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Dietary Intake and Health Risk Assessment of Polybrominated Diphenyl Ethers in the Netherlands Based on Data Collected in 2004 and 2008

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Author's contribution

This work was carried out in collaboration between all authors. Author MJZ supervised the research in the manuscript, drafted the manuscript and made the revisions. Author CWN developed the design of the intake study, performed all research logistics and contributed to the first draft of the manuscript. Author BGHB carried out BMD calculations (EFSA, 2011) and contributed to their interspecies extrapolation. Author JDTB performed the intake calculation. Author MJBM contributed ideas throughout the preparation and the revision of the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Brominated flame retardants, like polybrominated diphenyl ethers (PBDEs), are environmental contaminants which have entered the human food chain. In this context the concentrations of several PBDEs were measured in food items commonly available in the Netherlands in 2004 and 2008. In food BDE-47, -99 and -100 were analysed and detected in 2004 and 2008, whereas BDE-209 was only analysed and detected in 2008. The highest BDE concentrations were found in seafood (fatty fish and crustaceans). The life-long dietary intake of these compounds in humans was calculated using the concentration data. For BDE-47, -99 and -100 the intake in 2008 was higher than in 2004.
A risk assessment based on the most sensitive toxic effects of PBDEs in experimental

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animals was possible for BDE-47, -99 and 209 (but not for BDE-100, [3]). These effects consist of neurodevelopmental toxicity resulting from the disturbance of growth of the central nervous system (BDE-47, -99 and -209) and reproductive toxicity resulting from the disturbance of spermatogenesis after intrauterine exposure (BDE-99).

A risk assessment based on the dietary exposure of individual PBDE congeners revealed that in The Netherlands the dietary exposure to PBDE-47 and -209 does not pose a health concern with respect to neurodevelopmental toxicity. However, with regard to reproductive toxicity and neurodevelopmental toxicity the dietary exposure in The Netherlands to BDE-99 is of potential health concern.

Keywords: PBDE; brominated flame retardants; food products; dietary intake; risk assessment.

1. INTRODUCTION

Brominated flame retardants are a group of brominated organic substances which have an inhibitory effect on the ignition of combustible materials. Therefore brominated flame retardants are widely applied in textiles, wiring, furniture, industrial paints and incorporated into plastics and foams, and are commonly used in electronic products to reduce the flammability of the product. About one-third of the total world production of brominated flame retardants consists of polybrominated diphenyl ethers (PBDEs) [1,2]. PBDEs are not chemically bound to the plastics or textile and therefore may be released from consumer products.

The human intake of PBDEs occurs via the diet, ingestion of house dust, inhalation of indoor air and, in the case of suckling infants, via breast milk. Of these routes the dietary intake of PBDEs is the dominant route of intake for adults, whereas for infants the ingestion via house dust and/or breast milk forms an important additional route of exposure too [3,4]. PBDEs are widespread in food products with high concentrations being found in fish and lipid rich food [5 -14].

Using PBDEs levels in Norwegian and Swedish breast milk as a proxy for levels in food indicated that levels of BDE-47 doubled every four years in the period between the 1980s and 1990s [15,16]. Though a two-fold decrease has been reported thereafter for the period 2000-2004 in Swedish breast milk [16] this decreasing time-trend was not confirmed through the years 2004-2010 [17], as cited in [3]). This is in concordance with similar levels of PBDEs in breast milk from Spain in 2002 and 2007 [18]. In contrast, a time-trend analysis of PBDEs in breast milk from Germany showed a relative small, though consistent, decreasing time-trend for BDE-47, -99, 100 and -153 in the period between 2006- 2009 (20–25% decrease, [19]).

In The Netherlands the dietary exposure has previously been determined in 2004 (BDE-47, -99 and -100, [20]). In the present study, this was repeated and extended with food products from various food categories purchased in the Netherlands in 2008. Food categories representing the majority of the food products containing PBDEs were analyzed on the occurrence of nine PBDEs, i.e. BDE-28, -47, -49, -99, -100, -153, -154, -183 and -209. The dietary exposure to PBDEs in the Dutch population was estimated using PBDE concentration data in Dutch food categories collected in 2004 and 2008 in combination with consumption data of the third Dutch National Food Consumption Survey 1997/1998

(DNFCS-3). The intake calculation of BDE-209 in 2008 is the first one using the 'total diet method', for BDE-209 was not measured in 2004.

Due to the absence of reference values such as health based guidance values the risk assessment of the dietary exposure to PBDEs has been limited so far. Bakker et al. [20] applied a methodology as applied in dioxin risk assessment ("body burden" approach, see [21] to derive a (preliminary) reference value for BDE-99. Recently this methodology has been adopted by the European Food and Safety Authority (EFSA) on the risk assessment of BDEs -47, -99, -153 and -209. The present study therefore compares the outcome of the PBDE intake calculations in The Netherlands with reference values as developed by EFSA to characterize the health risk of these compounds.

2. MATERIALS AND METHODS

2.1 Food Consumption and Sampling

The sampling program focused on representative data on concentrations of lipophilic compounds like dioxins and PBDEs in foods consumed by the general population in The Netherlands. Details of the food sampling are described in [22] (dioxins, 2004), [23] (dioxins, 2008) and [20] (PBDEs, 2008). Here the basic assumption is that substances like dioxins and PBDEs concentrate in the fat fraction of food products. The selection of foods was based on the most recent food consumption survey for the whole Dutch population (Dutch National Food Consumption Survey 1997/1998, DNFCS 3, 2-day dietary survey including the food consumption of 6250 individuals (1–97 years of age) over the entire week and over a whole year, [24,25]. 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, [26]). For 714 of these products the fat percentage was available. These products were ranked into 15 main food categories according to type of fat/oil animal or vegetable origin). The food categories were: fatty fish, lean fish, crustaceans, milk, butter, cheese, beef, pork, chicken/poultry, eggs, vegetable oils and fats, industrial oils and fats (products like margarine), vegetables/fruit, flour and bakery products.

The actual sampling consisted of the purchase (by 15 volunteers) of individual food products underlying the 15 food products as available in nation-wide Dutch supermarkets covering 95% of the fat intake of each food category and 95% of the product intake for vegetables/fruit. For example, according to the DNFCS-3 95% of the fat intake "fatty fish" consumption resulted from the consumption of herring (55%), eel (4%), mackerel (8%) or salmon (33%). Likewise, to characterize the food product category "fatty fish" 15 herrings, 15 eels, 15 mackerels and 15 salmons were purchased as available and mixed into one pool sample of 249 grams in the proportion of 15 x 9.1 = 136.5 grams herring, 15x0.6 = 9 grams eel, 15 x 1.3 = 19.5 grams mackerel and 15 x 5.6 = 84 grams of salmon.

(See Supplementary Material S1 for an overview of the composition of the pool samples of each food category).

All food samples were stored at –20ºC until chemical analysis.

2.2 Analytical Method

The analytical method applied on the pooled food samples collected in 2004 is described in detail in [20]. The analysis comprised BDE-17, -28, -47, -66, -85, -99, -100, -138, (the sum of) of BDEs -153 and -154 and BDE-183. For these PBDEs the method showed the lowest limit of detection (LOD) (pg/g pooled product) in milk, i.e. 0.3 – 0.5 pg/g product. In the remaining food categories the LODs varied between product categories as follows: BDE-47: 3 -24pg/g,BDE-99 and -100: 5 – 41 pg/g, BDE-153: 4-34 pg/g and BDE-154: 5-41pg/g.

