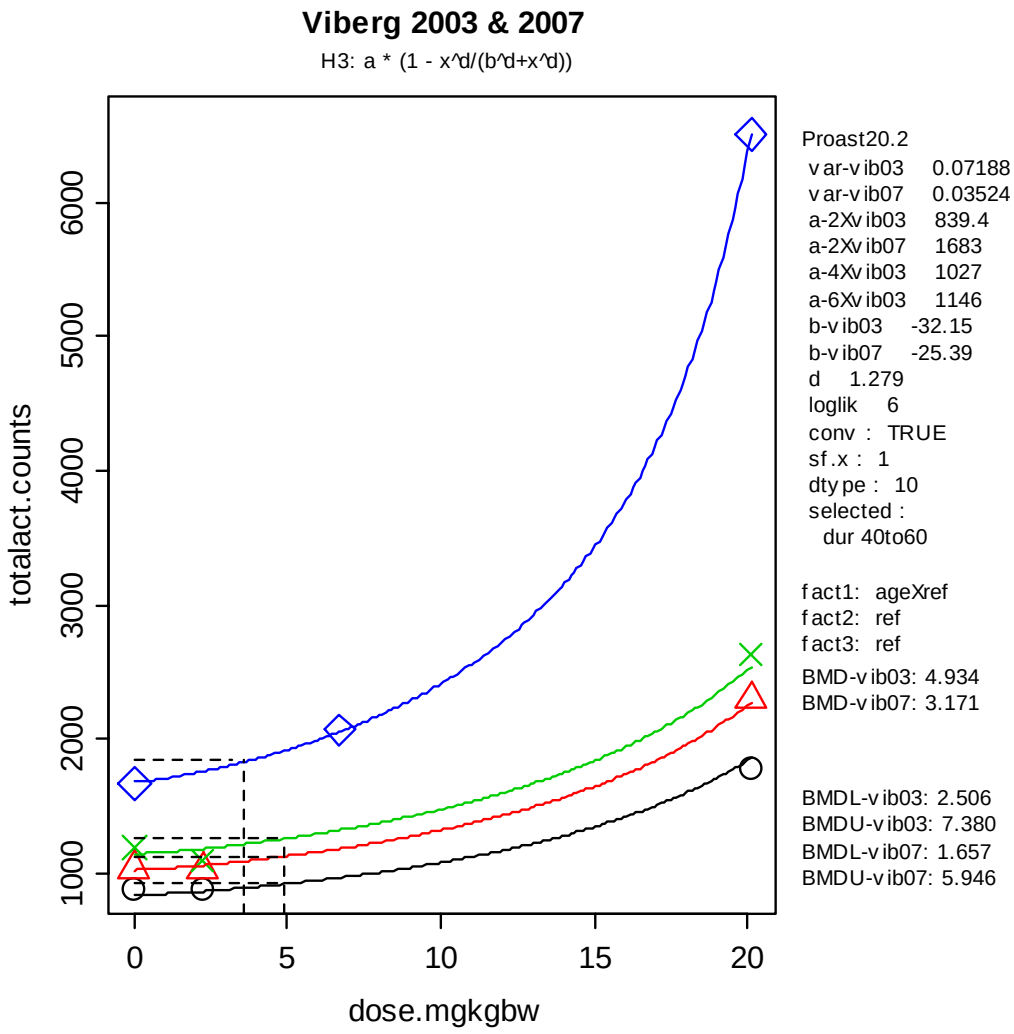

Figure G5: Dose-response analysis of total activity (counts) against BDE-209 dose for the 40-60 minute observation interval in 2, 4 and 6 month old mice. Model fit: Hill model, BMR: 5%. Data from Viberg et al. (2003b, 2007). Obtained BMDs are reported in Table G5.

The curves indicate sustained exploratory activity in the Eriksson study protocol of treated mice during the observation period, indicating a delayed habituation response in exploring a new environment.

