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Research Article

Dietary intake and risk evaluation of polybrominated diphenyl ethers in The Netherlands

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The current study aims at estimating the dietary intake of PBDEs in the Netherlands and evaluating the resultant risk. Dietary intake was estimated using results of PBDE analyses in Dutch food products from 2003/2004 and consumption data of the third Dutch National Food Consumption Survey (1997/1998). Assuming that non-detects represent levels of half the detection limit, the median long-term intake of the Dutch population of the sum of five major PBDEs (namely PBDEs 47, 99, 100, 153+154) is 0.79 ng/kg body weight bw/day (P97.5: 1.62 ng/kg bw/day). When non-detects are considered as zeros the values are 0.53 (median) and 1.34 (P97.5) ng/kg bw/day. Environmental concentrations of PBDEs in Europe are expected to decline in the near future because of the ban on penta- and octaBDE technical products. However, it will take at least a decade before this will result in lower PBDE concentrations in food products. Hence, a regular monitoring program for PBDEs is recommended. A risk evaluation at the most sensitive endpoints of BDE 99 carried out in this paper indicates that, although the long-term exposure to BDE 99 is well below the human exposure threshold level for neurodevelopmental toxicity, it may be close to that for reproductive toxicity.

Keywords: Dietary exposure / Dietary intake / Polybrominated diphenyl ethers / Risk evaluation / Risk assessment

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1 Introduction

Brominated flame retardants (BFRs) are widely used in electronic household equipment (*e.g.*, personal computers and television sets), plastics, textile, and polyurethane foam in furniture and cars. In 1999, about one-third of the total world production of BFRs consisted of polybrominated diphenyl ethers (PBDEs) [1, 2]. The number of bromine atoms in PBDEs ranges from one to ten, resulting in 209 different possible congeners. For example, there are 42 tetrabromodiphenyl ether congeners, but only a few of them, specifically BDE 47 and occasionally BDE 66, are found in the product formulations and in the environment [3]. Three commercial PBDE formulations were produced: the penta formulation (mostly penta- and tetraBDE congeners), the octa formulation (mostly hepta- and octaBDE congeners), and the deca formulation (97% decaBDE with some nona- and octaBDE congeners) [2, 4]. The use of pentaBDE and octaBDE technical products in all applications for the EU market has been formally banned since August 2004 (the production of pentaBDE being already voluntarily terminated in the EU during the last decade). The use of pentaBDE and octaBDE in new electric and electronic equipment has been banned in the EU since July 2006. Also in the USA, the penta and octa formulations were voluntarily

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Abbreviations: BFR, brominated flame retardant; **BB**, body burden; **BDE**, brominated diphenyl ether; **bw**, body weight; **CPAP**, conversion model for primary agricultural products; **DNFCS**, Dutch National Food Consumption Survey; **EFSA**, European Food Safety Authority; **GD**, gestational day; **JECFA**, Joint FAO/WHO Expert Committee on Food Additives; **LOAEL**, lowest observed adverse effect level; **NEVO**, Netherlands Food Composition Table; **NOAEL**, no observed adverse effect level; **PBDE**, polybrominated diphenyl ether; **PCB**, polychlorinated biphenyl; **RIVM**, National Institute of Public Health and the Environment, The Netherlands; **RIVO**, Netherlands Institute for Fisheries Research; **STEM**, statistical exposure model

withdrawn from the market by their manufacturers at the end of 2004 [5 – 7].

PBDEs are additives mixed into polymers and are not chemically bound to the plastic or textile. Therefore they may be released relatively easily from consumer products. Potential routes of PBDEs into the environment are through PBDE manufacture and incorporation into products, through volatilization or formation of dusts from treated products during their lifetime, and through recycling and disposal of treated products [4, 7]. The environmental fate of PBDEs is similar to the fate of other persistent organic pollutants, such as PCBs (polychlorinated biphenyls) and dioxins (polychlorinated dibenzofurans and polychlorinated dibenzodioxins) [2]. PBDEs have been shown to be present in air, sewage sludge, sediments, fish, birds, and mammals, including human breast milk, blood, and adipose tissue (*e.g.* [1, 4, 8]). The predominant PBDEs in the environment and human tissue are BDE 47, 99, 100, 153, 154, 183, and 209 [4, 8]. PBDEs are persistent and bioaccumulative (*e.g.*, [2]). In general terms, PBDEs affect thyroid hormone levels (*e.g.*, BDE 47 [9, 10]) and can cause developmental toxicity (*e.g.*, BDE 99 [11]) and developmental neurotoxicity (*e.g.*, BDE 47, [12]). In comparison with PCBs and dioxins, the amount of toxicity data on PBDEs is limited. For this reason, until now, limit values based on toxicological evaluations (such as a tolerable daily intake) have not been set for these substances. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded in a recent evaluation of PBDEs that these substances do not have a common toxic mechanism [13]. Hence it is not possible to use one PBDE as a standard for the toxicity of the other congeners as is the case for dioxin-like compounds. The JECFA concluded that the ratio between the lowest reported toxic effect dose in test animals and the exposure to man *via* food (margin of exposure) appears to be large enough to preclude a concern for human health.

The intake of PBDEs mainly occurs *via* food, the ingestion of house dust, and inhalation of indoor air (*e.g.*, [7, 14]). A recent model estimate suggested that the ingestion of house dust is the largest contributor to human exposure (except for breast-fed infants) in the Toronto area in Canada (60% for an average adult), followed by the dietary ingestion of animal and dairy products (33%) [7]. Indeed, statistically significant, positive associations between PBDE concentrations in breast milk and house dust, as well as with reported dietary habits, have been recently shown [15]. Results of another recent study, in which indoor air and dust samples from Canadian households were analyzed, indicate that for adults, at mean dust ingestion rates, 14% of the total daily exposure to PBDEs is due to dust ingestion, when compared with diet (82%) and inhalation (4%) [7]. Toddlers were found to get 80% of their daily intake *via* dust ingestion. At high dust ingestion rates the percentages for the dust ingestion pathway rise to 80% for adults and 89% for toddlers [7]. Earlier estimates of median exposures to PBDEs in the UK indicated that diet and inhalation contribute 93 and 7% to the total human exposure, respectively [16]. Lorber [5] evaluated available literature data and concluded that for North Americans, 82% of the total intake originates from indoor house dust exposures *via* ingestion and dermal contact, with inhalation and food/water ingestion explaining the remaining 18%. Note that the use of PBDEs in North America is more widespread than in Europe [1]. As a consequence, the contributions of the different routes of exposure to the total intake may differ between the two continents.