The food samples in 2008 were analyzed with a slightly modified analytical method and included BDE-209. In short ^{13}C-internal standards were added to 2.5–5grams of the pooled food samples. Thereafter the samples were homogenized and extracted with cyclohexaan/isopropanol to isolate the fat faction containing the PBDEs. Clean-up of the isolated fat fraction was by elution through a Florisil column (fat fraction dissolved in 3 x 5ml DCM). The collected eluate was evaporated under nitrogen and dissolved in 400µl 50% DCM. GC/MS Agilent 5973 analyses were performed on a selective mass quadrulope MS coupled to a Silica-CN LC column Phenomenex Luna-CN 50-2 mm 3 µm. The GC temperature program consisted of an initial isothermal period (70ºC, 4 min), a rise of 10ºC/min to 250ºC, followed by 25ºC/min to 320ºC, and finally a second isothermal period of 15 min at 320ºC. Samples of 120µl were injected with an injection speed of 5µl/s by means of an autosampler (AS2000). Helium was used as carrier gas with a constant pressure of 120kPa.

Recovery of the internal standards was >80%, with the exception of BDE-209 (recovery ca. 40%).

The sensitivity of this method was similar as the one used for measuring the 2004 food products. For PBDEs up to BDE-153 the LOD was 5 to 10pg/g, increasing to 25pg/g for BDE-183 and 100pg/g for BDE-209.

2.3 Linking PBDE Concentrations with Food Products

As shown in Supplementary Material S1 PBDEs were analysed in 60 different pooled food samples. When these food commodities were reported in the DNFC-3 food consumption survey the measured concentration in the pooled sample was directly attributed the consumed food commodity. However, the majority of the consumed products consisted of composite food products, i.e. the resultants of different primary agricultural products. To couple this to the available PBDE measurements a conversion model for primary agricultural products (CPAP, [27]) was used to split food products into their constituting primary products (including their fat mass fractions). For example, pizza was split into flour, vegetables and cheese. Then, given the constituting food product fractions the PBDE congener concentrations as measured in the pooled samples of the flour, cheese and vegetables were attributed to these fractions. Taking the latter into account then resulted in the PBDE congener concentration in the consumed composite food product.

As no information on the effect of processing such as cooking, baking and frying on the concentration of PBDEs in food products is available, no correction for such effects was made.

2.4 Individual Intake Assessment

The total daily intake was derived by coupling the food consumption data with the corresponding 2004 and 2008 PBDE concentrations for each individual in DNFCS-3. In this way a total of 12.500 PBDE intakes (pg/kg bw/day) were obtained, containing individual PBDE intakes over two, consecutive, days.

2.5 Statistical Analysis of Individual Intakes

Regarding the human health risk of PBDE, the persistent nature of these compounds in the human body together with the chronic nature of the dietary intake warrants the calculation of the long-term intake of these compounds. Just averaging the calculated 12.500 intakes mentioned above over the two day observation period results in an intake distribution of 6250 individual average exposure levels. However, this distribution contains both the (wanted) variation between individuals as well as the (unwanted) variation between the consumption days of one individual. In the long-run the latter will level out. In order to filter the inter-individual variability from the intake distribution the so called Beta-Binomial-Normal (BBN) model ([28-30]) as implemented in the software package Monte Carlo Risk Analysis (MCRA, release 6.1 and 6.2, [31]) was used. The BBN model separately models inter-individual variability in consumption frequencies and consumed amounts, followed by an integration step to arrive at the long-term dietary intake distribution as a function of age and sex. The BBN method allows for the calculation of statistical intake characteristics as percentile values and their corresponding confidence intervals.

2.6 Risk Assessment: Neurodevelopmental Toxicity of BDE-47 and -99.

BDE-47 and -99 may be considered as persistent cq. bioaccumulating in experimental animals and in man (for details, see [3,20,32]. As a consequence these PBDEs are expected to accumulate in the body after repeated chronic, i.e. dietary, exposure. In the long-run this leads to an amount in the body ("body burden", expressed as the total amount in the body divided by body weight) which vastly exceeds the absolute daily intake per kg body weight and on the long-term will become more or less constant (assuming a *constant* daily intake). For this reason the "body burden" [3,21,33–36] rather than the daily intake [37–39] is recommended as the starting point for the risk assessment of the long-term exposure to persistent chemicals like dioxins and PBDEs.

Taking the procedure as recommended by EFSA [3] a risk assessment based on the "body burden" approach focuses on the estimation of the human "body burden" at which toxicity is expected. In the case of PBDEs this "body burden" was obtained by extrapolation of animal toxicity data from experimental animals to man [3]. In this context the referred animal toxicity relates to neurodevelopmental and reproductive toxicity, the most sensitive toxic effects of PBDEs in experimental animals [3,37–39].

The neurodevelopmental toxicity consisted of the disturbance of the habituation response in neonatal mice which had been exposed to a single p.o. dose of BDE-47 or -99 at Post Natal Day (PND) 10 [3,37-39]. This effect is thought to be caused by disturbance of the development of the central nervous system. In the mouse this development occurs in the first 3-4 week after birth with a clear maximum activity (Brain Growth Spurt (BGS)) at PND 10. For this reason PND 10 was chosen as the time period in which the mouse brain shows its maximum sensitivity for the neurodevelopmental toxicity of PBDEs [40].

The available neurodevelopmental toxicity data allowed for a dose-response analysis. Analyzing the data with Benchmark Dose (BMD) modelling resulted in the following dose level (Bench Mark Dose Lower confidence limit, $BMDL_{10}$) corresponding with a 10% change in response, i.e. a 10 % reduction of the habituation response in exposed animals in comparison with untreated control animals: BDE-47: 309µg/kg bw and BDE-99: 12 µg/kg bw (See Supplementary Material 2, note the available toxicity data for BDE-100 do not allow for the derivation of a $BMDL_{10}$ value, [3]). The animal body burden corresponding with the $BMDL_{10}$ was estimated.

In extrapolating this animal body burden to man it was realised that, in contrast to the mouse, in humans the BGS is not confined to a relative narrow time period in development showing a clear peak in brain growth. In fact, in humans the BGS starts during the third trimester of pregnancy. Growth rapidly increases to a maximum which is reached just before birth, in order to continuously decrease thereafter until adulthood is reached. The starting point for the risk characterisation therefore was that, at any time in life the human body burden of PBDEs may not exceed a level which indicates the disturbance of neurological development. This human body burden was obtained as follows. First at PND10 the animal body burden corresponding with the animals $BMDL_{10}$ was estimated (see above). Taking inter- and intra-species differences in PBDE toxicokinetics and toxicodynamics into account this animal body burden was extrapolated to man, resting in the "body burden" in the "sensitive" human, i.e. the human body burden at which a 10% effect on the habituation response is expected. The thus obtained human "body burden" was considered as the "body burden" which does not raise a health concern. Finally the corresponding chronic human daily intake leading to this body burden was calculated by means of one-compartmental "steady state" kinetic modelling.