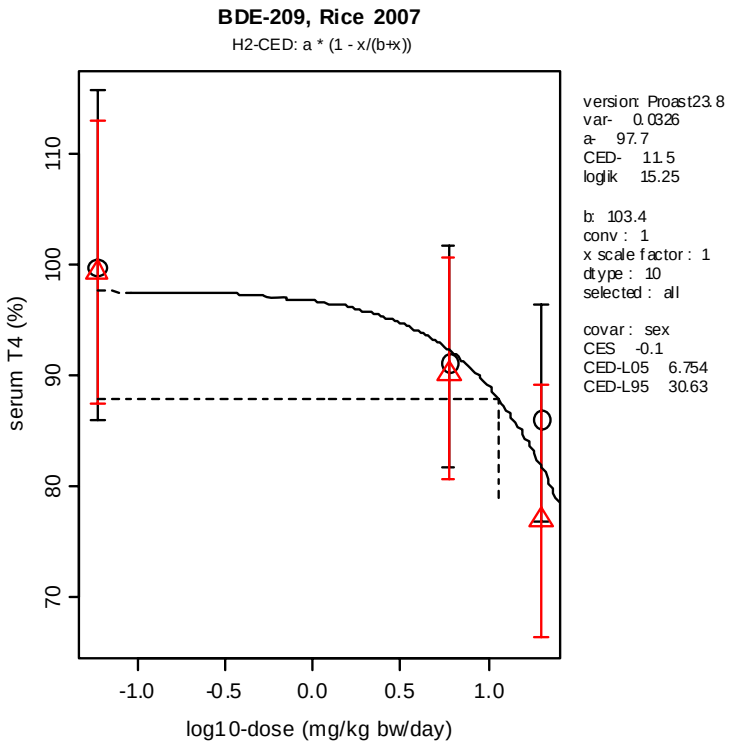

Figure G6: Dose-response analysis of serum T4 (% of control) against BDE-209 dose in male and female mice. Model fit: Hill model, BMR: 10 %. Data from Rice et al. (2007). Obtained BMDs are reported in Table G5. Males and females show the same dose-response characteristics.

ABBREVIATIONS

ABS	Acetylnitrile-butadiene-styrene
ADHD	Attention deficit/hyperactivity disorder
AED	Atomic emission detection
ALH	Amplitude of the lateral head displacement
ALT	Alanine transferase
AFSSA	French Food Safety Agency, currently ANSES
AhR	Aryl hydrocarbon receptor
ANSES	French Agency for Food, Environmental and Occupational Health and Safety, former AFSSA.
AR	Androgen receptor
AST	Aspartate transferase
AT	Austria
ATP	Adenosine triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry
BAFs	Bioaccumulation factors
BB	Body burden
BCFs	Bioconcentration factors
BE	Belgium
BFR	Brominated Flame Retardant
BG	Bulgaria
BMD	Benchmark dose
BMDL	Benchmark dose lower confidence limit; 95 %-confidence lower bound
BMDU	Benchmark dose – upper limit
BMFs	Biomagnification factors
BMI	Body mass index
BMR	Benchmark response
Br	Bromine
BTBPE	bis(2,4,6-tribromophenoxy)ethane
b.w.	Body weight
CAR	Constitutive androstane receptor
CAS	Chemical Abstracts Service
CBV3	Human coxsackievirus B3
CGN	Cerebellar granule neuron
CHex	Cyclohexane
CHO	Chinese hamster ovary
CI	Confidence interval

CONTAM Panel	Panel on Contaminants in the Food Chain
COT	Committee on Toxicity
CRM	Certified Reference Material
CZ	The Czech Republic
CYP	Cytochrome P450
$D_{r,h}$	Chronic dietary intake
DA	Dopamine
DAPK	Death associated protein kinase
DATEX	Data collection and Exposure Unit (EFSA), currently DCM Unit (EFSA).
DBDPE	Decabromodiphenyl ethane
D/H	Deuterium/hydrogen ratio
DCM	Dietary and Chemical Monitoring Unit (EFSA), former DATEX Unit (EFSA)
DD	Duplicate diet
DDE	1,1-*bis*-(4-chlorophenyl)-2,2-dichloroethene
DE	Germany
DEs	Diphenyl ethers
DecaBDE	Decabromodiphenyl ether commercial mixture
DK	Denmark
DOPAC	dihydroxyphenylacetic acid
DR-CALUX	Dioxin Responsive - Chemically-Activated LUciferase eXpression
E2	17β-estradiol
EA	Early antigen
EBV	Epstein-Barr virus
ECB	European Chemicals Bureau
EC	European Commission
EC_{50}	Effect concentration 50 %
ECHA	European Chemicals Agency
ECNI	Electron capture negative ionization
EE	Estonia
EFSA	European Food Safety Authority
EI	Electron Ionization
ELISA	Enzyme Linked Immunosorbent Assay
EPA	Environmental Protection Agency
ER	Estrogen receptor
EROD	Ethoxy-resorufin-O-deethylase
ES	Spain
EU	European Union

EXPOCHI	EFSA Article 36 project "Individual food consumption data and exposure assessment studies for children" (acronym EXPOCHI)
FAO	Food and Agriculture Organization
FI	Fixed-interval
FI	Finland
FR	France
FoodEx	Food classification system developed by EFSA DCM Unit
GC	Gas chromatography
GD	Gestational day
GEMS/Food	WHO-Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
GPC	Gel permeation chromatography
GR	Glucocorticoid receptor
GSH	Glutathion
GSSG	Glutathion disulfide
HBCDD	Hexabromocyclododecane
Hex	Hexane
HIPS	High impact polystryrene
HRMS	High resolution MS
HU	Hungary
IC_{50}	Inhibitory concentration 50 %
IE	Ireland
IgA	Immunoglubulin A
IGF-I	Insulin-like growth factor-I
ILS	Interlaboratory study
IOM	Institute of Medicine of the U.S. National Academies of Sciences
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IT	Italy
IUPAC	International Union of Pure and Applied Chemistry
i.v.	Intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LB	Lower bound
LD_{50}	Lethal dose
LDH	lactic dehydrogenase
LLA	Life-Long average
LLE	Liquid–liquid extraction
LRTAP POPs	Long-range transboundary air pollution on persistent organic pollutants