Since PBDEs bioaccumulate in a similar way to PCBs and dioxins, fatty food products of animal origin are expected to be the major contributors to dietary intake. In the present study, food products from relevant food groups purchased in The Netherlands were analyzed for five predominant PBDEs of toxicological concern (tetraBDE 47, pentaBDEs 99 and 100, and hexaBDEs 153+154). The measured concentrations were used to calculate the dietary exposure to PBDEs in the Dutch population. Whether this exposure is of toxic relevance rests on the comparison with toxic exposure levels. In the absence of human toxicity data the latter are to be derived by extrapolation of animal toxicity to man. For persistent chemicals like PBDEs, such interspecies extrapolation is to be based on the so-called body burden approach [13, 17 – 19]. This approach takes the accumulated amount in the animal body, rather than the administered dose, as the dose metric for toxicity and, hence, for the interspecies extrapolation of toxicity. In order to bring the calculated exposure in perspective with PBDE toxicity, this paper reviews the available animal toxicity studies with respect to their suitability for PBDE risk assessment.

2 Materials and methods

2.1 Food sampling

A sampling program was designed to obtain representative data on concentrations of lipophilic compounds like PBDEs in foods consumed by the general population in The Netherlands. The sampling strategy was based on the assumption that these substances are almost entirely present in the fat fraction of the foodstuffs. For the selection of foods, the most recent food consumption survey for the whole Dutch population, the database of the Dutch National Food Consumption Survey 1997/1998 (DNFCS 3), was used. The survey has been described in detail elsewhere [20, 21]. In short, the food consumption of 6250 individuals (1 – 97 years of age) in 2770 households was assessed by a 2-day dietary record method, equally distributed over the 7 days of the week and over a whole year. This resulted in consumption data of 1207 different food products. For each food product, a comprehensive description, including the fat percentage, was available from the Netherlands Food Composition Table

(NEVO Table) [22]. Of these, 714 products were expected to contain PBDEs and were ranked into 16 food categories according to type of fat or oil. The food categories were divided into four groups. Samples of Group 1 (butter, cheese, eggs, vegetable oils and fats, industrial oils and fats, bread, fruit, canned tuna, $n = 11$) and 2 (beef, pork, poultry, mixed meat, milk, $n = 4$) were collected (May – September 2004) and were analyzed by the National Institute of Public Health and the Environment in The Netherlands (RIVM). The sampling consisted of the purchase of a set of food products in supermarkets covering 95% of the fat intake of each food category, and 95% of the product intake for cereals and fruit. Fish and crustaceans (Group 3) were collected in May – September 2003 (from research vessels, fish auctions, fishermen, or wholesale) by The Netherlands Institute for Fisheries Research (RIVO) and were analyzed by the same institute. For Groups 1 and 2, one composite sample was analyzed, for Group 3 more than one sample was available (wild eel: $n = 13$; herring: $n = 4$; mackerel and mussels: $n = 3$; farmed eel, plaice, sole, shrimp, salmon, flounder, pollack, cod: $n = 2$). Every fish sample consisted of 9 – 25 individual fishes. The composite sample of mussels consisted of a homogenate of 100 g mussel meat (out of *ca*. 500 g mussels). Shrimps (500 g) were homogenized and analyzed as whole organisms (uncooked and unpeeled). All samples were stored at −20°C until chemical analysis. (For full details of the sampling procedure of the fish and crustaceans, see [23]). PBDE concentrations in the remaining food categories (Group 4: vegetables, complex dishes, bakery products, and sweets) were not measured but estimated with the conversion model for primary agricultural products (CPAP) [24], based on their composition.

2.2 Chemical analysis

The samples of Group 1 and 2 were extracted with organic solvent(s) in order to isolate the fat fraction containing the PBDEs. To the extracted and dried fat samples, 0.5 – 1.0 mL ^{13}C-labeled standards of the PBDEs were added. Clean-up of the samples was performed with a normal phase HPLC system, equipped with a silica column. Details of the preparation and extraction procedures carried out for the different food products are similar to the procedures of analyses of non-planar PCBs as described elsewhere [25]. GC/MS analyses were performed on a quadrupole MS (type Voyager) coupled to a GC8000 Top (Thermo Finnigan, Breda, The Netherlands) gas chromatograph. GC separations were carried out on a non-polar column (30 m DB-5MS; J W Scientific, Folsom, USA; 0.25 mm id, 0.10 μm film thickness). The temperature program consisted of an isothermal period (50°C, 5 min), a rise of 30°C/min to 180°C, then of 10°C/min to 300°C, and finally a second isothermal period of 10 min at 300°C. Using an Optic PTV-injector (ATAS, Veldhoven, The Netherlands) samples of 100 μL were injected with an injection speed of 10 μL/s in a packed liner (Supelcoport 60/80 mesh, Supelco, Zwijndrecht, The Netherlands). The temperature and pressure of the liner were 50°C and 250 kPa, respectively. Hexane was blown off *via* the split-valve over 30 s, after which the split-valve was closed for 1.7 min. During this latter time period the temperature of the liner was raised by 4°C/min to 330°C and the PBDEs were trapped at the front-end of the GC-column (temp. 50°C). After this procedure the pressure of the liner was reduced to 150 kPa. Helium was used as carrier gas with constant pressure at 150 kPa. The GC/MS interface was maintained at 300°C in all cases and the source temperature was 250°C. Ionization of samples was performed in the electron ionization mode with 70 eV electrons. Detection was performed using the selected ion mode.

Accuracy and reproducibility of the RIVM data were established by a regular quality control procedure, which includes all analytical series to be accompanied by control samples of cow's milk and human milk. The reproducibility of the PBDE method is good (RSD < 16%).