As shown in the Supplementary Material this led to the following reference human intake levels which do not raise a health concern with respect to neurobehavioral toxicity: BDE-47: 172ng/kgbw/day; BDE-99 4.2ng/kg bw/day (referenced as $I_{d,h}$ in the Supplementary Material S2 and below, [3]). Note that, after life-long exposure, these intake levels thus lead to the accumulation of PBDEs in the human body which do not raise a health concern.

According to EFSA [3] a Margin of Exposure (MOE) greater than 2.5 between the reference human intake values mentioned above for neurobehavioral toxicity ($I_{d,h}$) and the actual intake ($I_{c,h}$) does not indicate a potential health concern. Or, in other words, the absence of a potential health concern holds when the following condition is met:

$$MOE \geq 2.5$$

or:

$$\frac{I_{d,h}}{I_{c,h}} \geq 2.5$$

Which is equivalent to:

$$\frac{(I_{d,h} / 2.5)}{I_{c,h}} \geq 1$$

In this way the following human *life-long* intakes which, when exceeded, are indicative for a potential health concern with respect to neurodevelopmental toxicity: BDE-47: 172/2.5 = 69ng/kg bw/day and BDE-99 4.2/2.5 = 1.7ng/kg bw/day.

2.7 Risk Assessment: Neurodevelopmental Toxicity of BDE-209

Analyzing the data with Benchmark Dose (BMD) modelling of the BDE-209 neurodevelopmental toxicity data resulted in a $BMDL_{10}$ of 1,7mg/kg bw (EFSA, 2011). As BDE-209 does not show a significant interspecies difference in kinetics a classical extrapolation procedure, without the explicit quantification of interspecies differences in kinetics by means of one-compartmental modelling as applied on BDE-47 and -99, was deemed necessary. Consequently, the application of the default factor for interspecies differences in toxicodynamics on the animal $BMDL_{10}$ resulted in 1.7/2.5 = 680µg/kg bw/day for the human reference intake which is indicative for a potential health concern with respect to the neurodevelopmental toxicity of BDE-209.

2.8 Risk Assessment: Reproductive Toxicity of BDE-99

The reproductive toxicity consisted of the disturbance of sperm production in offspring of pregnant dams which had been exposed to a single dose of BDE-99 [41].

In contrast to the neurobehavioral toxicity data a BMD analysis could not be performed for the reproductive toxicity. The reason for this is that the available toxicity data relate to two administered dose levels of 60 and 300µg/kg bw, with both doses inducing the same level of toxicity and therefore do not provide suitable dose-response information. In this case the BMDL10 would be somewhere between zero and 60µg/kg bw in the animal. Using the body burden approach (for details, see [3,20] led to a chronic human intake level between zero and 0.23ng/kg bw/day as reference for human health concern. So, an intake level exceeding 0.23ng/kg bw/day is indicative for a potential health concern with respect to neurodevelopmental toxicity.

3. RESULTS

3.1 Occurrence

BDE-47, -99 and -100 were found in the majority of the analyzed food samples. In addition BDE-209 could be detected in all of the food categories collected in 2008. The concentrations of these congeners are presented in Tables 1 (2004) and 2 (2008) and Fig. 1 (2008). The food categories milk, flour and vegetable/fruit contained the lowest PBDE concentrations. Highest concentrations of BDE-47, -99, and -100 were observed in fatty fish and crustaceans. BDE-209 showed high levels in the majority of the food categories.

When PBDE concentrations were not detected, values are presented as ½LOD. In 2004, this was the case for the food category bread (BDE-100), pork (BDE-100), vegetables (BDE-99 and -100), fruit (BDE-99 and -100), beef (BDE-100), chicken (BDE-100), butter (BDE-100), vegetable oil (BDE-47 and -100) and industrial oil (BDE-47, -99 and -100).

Table 1. Concentrations of PBDEs (pg/g product) in pooled food sampled in the year 2004 (non-detects are assigned ½LOD)

Category	Fat %	Concentrations		
		PBDE-47	PBDE-99	PBDE-100
Fatty fish	[a]	1725	490	530
Bread	1	10	4	1*
Pork	26	37	36	15*
Eggs	10	22	22	13
Crustaceans [b]	[a]	455	315	135
Vegetables	0	4	1*	1*
Cheese	31	65	57	24
Fruit	0	4	1*	1*
Beef	16	18	20	10*
Chicken/poultry	9	17	19	5*
Butter	81	10	19	20*
Lean fish	[a]	171	33	88
Vegetable oil	57	10*	26	15*
Industrial oil	35	15*	20*	25*
Milk	1	28	1*	1*

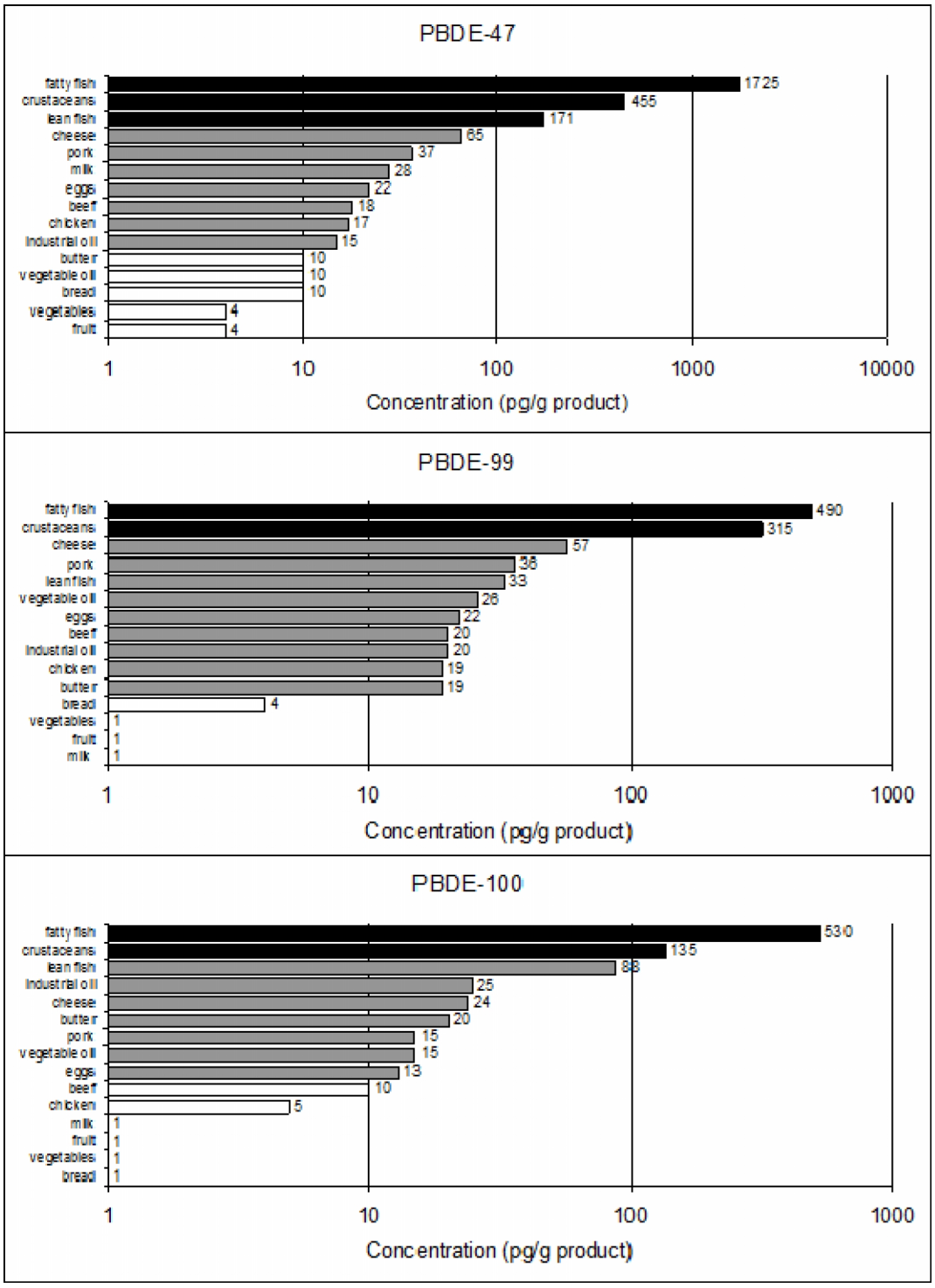
** Value is ½LOD[a] No percentage: average concentrations of multiple species fish (lean fish: Dutch Consumers' Association mentions a mean of 1.8% for cod, coalfish, plaice, sole and tilapia whereas VU/IVM mentions 1.5% for lean fish, RIVM 1.2% and RIKILT 1.4%; fatty fish: Dutch Consumers' Association mentions a mean of 20.6% for herring, eel, mackerel and fresh salmon, VU/IVM mentions 12.4% and, RIVM 9.4% and RIKILT 13.1%).[b] Average of mussel and shrimp including samples <LOD = ½LOD. Mussel and shrimp samples consisting of a pool of 15 different subsamples*