LOAEL	Lowest-observed-adverse-effect level
LOD	Limit of detection
LOEL	Lowest-observed-effect level
log K_{ow}	Octanol-water partitioning coefficient
LOQ	Limit of quantification
LRMS	Low resolution MS
LV	Latvia
MAE	Microwave-assisted extraction
MB	Market basket
MCRA	Monte-Carlo risk assessment
Mct8	Monocarboxylate transporter 8
MDA	Malondialdehyde
MeO	Methoxylated
MLs	Maximum levels
MMP	Mitochondrial membrane potential
MOD	Malonic dialdehyde
MOE	Margin of exposure
MOS	Margin of safety
mPXR	Murine pregnane X receptor
MS	Mass spectrometry
MTT	3-(4,5-Dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide
NAS	Nucleophilic aromatic substitution
ND	Non detects
NHL	Non-Hodgkin's lymphoma
NL	The Netherlands
NFA	Swedish National Food Administration
NHANES	National Health and Nutrition Examination Survey
NHL	Non-Hodgkin's lymphoma
NIST	National Institute for Standards and Technology (USA)
NO	Norway
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NTP	National Toxicology Programme
OctaBDE	Octabromodiphenyl ether commercial mixture
OHC	Organohalogen compounds
OH-PBDEs	Hydroxylated polibrominated diphenyl ethers
OR	Odds ratio

PBBs	Polybrominated biphenyls
PBDD/Fs	Polybrominated dibenzo-*p*-dioxins and furans
PBDEs	Polybrominated diphenyl ethers
PBPK	Physiologycalli based pharmacokinetic
PBT	Polybutylene terephtalate
PCBs	Polychlorinated biphenyls
PCDDs	Polychlorinated dibenzo-*p*-dioxins
PCDFs	Polychlorinated dibenzofurans
PentaBDE	Pentabromodiphenyl ether commercial mixture
PHC	Polyhalogenated compounds
PI	Propidium iodide
PKC	Protein kinase C
PL	Poland
PLE	Pressurized liquid extraction
PM	Particulate matter
PND	Postnatal day
POPs	Persistent organic pollutants
PPS	Preputial separation
PR	Progesteron receptor
PROD	Pentoxyresorufin-O-deethylase
PTV	Programmable temperature vaporizing injector
PXR	Pregnane X Receptor
QC/QA	Quality control and quality assurance
RAR	Risk assessment reports
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	Reference dose
RoHS	Restriction of the use of certain hazardous substances
ROS	Reactive oxygen species
RR	Relative risk
RSV	Respiratory syncytial virus
SAF	Sampling adjustment factors
SD	Standard deviation
SE	Sweden
SFE	Supercritical fluid extraction
SK	Slovak Republic
SL	Slovenia
SOD	Superoxide dismutase

SPE	Solip-phase extraction
SRM	Standard reference material
STEM	Statistical exposure model
SV	Seminal vesicle
SXR	Steroid X receptor
T	Testosterone
T3	Triiodothyronine
T4	Thyroxine
TBBP-A	Tetrabromobisphenol A
TCDD	2,3,7,8- tetrachlorodibenzo-*p*-dioxin
TchE	Acetylcholinesterase
TDI	Tolerable daily intake
TDS	Total diet study
TEF	Toxicity equivalency factor
TEQ	Toxic equivalents
TH	Thyroid hormone
TK locus	Thymidine kinase locus
TNF	Tumor necrosis factor
Tol	Toluene
TR	Thyroid hormone receptor
TRE	Thyroid hormone response element
TSH	Thyroid stimulating hormone
TTP	Time to pregnancy
TTR	Transthyretin
UB	Upper bound
UF	Uncertainty factor
UGT	Uridine diphosphoglucuronosyl transferase
UK	United Kingdom
UNECE	United Nations Economic Commission for Europe
USA	United States of America
US-EPA	United States Environmental Protection Agency
UV	Ultraviolet
VAP	Angular progressive sperm velocity
VCL	Curvilinear sperm velocity
VP	Ventral prostate
VSL	Straight–line sperm velocity
WBC	Whole body concentration

WEEE	Waste electrical and electronic equipment
WHO	World Health Organisation
w.w.	Wet weight
XIAP	x-chromosome linked inhibitor of apoptosis