The method employed by RIVO for analysis of the samples of Group 3 (fish and crustaceans) consisted of Soxhlet extraction of the samples with a hexane-acetone solvent mixture, followed by removal of the lipids *via* gel permeation chromatography. Subsequently, the eluate was further purified using silica gel clean-up and concentrated sulfuric acid purification of the extract. After concentration, the extracts were analyzed by GC/MS using negative chemical ionization in the selected ion mode with *m/z* values of both Br isotopes (*m/z* 79 and 81). Further details can be found elsewhere [26]. The quality assurance of the RIVO data is accomplished by the analysis of an in-house quality control sample, blank and duplicate tests, and participation in interlaboratory studies for which good results are obtained. The repeatability of the method is good for all compounds (RSD < 16%).

RIVM analyzed BDE 47, 99, 100, and 153 + 154. The analyses at RIVO include all congeners measured by RIVM, except BDE 153.

The concentrations of BDE 154 reported for the fish data by RIVO may possibly be influenced by the co-eluting brominated biphenyl (BB) 153. However, given its low production and application volumes compared to the PBDEs [27, 28], it is unlikely that BB 153 is found at significant concentrations in the analyzed fish samples and will therefore presumably not add significantly to the BDE 154 signal.

Samples containing PBDE concentrations below the LOD were assigned levels equal to 0.5 × LOD (medium bound estimates) or zero (lower bound estimates). LODs were reported for each analysis.

2.3 Dietary intake of PBDEs

The food consumption of the Dutch population was estimated using the data of the DNFCS 3 (see Table 3 for the mean daily consumption of the different food categories).

The measured PBDE concentrations in the food categories were converted to concentrations in all 714 relevant consumed food products as recorded in the DNFCS 3 (the so-called NEVO foods, after the Dutch Food Composition Table NEVO). The PBDE concentrations were assigned to the NEVO foods by combining information from the chemical analyses of the food categories (Group 1 – 3) with the CPAP as described elsewhere [24]. In CPAP, every NEVO food is expressed as a combination of primary agricultural products (including their mass fractions). The effect of processing (e. g. cooking, frying, peeling) is included in the model. For details, see Supporting Information – Part I.

The PBDE concentrations in NEVO foods were calculated for five congeners (47, 99, 100, 153 + 154). In addition, the exposure to the sum of these five congeners was calculated. Since the concentrations of BDE 153 in fish have not been determined in the current study, these were estimated using the concentration ratios between BDE 153 and 154 in fish samples from 1991 and 2001. These BDE 153/154 ratios were 0.8, 1.0, and 1.3 for lean fish, fatty fish, and crustaceans, respectively (RIVM, unpublished results).

To calculate the short-term PBDE intake of the population, for each participant of the DNFCS the PBDE intake for the two consecutive days considered in the survey was computed. A frequency distribution of these intakes yields information on the variability of daily intakes in the population. Such a distribution shows the variation in short-term intake, but is unsuitable for an assessment of the long-term intake, which is required to assess the possible health risks of this intake. A distribution of the long-term intakes would be considerably narrower than the distribution of daily intakes, because within-subject variations disappear. An estimation of long-term intake was made by statistical analysis applying the statistical exposure model (STEM), developed by Slob [29]. STEM is intended to model the mean dietary intake as a function of age. It combines regression analysis on age by fitting a regression curve to the daily intake data, and nested variance analysis to separate within-subject variance from between-subject variance. The within-subject variance is estimated by analyzing the differences between the intakes on the two consecutive days for each person. By subtraction of the within-subject variance from the total variance, an estimate can be made of the long-term between-subject variance. STEM has previously been applied in dietary intake studies of various compounds [25, 30, 31].

To obtain the 'life-long' average intake for the population, the intakes of all age classes were summed and this sum was divided by the number of age classes.

2.4 Risk evaluation of PBDEs – Interspecies extrapolation of toxicity

Just like the interspecies extrapolation of toxicity on the basis of the administered (external) dose, the extrapolation on the basis of the accumulated amount starts with the selection of suitable toxicity studies and the derivation of a "no observed adverse effect level" (NOAEL) or "lowest observed adverse effect level" (LOAEL) for the most sensitive toxic endpoint observed. Next, the accumulated amount in the animal body corresponding with this NOAEL/LOAEL is calculated. The calculated body burden in the animal is then extrapolated to man by means of (a combination of) uncertainty factors. Finally, the chronic daily human exposure (external dose) which leads to the calculated human body burden, *i. e.*, the expected human "no adverse effect level" (NAEL), is calculated by means of a pharmacokinetic model. In this calculation a one-compartmental kinetic model may be used as a default approach [13, 17 – 19].

2.5 Animal toxicity studies

PBDEs have shown various toxic responses, some of which have also been reported for dioxins, in particular 2,3,7,8-TCDD. Among these are Ah-receptor-dependent responses such as thyroid hormone perturbation [32 – 35], hepatic CYP 1A1 enzyme induction [36], and impaired spermatogenesis [11]. The use of an Ah-receptor endpoint for the evaluation of PBDE toxicity, however, necessitates a high purity of the PBDE solutions used in toxicity studies. For example, PBDE impaired *postnatal* spermatogenesis resulting from *prenatal* exposure has been reported as the most sensitive toxic effect of PBDE toxicity with a LOAEL in rats of 60 μg/kg body weight (bw) [11]. However, for the same effect a NOAEL of 12.5 ng/kg bw was reported for 2,3,7,8-TCDD [37]. Thus, a BDE 99 solution of more than 99.99% purity is needed to exclude 2,3,7,8-TCDD as cause for the observed toxicity. This is significantly higher than the reported 98% purity of the solution actually used [11]. As none of the BDE solutions used in toxicity studies fulfills the mentioned purity criterion, the outcome of these studies is ambiguous. For this reason reported Ah-receptor-dependent PBDE toxicity studies were discarded from further analysis (for reasons of comparison, only the Kuriyama study was further elaborated).

Apart from Ah-receptor-dependent toxicity, PBDEs have consistently shown neurodevelopmental toxicity, as assessed well after birth, in mice which are orally exposed by gavage shortly after birth (BDE 47, 99 [12, 38]; BDE 153, 99, 209, hepta, octa and nonaBDEs [39 – 42]; BDE 99 [43]; BDE 71 [44]). As these effects were described for the period shortly after birth and were induced by a non-food route of exposure (p.o., gavage), they cannot directly be linked to the exposure calculations reported in this paper (which furthermore relate to exposure *via* food in children, adolescents, and adults, and not, as in the animal experiments, to direct exposure of neonates). For this reason the results of these mice toxicity studies were not elaborated further.