Table 2. Concentrations of PBDEs (pg/g product) in pooled food sampled in the year 2008 (non-detects are assigned ½LOD)

Category	Fat %	Concentrations			
		PBDE-47	PBDE-99	PBDE-100	PBDE-209
Fatty fish	14	694	146	179	316
Flour	2	25	4	2*	61
Pork	21	73	40	15	150
Eggs	9	56	21	13	291
Crustaceans	2	189	89	52	120
Bakery products	17	76	55	16	135
Vegetables/fruit	0	14	3	2*	31
Cheese	28	84	34	14	253
Beef	13	69	25	14	332
Chicken/poultry	9	73	39	18	177
Butter	79	142	83	25	191
Lean fish	1	74	13	16	133
Vegetable oil	65	193	62	3*	516
Industrial oil	84	97	60	20	359
Milk	1	17	5	3	33

** Value is ½LOD*

2004


PBDE-47
fatty fish
crustaceans
lean fish
cheese
pork
milk
eggs
beef
chicken
industrial oil
butter
vegetable oil
bread
vegetables
fruit
1725
455
171
65
37
28
22
18
17
15
10
10
10
4
4
1
10
100
1000
10000
Concentration (pg/g product)
PBDE-99
fatty fish
crustaceans
cheese
pork
lean fish
vegetable oil
eggs
beef
industrial oil
chicken
butter
bread
vegetables
fruit
milk
490
315
57
36
33
26
22
20
20
19
19
4
1
1
1
1
10
100
1000
Concentration (pg/g product)
PBDE-100
fatty fish
crustaceans
lean fish
industrial oil
cheese
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pork
vegetable oil
eggs
beef
chicken
milk
fruit
vegetables
bread
530
135
88
25
24
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13
10
5
1
1
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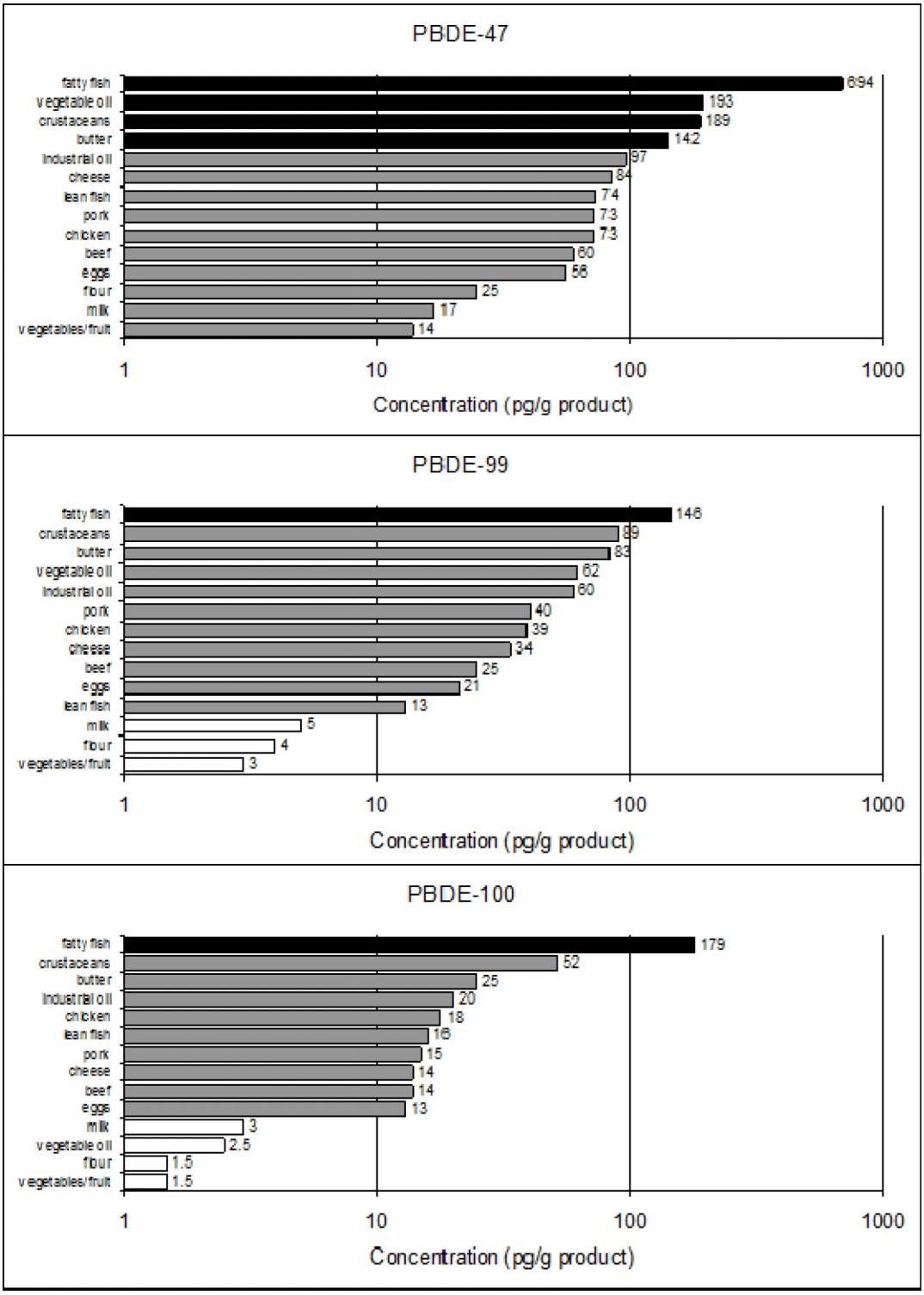
10
100
1000
Concentration (pg/g product)

2008


PBDE-47
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vegetable oil 193
crustaceans 189
butter 142
industrial oil 97
cheese 84
lean fish 74
pork 73
chicken 73
beef 60
eggs 56
flour 25
milk 17
vegetables/fruit 14
1
10
100
1000
Concentration (pg/g product)
PBDE-99
fatty fish 146
crustaceans 89
butter 83
vegetable oil 62
industrial oil 60
pork 40
chicken 39
cheese 34
beef 25
eggs 21
lean fish 13
milk 5
flour 4
vegetables/fruit 3
1
10
100
1000
Concentration (pg/g product)
PBDE-100
fatty fish 179
crustaceans 52
butter 25
industrial oil 20
chicken 18
lean fish 16
pork 15
cheese 14
beef 14
eggs 13
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vegetable oil 2.5
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Concentration (pg/g product)

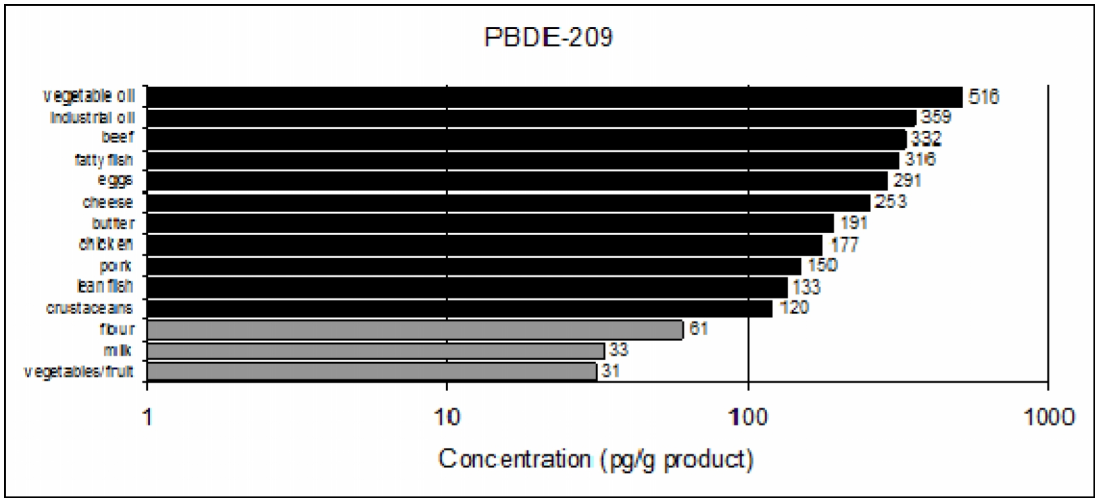

Fig. 1. The concentration (pg/g product) of BDE-47, -99 and -100 in food categoriesin 2004 and 2008. White bar: concentration < 10 pg/g, grey bar: concentration between 10-100 pg/g, black bar: concentration > 100 pg/g

In 2008, BDE-100 was not detected in the food categories flour, vegetables/fruit and vegetable oil, and those values are ½LOD. PBDEs other than BDE-47, -99, -100 or -209 were not detected in any of the food categories, with the exception of BDE-49 which was measured in crustaceans (26 pg/g), of BDE-153 which was measured in butter (18pg/g) and of some other PBDEs which were detected in fatty fish (BDE-28 (40 pg/g), BDE-49 (131 pg/g), BDE-153 (29 pg/g), and BDE-154 (71 pg/g)).

3.2 Individual 2-day Intake

The 'total diet method' allows for the analysis of the contribution of various food categories to the total *individual* intake (as obtained from the two consecutive days in the DNFCS-3 conducted in 1997-1998). Fig. 2 presents these contributions for the 2004 and 2008 intake calculations for BDE-47, -99, -100, and -209. In general, the contribution of a category is high when a particular category is frequently consumed in relative large amounts containing high concentrations of PBDEs.

For BDE-47 milk is the most important source of the intake, accounting for 30-50% of the intake (note that dairy products are also included in the consumption data). The remaining was found divided over all other food categories, with none of them contributing more than 15% of the total exposure. A dominance of milk as revealed for BDE-47 was not found with BDE-99 and -100. The reason for this is the relative low concentration of these congeners in milk. Main contributions to the 2004 intake of BDE-99 are pork (21%), fatty fish (17%), cheese (14%) and vegetable/industrial oils (11%). In 2008 the main contributions to the BDE-99 intake were milk (27%), pork (16%) and vegetable/industrial oils (15%). In 2004 fatty fish, vegetable/industrial oils, pork and milk contributed 26, 14, 13 and 11% to the intake of BDE-100, respectively, to be compared with 6%, 6%, 14% and 33% in 2008.