Finally, neurobehavioral toxicity has been reported in offspring of dams which had been orally exposed by gavage to BDE 99 during gestational day (GD) 6 through postnatal day (PND) 21 [45]. In this study a LOAEL of 0.6 mg/kg bw/day was found for dams. Neurobehavioral toxicity in offspring was induced by intrauterine exposure during GD 6 – 21 and postnatal exposure *via* breast milk during PND 1 – 21. As the height of this exposure is directly linked with the maternal body burden of BDE 99 during this period, the latter was taken as the starting point for the interspecies extrapolation of toxicity.

2.6 Calculation of body burdens in animal experiments

As stated before, the maternal body burden of mouse dams which have been exposed to a daily dose of BDE 99 from GD 6 through PND 21 may be taken as the starting point for the interspecies extrapolation of neurodevelopmental toxicity from animals to man. This, however, necessitates knowledge of the maternal body burden of the dams during the exposure period. As shown in Supporting Information – Part II, the calculation of this body burden needs the following parameters: the daily administered dose (here: 600 μg/kg bw/day), the fraction of the administered dose which is absorbed (here: 0.60), and the half-lives of BDE 99 in mice due to metabolic and lactational clearance (here: half-life of 18 days for metabolic clearance as obtained from allometric scaling of an experimentally determined half-life of 33 days in the rat). As in particular the half-life of BDE 99 due to lactational clearance is unknown, body burdens can only be calculated under the restriction of assumed lactational clearance. In this respect lactational clearance was assumed to range between as efficient as and four times the metabolic clearance (total body half-lives: 18 or 3.6 days, respectively). Note that as lactational clearance is an efficient way of removing halogenated chemicals from the rodent body, the assumption of equal metabolic and lactational clearance is rather conservative, *i. e.*, it leads to the maximal estimation of the maternal body burden during the period of lactation. Given these specifications the (average) body burden of dams in the Branchi study during the period between GD 6 and PND 21 was calculated to range from 2344 to 3498 μg BDE 99/kg bw.

In a similar way, for the Kuriyama study a body burden of 29.2 μg/kg bw was calculated in rat dams at GD 16 (see Supporting Information – Part II).

2.7 Uncertainty factor

Both the Branchi and the Kuriyama study yielded a LOAEL. In order to extrapolate this value to a NOAEL, an uncertainty factor of 3 was applied [19]. In extrapolating this NOAEL to man, usually an uncertainty factor of 100 is used. This factor compensates for interspecies and intraspecies differences in toxicokinetics and toxicodynamics, *i. e.*, sensitivity for PBDE toxicity. In general a factor of 10 is used both for interspecies and intraspecies extrapolation, with $\sqrt{10}$ representing either the kinetic or the dynamic parts of the extrapolation factors [19]. Since, as with dioxins, the extrapolation procedure already compensates for interspecies differences in kinetics, this extrapolation factor may be omitted. Taking a (remaining) value of $\sqrt{10}$ for interspecies differences in toxicodynamics and 10 for intraspecies differences in kinetics and dynamics, one arrives at a total uncertainty factor of $\sqrt{10} \cdot 10 \cdot 3 = 95$ for the extrapolation of the observed BDE 99 toxicity. It might be argued that this extrapolation factor is too conservative. In the case of the dioxin 2,3,7,8-TCDD, no correction was applied for either inter- and intraspecies differences in toxicodynamics. In this case only a LOAEL to NOAEL correction factor of 3 and an intrahuman kinetic uncertainty factor of $\sqrt{10}$, resulting in an overall factor of 9.6, were applied. However, because, contrary to 2,3,7,8-TCDD, no data on the relative sensitivity of animals and man with respect to BDE 99 toxicity are available, uncertainty factors for inter- and intraspecies differences in sensitivity for BDE 99 toxicity were deemed necessary.

2.8 Calculation of expected human NAEL

As with the dioxin 2,3,7,8-TCDD, the expected human NAEL may be calculated by means of a "steady state" one-compartment kinetic model as shown in Eq. (1), [13, 17 – 19]. In this analysis it is assumed that the long-term daily intake of PBDEs will eventually lead to a constant amount in the body, *i. e.*, the "steady state" body burden. Deviating from 2,3,7,8-TCDD, the exposure of which mainly comes from one source, *i. e.*, food, PBDEs may have two potential routes of exposure: food and house dust. (In the present risk evaluation the exposure from inhalation and dermal contact is ignored.) Given a total intake from food and house dust then gives the following relation between chronic, daily, intake, and resulting "steady state" body burden:

$$I_{ma,f} \cdot F_{abs,f} + I_d \cdot F_{abs,d} = \frac{\ln 2 \cdot BB_{ma}}{t_{1/2} \cdot F_u} \quad (1)$$

with:

- $I_{ma,f}$ Maximal allowed long-term total intake from food (expected human NAEL, amount/kg bw/day)
- $F_{abs,f}$ Fraction of food intake which is absorbed into the body
- I_d Daily intake of dust (amount/kg bw/day)
- $F_{abs,d}$ Fraction of dust intake which is absorbed into the body
- BB_{ma} Maximal allowed human "steady state" body burden (amount/kg bw)
- $t_{1/2}$ Half-life of the compound in the human body (days)
- F_u Uncertainty factor for inter- and intraspecies extrapolation of toxicity

Substituting all parameters except $I_{ma,f}$ into Eq. (1) then allows for the solving of $I_{ma,f}$. In doing so the following parameters were used: $F_{abs,f}$: 0.89 [46], I_d: 1.8 ng/day [47] (see also Supporting Information – Part III), BB_{ma}: 2344–3498 μg/kg bw (see above); $t_{1/2}$: 1.9 –2.8 years (see Supporting Information – Part III), F_u: 95 (see above) and $F_{abs,d}$ to range between minimal 0 and maximal $F_{abs,f}$. In this way a range of 18.8–41.4 ng BDE 99/kg bw/day was calculated for the expected human NAEL for neurodevelopmental toxicity.

Using the same parameters except for a BB_{ma} of 29.2 μg/kg bw allows for the calculation of the expected human NAEL for impaired spermatogenesis. This calculation resulted in a range of 0.23–0.30 ng BDE 99/kg bw/day.