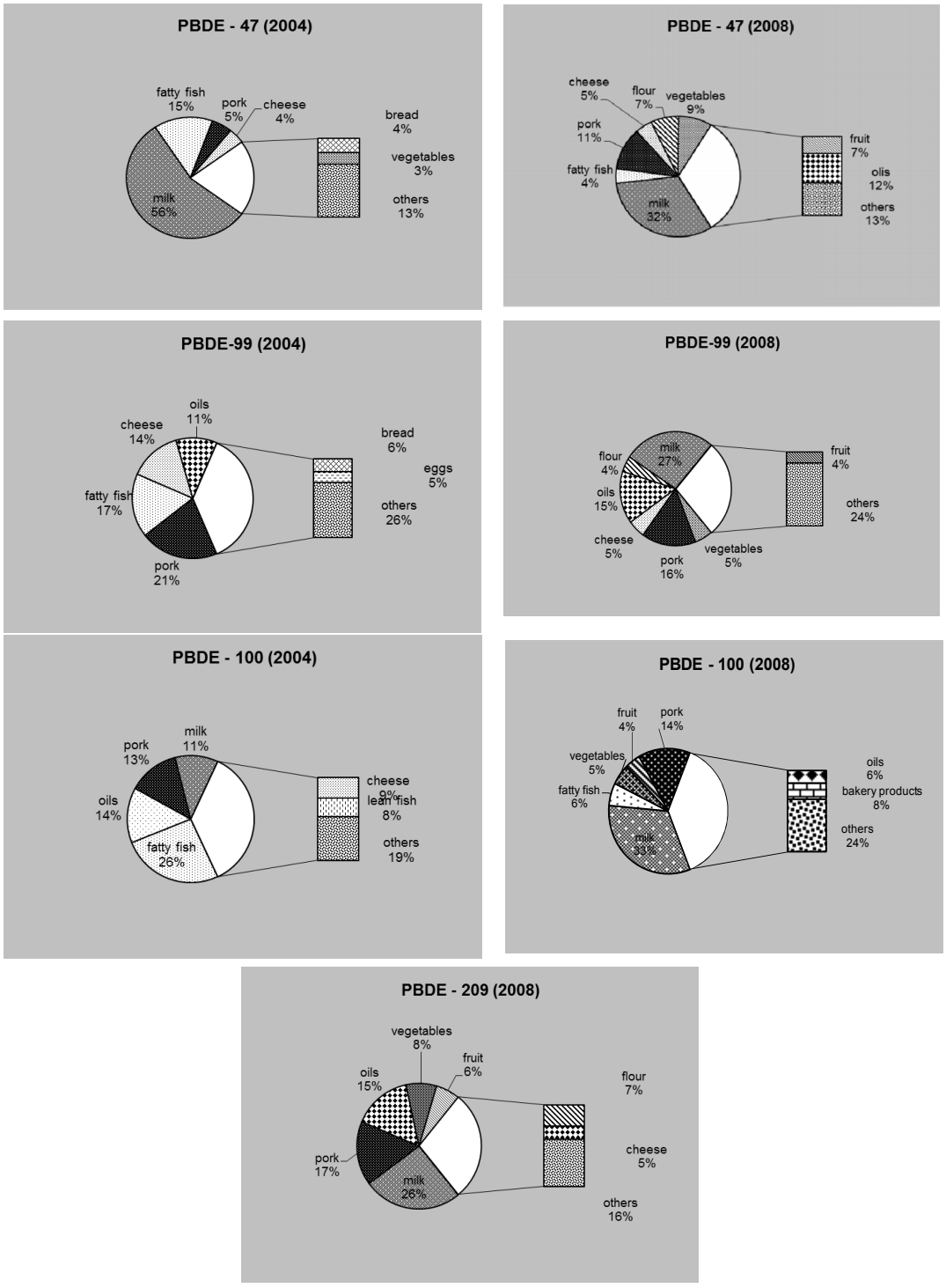

Fig. 2. The contribution of various food categories to the total individual 2-day intake of BDE-47, BDE-99, BDE-100 and BDE-209 in 2004 (left) and 2008 (right)

In the case of BDE-209 milk contributed in 2008 27% of the intake, pork 17% and vegetable/industrial oils 15%.

The intake is derived from both the concentration measured in food and the food consumption. The high contribution of milk (BDE-47) results from high consumption of milk and dairy products and the relative high concentration of this congener in milk, i.e. 17 – 28 pg/g product. However, for BDE-99 and -100 the concentrations are at (2004) or about (2008) the detection limit (2-5pg/g). Therefore, intake calculations based on BDE-99 and -100 concentrations in milk are rather uncertain.

3.3 Long-term Intake

For BDE-47, -99 and -100 the median life-long intakes (percentiles and corresponding 95% Confidence Intervals (CIs), are separately presented for males and females in Fig. 3 (see also Supplementary Material S3 for other intake percentiles). For BDE-47 the median life-long intake amounted 500pg/kg bw/day in 2004, while in 2008 the median intake amounted around 780pg/kg bw/day. For BDE-100, this was about 90pg/kg bw/day in 2004. In 2008, the median intake of BDE-100 was around 125pg/kg bw/day. The median life-long average intake of BDE-99 in 2004 amounted 140pg/kg bw/day and in 2008 (277pg/kg bw/day). As the 2004 and 2008 CIs of percentile values do not overlap it can be concluded that the life-long average intake of the PBDEs in 2008 was slightly, i.e. 1.5 to 2.0 fold, higher than in 2004.

The dietary intake of BDE-209 was found the highest when compared with the BDE-47, -99 and -100intake. In 2008 the median BDE-209 intake amounted around 1900pg/kg bw/day. In concordance with other POPs like dioxins [42] and PBDE themselves [9] the intake of PBDEs was found to be age-dependent (see Supplementary Material S4). The intake was found highest in young children, in order to decline gradually until a stable level is reached around the age of 20 years. After the age of 20 years the intake remained at a constant level. In concordance with previous results [9] the highest intake, i.e. the intake of 2-year old children, was 3-fold higher than the intake at adult age.

3.4 Risk Assessment

The median and P95 intakes presented in Fig. 3 and Supplementary material S3 for 2008 were used to calculate a MOE with respect to reference values for neurodevelopmental and reproductive toxicity, with MOE value lower than 1 indicating a potential health concern. As shown in Table 3 the MOEs of BDE-47 and -209 for neurodevelopmental toxicity were all found well above 1, i.e. to range from 54-88 and 2.3-3.6 x 10^5. In contrast, for BDE-99 the MOE for reproductive toxicity was found to be lower than 0.5 and 3.7-6.1 for neurodevelopmental toxicity.