3 Results

3.1 PBDE concentrations in foods

The results of the PBDE analyses are summarized in Tables 1 and 2 for each of the food categories analyzed by RIVM and RIVO. BDEs 47 and 99 were detected in almost all samples, whereas BDEs 100 and 154 were almost exclusively detected in fish and crustaceans and not in other food groups. Because the mechanisms of toxicity of the various PBDEs are different, the PBDEs cannot be summed up for the evaluation of risks and therefore should be considered as individual substances. However, in order to make comparisons between different food categories and different studies *etc*., it is convenient to express the concentrations as the sum of the five PBDEs (ΣPBDEs).

Doing so, it is shown that the highest concentrations were measured in fish and the lowest in fruit.

The highest concentrations in fish were found in fatty fish (herring: 4800 pg/g product). The lowest values were found in lean fish (*e.g.*, tuna: 10 pg/g product). The ΣPBDEs were calculated using estimated concentrations for BDE 153 (see above). On average the so-calculated PBDE 153 concentrations contribute 8 (fish) to 13% (crustaceans) to ΣPBDEs (data not shown).

ΣPBDE concentrations in fruit and cereals were relatively low: 8 and 16 pg/g product, respectively.

ΣPBDE concentrations in meat ranged from 50 to 113 pg/g product. Highest concentrations were found in pork.

3.2 Dietary exposure of the Dutch population to PBDEs

The life-long averaged dietary intakes for the individual PBDE congeners and for the ΣPBDEs calculated with STEM (lower bound and medium bound estimates) are given in Table 3. For the ΣPBDEs, the medium bound life-long averaged intake over all age classes is 0.79 ng/kg bw/day, while the P97.5 is 1.62 ng/kg bw/day. Differences between medium bound and lower bound estimates range from very small (BDE 47 and 99) to up to a factor of 8 (BDE 100). For BDE 153 + 154 the lower bound estimate could not be determined, due to a large number of zero intakes in the population.

BDE 47 shows the highest contribution to the dietary exposure to the ΣPBDEs: about 60–80% to the total (Table 3).

To illustrate the variation of intake with age, the long-term intake (medium bound estimate) at ages 2, 10, and 40 years and the life-long averaged intakes for the two most

Table 1. Mean PBDE concentrations (pg/g fresh product) in fish and crustaceans. Samples < LOD were assigned 0.5 LOD. Between brackets, the result when the samples < LOD were assigned 0

Fish	Fat[a] [%]	BDE 47	BDE 99		BDE 100		BDE 153[b]	BDE 154		BDE 153+154[c]		ΣPBDEs[d]	
Cod	1	200	5	(0)	200		n. d.	1		2		410	
Coalfish	1	200	50	(0)	80	(50)	n. d.	50	(0)	90	(0)	410	(250)
Plaice	1	250	30	(0)	80		n. d.	30	(20)	50	(30)	400	(350)
Sole	1	200	80	(50)	80	(50)	n. d.	50	(50)	90		440	(390)
Mackerel	11	670	520	(470)	130		n. d.	120	(100)	230	(200)	1,550	(1,460)
Herring	17	2,900	740	(680)	930		n. d.	130	(100)	250	(200)	4,810	(4,700)
Eel	28	2,500	320	(280)	880		n. d.	240		460		4,160	(4,120)
Salmon	12	820	380	(350)	180	(150)	n. d.	80	(50)	150	(100)	1,520	(1,420)
Mussels	2	530	200		220	(200)	n. d.	120	(100)	270	(230)	1,220	(1,160)
Shrimp	2	370	430	(400)	50	(0)	n. d.	130	(100)	290	(230)	1,140	(1000)
Tuna fish[e]	1	5	<1	(0)	1	(0)	3	1	(0)	4	(3)	10	(8)

a) Mean fat content of the samples
b) BDE 153 was not analyzed by RIVO
c) BDE 153 was estimated from ratio BDE 153/ BDE 154 of samples of lean and fatty fish and crustaceans at RIVM from total diet studies 1991 and 2001
d) Sum of BDE 47, 99, 100, 153 (estimated), and 154
e) Tuna fish was sampled and measured by RIVM, therefore BDE 153 was analyzed

Table 2. Mean consumption (g/day), fat content and mean PBDE concentrations (pg/g fresh product) in food categories measured at RIVM. Samples <LOD were assigned 0.5LOD. Between brackets, the result when the samples <LOD were assigned 0

Food category	Mean consumption[a] [g/day]	Fat[b] [%]	concentration BDE 47 pg/gay product		concentration BDE 99 pg/g product		concentration BDE 100 pg/g product		concentration BDE 153+154 pg/g product		concentration ΣPBDEs[c] pg/g product	
Butter	3	81	125		90		20	(0)	45	(0)	280	(215)
Cheese	27	31	65		57		24		20	(0)	166	(146)
Eggs	14	10	22		22		13		15	(10)	71	(66)
Veget. oils fats	27	57	10	(0)	27		15	(0)	30	(0)	82	(27)
Industr. oils fats	12	35	15	(0)	20	(0)	25	(0)	50	(0)	110	(0)
Bread (breakfast cereal incl.)	173	1	10		4		0.5	(0)	2	(0)	16	(14)
Fruit (juice incl.)	107	0	4		1	(0)	1	(0)	2	(0)	8	(4)
Beef (mixed meat excl.)	26	16	18		20		10	(0)	15	(0)	63	(38)
Pork (mixed meat excl.)	28	26	37		36		15	(0)	25	(0)	113	(73)
Poultry	17	9	17		19		5	(0)	8	(0)	49	(35)
Mixed meat	14	22	5	(0)	10	(0)	15	(0)	20	(0)	50	(0)
Milk	380	1	28		1	(0)	1	(0)	1	(0)	31	(28)

a) Consumption of other food categories: vegetables (potatoes incl.) 129 g/d, complex dishes 49 g/d, bakery products 42 g/d, sweets 41g/d
b) Mean fat content of the samples
c) Sum of BDE 47, 99, 100, 153, and 154

Table 3. Life-long averaged (*i. e.*, averaged for all age classes) dietary intakes (ng/kg bw/day) of PBDEs by the Dutch population calculated with STEM [23]

Compound	STEM <LOD = 0		STEM <LOD = 0.5 LOD	
	Median	P97.5	Median	P97.5
BDE 47	0.38	1.09	0.40	1.09
BDE 99	0.08	0.17	0.11	0.21
BDE 100	0.01	0.05	0.08	0.14
BDE 153+154[a]	–[b]	–	0.14	0.23
ΣPBDEs[c]	0.53	1.34	0.79	1.62

a) BDE 153 concentrations in fish estimated
b) Could not be determined due to too few positive intakes
c) The result for S PBDEs is not calculated by summing up the results for the individual congeners, but is the result of a separate statistical analysis with STEM. Therefore it is slightly different from the sum of the separate congeners

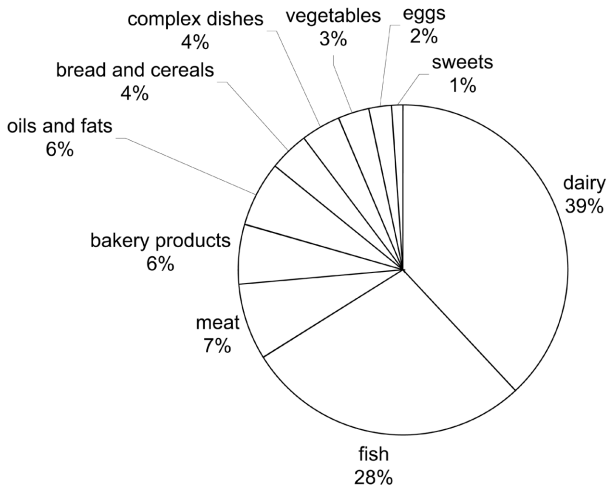

Figure 1. The contribution of different food categories to the intake of the sum of five PBDEs (medium bound estimates) by the Dutch population.

abundant congeners (namely, BDE 47 and BDE 99) are given in Table 4.

The most important food categories contributing to the mean intake of the ΣPBDEs were dairy, fish, and meat (Fig. 1).

3.3 Comparison with expected NAEL

When compared with the expected human NAEL for neurodevelopmental toxicity (18.8–41.4 ng/kg bw/day), the dietary intake of BDE 99 is roughly 100-fold lower.

However, the 99th percentile of the intake (0.24 ng/kg bw/day, see Table 4) is just lower than the expected NAEL for impaired spermatogenesis (0.23–0.30 ng/kg bw/day), indicating that the intake level is borderline to the exposure which is considered as the benchmark for this toxic effect.

4 Discussion

4.1 Uncertainty

4.1.1 Analytical uncertainty

In general, an important source of uncertainty in exposure assessment studies is the occurrence of samples with con-

Table 4. Percentiles of the long-term dietary intake distribution of BDE 47 and 99 (ng/kg bw/day) in the Dutch population at the age of 2, 10, and 40 years and life-long average (<LOD = 0.5 LOD), calculated with STEM [23]

Age (years)	BDE 47				BDE 99			
	Median	P90	P97.5	P99	Median	P90	P97.5	P99
2	1.40	2.69	3.80	4.58	0.23	0.34	0.38	0.47
10	0.53	1.01	1.42	1.71	0.14	0.20	0.23	0.28
40	0.30	0.57	0.80	0.97	0.10	0.15	0.17	0.21
Life-long average	0.40	0.77	1.09	1.32	0.11	0.17	0.19	0.24

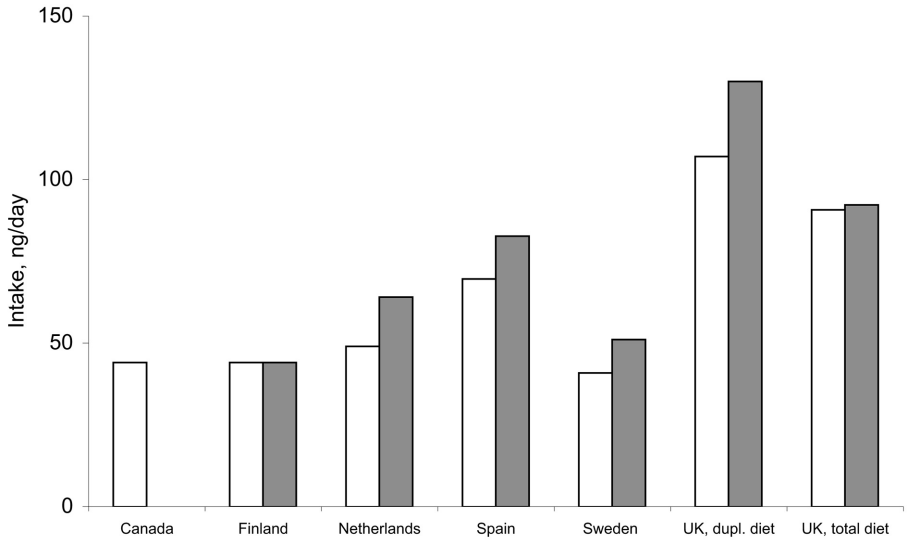

Figure 2. The estimated mean short term dietary intake of the sum of BDE 47, 99, 100, 153, and 154 for different countries (ng/day). White bars: lower bound estimate, gray bars: medium bound estimate. Data from Canada (36), Finland (35), the present study, Spain (37), Sweden (34) (lower bound estimate) and (2) (medium bound estimate) and the UK (duplicate diet study (12) and total diet study (FSA)).

centrations below the LOD, the so-called non-detects. In this study we have assigned a value of 0.5 × LOD (medium bound) or zero (lower bound) to the non-detects. For the sum of the five PBDEs, the difference between the lower bound and medium bound estimates of the median intake amounts to about 50%. This uncertainty can only be reduced by a decrease of the LOD as a result of an improvement of the analytical method.

On top of this uncertainty there is an uncertainty due to the inaccuracy of the analytical method. This uncertainty is estimated at 15 – 30%, based on information from within the laboratories involved and from interlaboratory studies (dependent on the congener and the difference between the concentration analyzed and the LOD).

4.1.2 Sampling uncertainty

Exposure calculations inherently include sampling uncertainty. This type of uncertainty is related to the high variability of input data used in the exposure assessment, in this case food consumption data and PBDE concentrations. The sampling uncertainty of the former is negligible in the present study, since the sample size is very large (6250 individuals × 2 days). As the relevant time frame for toxicity of PBDEs is long-term, the average concentration of the PBDEs in the food categories was determined. To this end, the samples of the food categories were pooled into one composite sample (or at least two composite samples for the fish and crustaceans). This implies that there is no information from this study on the variation of PBDE concentrations within the food categories.