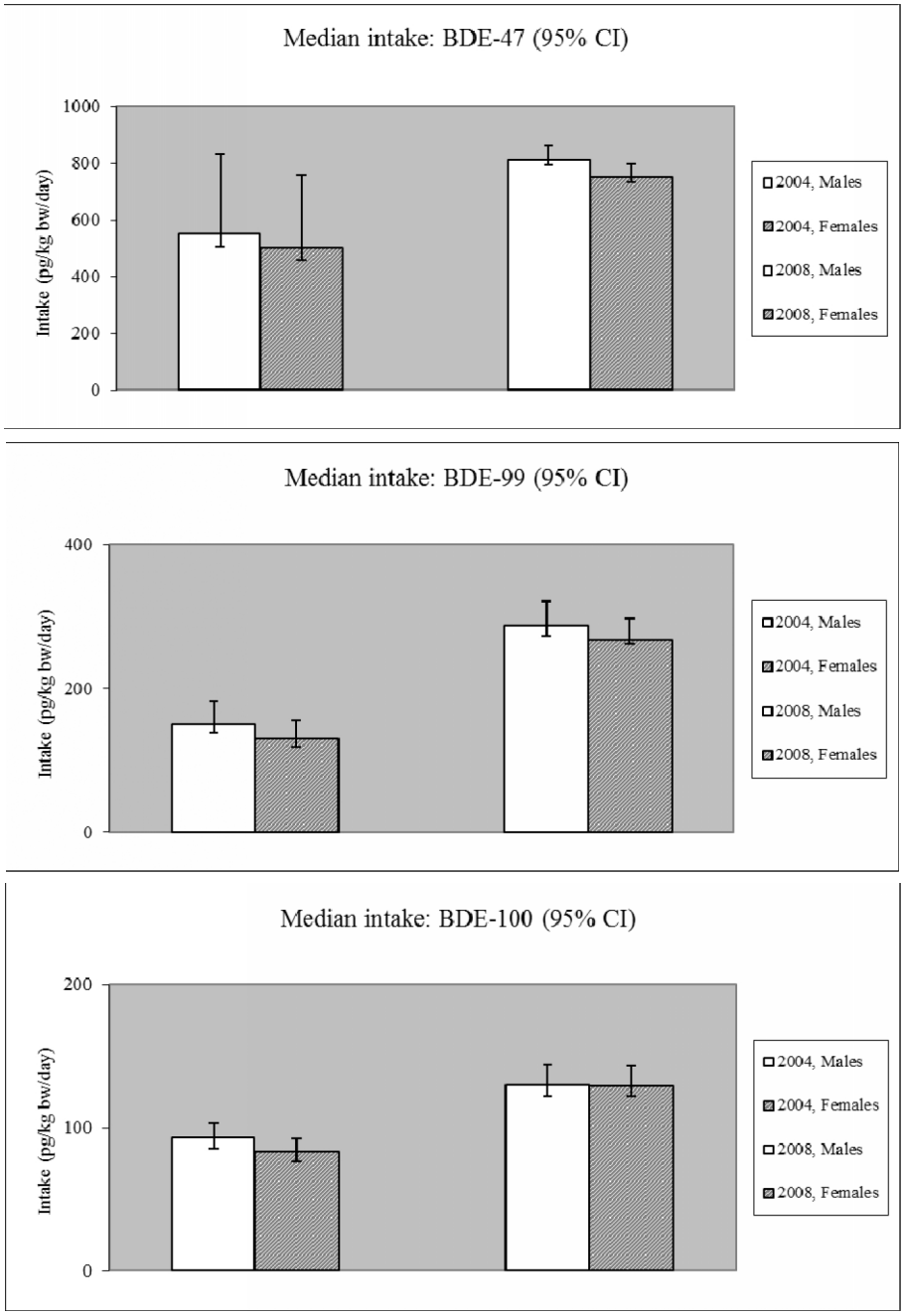

Fig. 3. Percentiles (P50 and P95) of the life-long median intake (pg/kg bw/day) based on concentrations in Dutch food products monitored in 2004 and 2008. Samples below the LOD were set at ½LOD. Between brackets: 95% confidence interval. A: BDE-47; B: BDE -99; C: BDE-100

Table 3. Margin of Exposure (MOE) of the life-long dietary intake in the Netherlands in 2008 and the reference values for neurodevelopmental and reproductive toxicity

Congener	Intake (ng/kg bw/day)		Reference value (ng/kg bw/day)		MOE		
			Neurotox	Reprotox	Neurotox		Reprotox
					This study	EFSA**	This study
BDE-47	Median	0.78	69	n.a.	88	36-236	n.a.
	High *	1.28	69	n.a.	54	15-64	n.a.
BDE-99	Median	0.28	1.7	< 0.23	6.1	2.6-15	<0.8
	High	0.46	1.7	< 0.23	3.7	1.6–5.6	<0.5
BDE-209	Median	1.9	680.000	n.a.	360.000	>240.000	n.a.
	High	3.0	680.000	n.a.	227.000	>148.000	n.a.

** P95 value;** EFSA calculated the range, i.e. the Lower and Upper Bound (LB/UB), of the dietary intake across Europe. The calculated values were then used for the calculation of (the range of the) MOE as mentioned in the Materials and Methods section*

4. DISCUSSION

4.1 Occurrence in Dutch Food

According to EFSA the most important PBDE congeners to be monitored in food are BDE-28, -47, -99, -100, -153, -154, -183 and -209 [3]. In this context BDEs -47, -99, -100 and -209 were consistently detected in Dutch food, with BDE-209 showing the highest levels, followed by BDE-47, -99 and -100.

The food categories flour/bread, vegetable/fruit and milk (except for BDE-47 in 2004) contained the lowest PBDE concentrations. Important notes on these findings are that the concentrations of BDE-99 and -100 in milk, flour and vegetable/fruit are at or below the detection limit (2-5 pg/g) and only one pooled measurement per food category was performed. The highest concentrations of BDE-47, -99, and -100 were observed in fatty fish, crustaceans and molluscs. High levels in fish were also observed by many others [7,11,43].

4.2 Comparison of Dietary Intake between 2004 and 2008

The intake data indicate a small, i.e. maximal 2-fold, increase in the period between 2004 and 2008. Unfortunately comparable data on the dietary exposure of PBDEs as measured at different points in time are scarce. Domingo et al. [9] mention a 23% decrease in PBDE intake in Spain between 2000 and 2006.

In this context it might be argued that a time period of four years between 2004 and 2008 is too short to draw conclusions about the time trend of the dietary exposure. However, as revealed by the analysis of Swedish breast milk data PBDEs may show clear short term time-trend characteristics. For, in the period between the 1980s and 1990s, Swedish breast milk showed a doubling of the PBDE concentration every four years and a two-fold decrease in the period between 2000 and 2004, in order to remain stable afterwards ([16,17, as cited in [3]). Furthermore, German data also indicate a small, though significant, decrease of PBDEs in breast milk between 2006 and 2009 [19]. It is therefore concluded that in the Netherlands the exposure to BDE-47, -99 and 100 has almost doubled between 2004 and 2008.

4.3 Uncertainties in the Intake Estimation

In interpreting the presented occurrence and intake data, next to sampling uncertainty, some other uncertainties of the intake calculations have to be taken into account:

a) The calculations reported here are based on food consumption data collected from April 1997 to March 1998. These consumption data were linked to PBDE measurements in food samples which were collected in 2004 and 2008. Changes in food consumption after 1998 have not been taken into account.
b) The food sampling protocol assures the sampling of almost all food items expected to contain PBDEs, i.e. the food items covered 95% of the daily fat intake together with vegetables, fruit and bread. Furthermore, as with the exception of the inclusion of bakery products as a food category in 2008, the same food sampling protocol was used for the 2004 and 2008 intake calculations.
c) In this report the BBN method was used for the 2004 and 2008 intake calculations. With regard to the year 2004, using the same food monitoring data and food consumption data, PBDE intake calculations have previously been performed with earlier statistical methods (*STEM*: [20,44]; Nusser: [23]. As with the BBN method, the Nusser method and the STEM method both estimate the long-term PBDE intake and its distribution characteristics (Boon *et al.,* 2011). Apart from the incorporation of an extended uncertainty analysis of the intake calculation in the BBN method (calculation of the uncertainty of distribution characteristics), the three methods contain some slight differences in the way individual PBDE intake data are statistically handled and therefore the application of different statistical methods would produce slightly different results. However, in the present study this effect as no significance as the intake in the year 2004 was recalculated with the BBN method.

4.4 Comparison with other European Countries

In the Netherlands the exposure to the sum of BDE-47, -99 and -100 amounted to 57ng/day in 2004 and 86ng/day in 2008. This intake is in concordance with the intake of PBDEs in other European countries as determined with comparable intake methods, i.e. a combination of food consumption surveys and targeted food monitoring. Across Europe this intake ranges from 23 to 81ng/day for the sum the PBDEs (Table 4).

Next to calculating the intake of PBDE from measurements in food and food consumption data this intake can also directly be determined by collecting the actual food which has been consumed over a 24 hour period, the so-called duplicate diet method. Using this method the intake of the sum PBDEs (BDE-47, -99) in The Netherlands was determined at 96ng/day in 2004 [4]. Comparable duplicate diet exposures are available for Germany (96ng/day for the sum of BDEs-47, -99, -100, -153, 154 and -183 [12]) and the UK (130ng/day for the sum of BDEs-47, -99, -100, -153, 154 [45].