4.2 Comparison of intake estimates with other countries

The PBDE dietary intake estimates were compared with results from other studies carried out in different countries. In studies from the UK (duplicate diet study, [16]), Sweden [4, 48], and Finland [49] the mean intake of the sum of the BDEs 47, 99, 100, 153, and 154 by the adult population is reported (Fig. 2). In a Canadian study [50], in addition to these congeners, BDE 28 was included, although the contribution of BDE 28 to the sum of the five congeners is known to be very small (Fig. 2). A recent British total diet study by the Food Standard Agency reported dietary intakes of 17 individual PBDEs [51]. The intakes of the five PBDEs considered in the present study were summed and are presented in Fig. 2. A Spanish study [52] reported the mean intake of the sum of tetra-, penta-, hexa, hepta-, and octaBDEs by the adult population of Catalonia. In order to compare the results of the Spanish study with those of the current study, the Spanish results were expressed as the sum of the tetra-, penta-, and hexaBDEs (Fig. 2).

The lower bound mean dietary intake of the sum of the five BDEs by the Dutch adult population (18 – 97 years; 49 ng/day) is similar to that in Canada, Sweden, and Finland, but lower than that in Spain and the UK. The medium bound estimate (64 ng/day) is in between the intakes of Sweden and Finland on the one hand, and those in Spain and the UK studies on the other. The higher intake of PBDEs by the Spanish compared to the Dutch population can be explained by a higher consumption of fish and meat in Spain (concentrations in these food categories are comparable in both countries) and a much higher concentration in vegetable fats and oils in Spain (consumption of vegetable fats and oils is similar in Spain and The Netherlands). The higher intake of the British total diet study [51] is also caused by higher concentrations, especially in oils and fats and in meat and meat products. An explanation for the relatively high British intakes of the duplicate diet study cannot be given, because in this type of study information on the consumption of different food items and the concentration of PBDEs is not available.

In addition to the studies shown in Fig. 2, there are a number of intake studies available in which the intake of more than five congeners was investigated, and from which the intake of the sum of five could not be deduced, so that they cannot be included in Fig. 2.

Schecter *et al*. [6] reported concentrations of 13 PBDE congeners in food products purchased in supermarkets in Dallas (USA) and dietary intakes calculated with these data. The reported concentrations of the specific PBDE congeners in the USA are generally similar to those in The Netherlands, except for butter and meat which have higher concentrations in the USA. Although at first this seems rather surprising, as the body burdens in North America are generally 10 – 20 times higher than in Europe [5, 8], and this is in agreement with the results of Lorber [5], who reported that levels in food in the USA are comparable to those in Europe. The difference in body burdens between Europe and USA may be explained by differences in the dust ingestion route in the two continents, as concentrations in indoor dust are higher in the USA than in Europe. The median daily intakes of the sum of 13 PBDEs of males and females of different ages in the USA range from 2.7 pg/kg bw/day for 2 – 5-year-old children to less than 1 pg/kg bw/day for people over 60 years of age [6]. As expected, these are higher than the reported intakes of the sum of five PBDEs of the present study. For example, for males and females of 40 – 59 years of age the (medium bound) short-term daily intakes of the sum of 13 PBDEs is 1.2 and 0.9 ng/kg bw/day, respectively. The Dutch counterparts of these values are 0.6 ng/kg bw/day for both sexes. The congener mainly responsible for the differences between the intake of the sum of five and 13 PBDEs is BDE 209, which substantially contributed to the total intake in the Schecter study (for most food groups about 12%, for cheese and milk 34%) [6]. On the other hand, Schecter and co-workers did not include the contributions of cereals, bakery products, vegetables, fruit, and sweets, which contribute about 14% to the Dutch intake.

Another, more recent, Spanish study [53] reported an intake of 38.5 ng/day for the sum of 15 PBDEs (upper bound estimate, *i.e.*, non-detects are assumed to equal the LOD). The authors reported a large contribution of hepta- to decaBDEs, principally BDE 209 to the total intake. Even so, the upper bound intake estimate of the sum of 15 is low compared to the medium bound estimates of the sum of five of the other European studies (including the Spanish one) shown in Fig. 2. The reason for the difference is probably the lower concentrations reported in the different food categories (especially fish and dairy). In addition, vegetables, fruit, and cereals were not included in this recent Spanish study, whereas these food groups were included in the present study.

A recent market-basket study in Belgium [54] reported an average daily intake of seven PBDEs (the five congeners presented in the present study plus BDE 28 and 183) of 23 ng/day (lower bound) and 35 ng/day (medium bound; not included in Fig. 2 because only the sum of seven PBDEs was reported). These values are lower than those presented in the current study, most likely because of the fact that the Belgian market-basket was not representative of the whole diet; the number of foods was limited to fish, meat, cheese, eggs, and butter. In the Belgian study, BDE 209 was analyzed in the foods, but was never found to exceed the LOQ. This is in sharp contrast with the study of the British FSA in which the dietary intake of PBDEs was dominated by BDE 209. As BDE 209 was not measured in other European studies, more attention should be given to this congener in upcoming studies, a conclusion also drawn by Lorber [5].

4.3 Monitoring of BFRs

The available information on the concentrations of PBDEs in food products on the Dutch market is limited to two time points: 2001 [55] and 2003/2004 (present study). Hence, at the moment it is not possible to present a time trend of the dietary exposure. Studies on the PBDE concentrations in the environment show that, in Europe, an increase since the 1970s is followed by a decrease or leveling off of the PBDEs present in the technical pentaBDE product. This decrease or leveling off started in the late 1980s to the early 2000s [56, 57]. This is the result of the voluntary production stop and later ban of the technical pentaBDE product in the EU during the last 10 years. The rate of decline depends on the amount of PBDEs used, as well as on the local and regional PBDE emission sources. Due to the official EU ban, the decreasing PBDE trend in Europe will likely continue. However, because of their widespread presence in the environment and their persistent character it is expected that PBDEs will continue to be present at relatively high levels in food and food products for several years to come.