Table 4. Comparison of the dietary intake of PBDEs in Europe: 1999-2008

Country	Type of study[1]	Year	Statistic (unit)	47	99	100	SUM	Source
The Netherlands	TDS	2004	M ng/kg bw/day	0.53	0.14	0.09	0.76	This study
			M ng/day[3]				57	
		2008	M ng/kg bw/day				1.15	
			M ng/day	0.78	0.28	0.09	86.3	
The Netherlands	TDS	2004	M ng/kg bw/day	0.40	0.11	0.08	0.79	[20]
			M ng/day	30	8.3	6	59.3	
Sweden	TDS	1999	A ng/day	26.5	n.r.	n.r.	50.9	[7]
Finland	TDS	1997-1999	A ng/day	n.r.	n.r.	n.r.	44.0	[6]
Belgium	TDS	2005	A ng/day	n.r.	n.r.	n.r.	23-48	[8]
Germany	DD	2005	A ng/day	15	22.5	6	96	[11]
UK	DD	1999-2000	A ng/day	46.3	49.4	10.0	130	[45]
The Netherlands	DD	2004	A ng/dag[3]	58	37.5	n.d.[5]	95.5	[4]
Norway	TDS	2002-2006	A ng/kg bw/day	0.69	0.16	0.11	1.08	[10]
			A ng/day	51.8	12	8.3	81	

1Total Diet Study, i.e. food sampling based on a food consumption survey, intake calculations based on a statistical analysis of combining PBDE measurements in the sampled food products with food consumption data; DD: Duplicate Diet
[2]M: Median; A: Arithmatic mean; 3based on body weight of 75kg

4.5 Comparison with EFSA

In 2011 EFSA issued its Scientific Opinion on Poly Brominated Diphenyl Ethers (PBDEs) in Food. This opinion included a European wide dietary exposure and risk assessment of BDE-28, -47, -99, -100, -153, -154, -183 and -209, amongst country specific intake estimations. Country specific food occurrence data were collected from 2005 to 2010 and merged into one compiled data base. With regard to the occurrence PBDEs in EFSA's data base were mainly found in food of animal origin (fish, meat, dairy products, animal oils and fats).

Although the sensitivity of analytical method in the present study was comparable with the ones underlying EFSA's data base the occurrence of BDE-47, -99, -100 and -209 in the various food categories in the Netherlands was comparable for the food categories fish and other seafood and meat and meat products, but at EFSA's lower bound for egg and egg products, fats and oils of animal origin and milk and dairy products. Next to BDEs -47, -99, -100 and -209, EFSA mentioned comparable levels of BDE-153, -154 and -183 in the various food categories. In Dutch food the sum of BDE-153 and -154 was detected in the majority of food products in 2004, however in 2008 in fatty fish only. BDE-183 was not detected neither in 2004 or 2008 in Dutch food. This difference may stem from the use of European wide occurrence data (EFSA) vs. country specific data (this study).

By combining country specific food consumption surveys with the occurrence data in EFSA's data base country specific intakes were calculated. For the Netherlands EFSA used the DNFCS-3 for adult food consumption (19-30 years) and a specific data base for the consumption of children (VCP-Kids, [46]). For all four congeners of interest the long-term dietary intakes as calculated in this study are similar to the intakes as calculated by EFSA (see Supplementary Material S5 for a direct comparison of the intakes as calculated with both methods). The same conclusion could be drawn for the age-dependency of the intake. For example, EFSA reported a 4-fold increase of the intake of 1-3 year olds relative to adults for either of the four PBDEs of interest, to be compared with a 3-fold increase in this study.

4.6 Risk Assessment

As BDE-47, -99 and -100 are considered as bioaccumulating chemicals in experimental animals and in man the risk assessment of these chemicals is to be based on the accumulated amount of these compounds in the body [3,21,33-36]. In this context Bakker et al. [20] and EFSA [3] provide reference values for the long-term exposure corresponding with (expected) human toxicity, which can be compared with the actual human exposure to PBDEs. The available reference values refer to neurodevelopmental toxicity, i.e. the disturbance of the growth of the central nervous system (BDE-47, -99 and -209) and reproductive toxicity, i.e. disturbance of spermatogenesis after intrauterine exposure (BDE-99). For both effects MOEs were calculated between the mentioned reference values and the actual dietary exposure, with MOEs below 1 indicating a potential health concern.

The MOEs indicate that the long-term dietary exposure to BDE-47 and -209 does not pose a health concern in The Netherlands. However, in the case of reproductive toxicity the calculated MOEs for BDE-99 is lower than 1, indicating a potential health risk whereas in the case of neurodevelopmental toxicity the MOE was just larger then 1 for this congener. Unfortunately the available animal toxicity data do not allow for a dose-response analysis resulting in the quantification of the magnitude of the induced effect, i.e. disturbed sperm formation after birth. This warrants additional research on the reproductive toxicity of BDE-99

(and other PBDEs). At present the results of this study are in line with EFSA's opinion on PBDEs, i.e. that BDE-99 poses a potential health concern with respect to dietary exposure.

4.7 Need for Refinement

With respect to the conclusion drawn for the PBDE toxicity it should be kept in mind that, though toxicity studies have shown that different PBDE congeners may induce the similar type of toxicity (neurodevelopmental toxicity), the calculated MOEs apply to *individual* congeners only [3]. Here, in the absence of proper mechanistic studies which might hint on a common mode of action [3] the possibility of dose-addition was neglected. On the other hand, in the case such as neurodevelopmental toxicity unjustly ignoring dose-addition leads to underestimation of the toxic risk. For expressing the toxic potency of PBDEs relative to the congener showing the highest toxic potency, i.e. BDE-99, would lead to expressing the total PBDE exposure in terms of BDE-99 equivalents and hence to an increase of the already critical BDE-99 exposure. This therefore warrants mechanistic animal studies to reveal whether or not PBDE exert neurodevelopmental toxicity via a common mode of action.

Furthermore, the presented MOEs are confined to the dietary exposure only. In this the co-exposure to PBDEs from other sources as consumer products, house dust and breast milk were not taken into account. These sources may outweigh the dietary exposure to PBDEs. For example, assuming a daily breast milk intake of 800 ml, the intake of PBDE may be as much as 600 – 13.800 (BDE-47), < 140 – 510 (BDE-99) and 46 – 11.000pg/kg bw/day (BDE-209, [3]). Such an intake may exceed the dietary exposure manifold. Next to breast milk the intake of house dust may be a significant route of exposure, in particular in young children. For example, the intake of BDE-209 with house dust by toddlers may amount up to 5.6 – 27.1ng/kg bw/day [3]). As these additional exposures just occur during the period in which the developing human brain shows its maximal growth a risk assessment based on only the dietary intake may underestimate the neurotoxic risk of PBDEs in young children. It is therefore recommended to perform an integrated risk assessment on the basis of the combined exposure to PBDEs, i.e. the (age-dependent) intake of PBDEs from food, house dust, consumer products and breast milk (see for example [47]). Furthermore, there is a clear need for epidemiological studies on the occurrence of PBDE induced neurodevelopmental and reproductive toxicity [14].

5. CONCLUSION

Occurrence data of PBDE -47, -99, -100 and -209 in food items commonly available in The Netherlands in 2004 and 2008 were combined with food consumption data.The resulting long-term dietary intake indicates a 2-fold increase in the period between 2004 and 2008 for BDE-47, -99 and 100.

When compared with reference values for neurodevelopmental toxicity (disturbance of pre- and postnatal growth of the central nervous system) and reproductive toxicity (disturbance of spermatogenesis after intrauterine exposure) it is concluded that the long-term dietary exposure to BDE-47 and 209 does not pose a health concern in The Netherlands. However, in the case of reproductive toxicity it is concluded that BDE-99 poses a potential health concern with respect to dietary exposure.

This study is based on an evaluation of individual BDE congeners. Here the possibility of dose-addition has been neglected. As this may have led to an underestimation of the toxic

risk mechanistic studies revealing whether or not PBDEs share a common mode of action in inducing toxicity are warranted.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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