Hence, the European population will be exposed to these substances *via* food for a long period of time. Since PBDEs accumulate in the body, the body burden of PBDEs will lag behind a decreasing trend in the environment at least a decade and may therefore still increase over time in the coming years. As a consequence, it is recommended to maintain a regular monitoring of PBDEs in food products (and human milk). Recently, the European Food Safety Authority (EFSA) advised a regular monitoring program of PBDEs (and other brominated flame retardants) as well [58].

4.4 Risk evaluation

4.4.1 Exposure *via* food

The risk assessment presented here comprises the hitherto most sensitive endpoints of BDE 99 toxicity, *i.e.*, neurodevelopmental toxicity and impaired spermatogenesis.

The neurodevelopmental toxicity can be induced by either combined pre- and postnatal exposure of dams, leading to fetal exposure by placental transfer and neonatal exposure *via* breast milk, or by gavage exposure of neonatal animals shortly after birth. Similarly, impaired spermatogenesis may be induced by prenatal exposure of dams, thereby leading to intrauterine fetal exposure only. Of these exposures, both placental and lactational transfer of BDE 99 are directly linked to the dam's body burden, whereas neonatal exposure by gavage, of course, is not. The relationship of the latter exposure to the dam's body burden can only be made indirectly, for example, by converting a gavage dose to an equivalent exposure *via* breast milk, which in itself can then be linked to a dam's body burden. This, however, needs information on the daily breast milk production of the dam, as well as the relation between the levels of BDE 99 in breast milk and the dam's body burden of this compound. Because such information is not available for BDE 99, the animal toxicity studies which are based on a gavage dose to offspring shortly after birth can be related with levels in breast milk (see below), but not with the corresponding maternal body burden. In conclusion, the results of these toxicity studies cannot be used to evaluate dietary BDE 99 exposure *via* food, because in this study, it is assessed for the age of 1 year and older.

For neurodevelopmental toxicity induced by intrauterine and lactational exposure to BDE 99, a different situation is at hand. For this effect, an expected human NAEL of 18.8 to 41.4 ng BDE 99/kg bw/day was calculated. Although this is well above the long-term dietary exposure of this compound calculated in this study, the assumptions underlying the calculation of the NAEL should be kept in mind. Firstly, in concordance with the risk assessment of 2,3,7,8-TCDD [13, 17 – 19], it is assumed that 60% of dietary BDE 99 is absorbed into the body. It might be argued that this absorption fraction should be increased to 1, which would have resulted in a 1.7 times higher NAEL. Secondly, in the calculation a half-life of 18 days was used for BDE 99 in the (non-lactating) mouse. This value was obtained by allometric scaling of the corresponding half-life in the rat. As such, the latter value was obtained from the experimentally observed decay of BDE 99 in growing rats, *i.e.*, it was not corrected for the effect of growth on the animal's body burden [46]. Animal growth will certainly have added to the observed BDE 99 decay and, when not corrected for, using the data as they are will have led to underestimation of BDE 99 half-life in the rat and its scaled half-life in the mouse. Consequently mouse body burdens as used in this paper might have been underestimated, as well as the NAEL which was calculated from them.

The half-lives of tetra-, penta-, and hexabrominated flame retardants in rats and humans show that these compounds display clear bioaccumulating properties in humans and in rats, with half-lives in man being much longer than in rats. The risk evaluation presented in this paper rests on the interspecies extrapolation of the toxicokinetics of the lower brominated BDE 99. Among others, this extrapolation incorporates the estimation of the half-lives of these PBDEs in humans. These half-life estimates were obtained by assuming "steady state" kinetics for these compounds in humans. Data from breast-milk fat in Sweden indicate that body burdens have increased from 1970 onwards until a maximum around 1997 – 1998, followed by a steady decline. These data suggest that, at least in Sweden, the exposure from food has followed a similar pattern, with breast-milk data lagging some time behind food exposure data (which might have already peaked some years earlier). Contrary to the situation in Sweden, data on the PBDE content of Dutch breast milk do not indicate a decline in the period between 1998 and 2003 (Zeilmaker, unpublished results), neither do food intake data point at a rapid decline in this period [59]. Thus, in The Netherlands the exposure to PBDEs from food might have been relatively constant when compared with Sweden, which might have resulted in a near "steady state" situation in the body. Nevertheless, the half-life estimates obtained from the Dutch and Swedish data agree remarkably well (see Supporting Information – Part III).

In conclusion, the current dietary intake of BDE 99 in The Netherlands is well below the exposure level which is associated with neurodevelopmental toxicity in mice. In the case of impaired spermatogenesis in male offspring resulting from intrauterine exposure, the expected human NAEL is close to the current dietary exposure. However, as it remains to be clarified whether this effect was caused by cross-contamination with chlorinated and/or brominated dioxins and furans, classifying it as BDE 99-related toxicity is ambiguous. Impaired spermatogenesis being the hitherto most sensitive reported toxic endpoint of halogenated contaminants, it remains to be sought out whether this effect is specific for BDE 99 and other PBDE congeners. Only then can a more definitive conclusion on the toxic risk of the dietary exposure of this class of chemicals be made.

4.4.2 Exposure *via* breast milk

As stated above, neurodevelopmental toxicity may also be induced by postnatal exposure to a single gavage dose of BDE 99. For this effect a NOAEL level in mouse offspring as low as 400 µg/kg bw when administered on PND 10 has been reported [41, 43]. As a comparison, the average daily exposure to BDE 99 from Dutch breast milk which was collected in 2003 may be estimated at around 4 ng/kg bw, *i. e.*, several orders of magnitude lower than the experimentally observed NAEL in mice (parameters used: concentration in breast milk: 0.76 ng/g milk fat; SD: 1.46 ng/g milk fat (Zeilmaker, personal communication); amount of breast milk consumed: 800 ml/day; fat fraction of breast milk: 4%; bw of suckling infant: 6 kg). Therefore, the current intake of BDE 99 from breast milk by Dutch infants is also well below the exposure level which is associated with neurodevelopmental toxicity in mice.

In conclusion, while the use of PBDEs in Europe has been restricted and environmental levels are therefore expected to decline in the near future, it will take at least a decade before this will result in lower PBDE concentrations in animal products and humans. Hence, a regular monitoring program for PBDEs is recommended, in particular to establish whether the trend in exposure is increasing or decreasing.

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