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Brominated flame retardants: occurrence, dietary intake and risk assessment

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Abstract

Brominated flame retardants: occurrence, dietary intake and risk assessment

Brominated flame retardants have entered the human food chain. For the time being the occurrence of these chemicals in Dutch food does not pose a human health risk. However, this might easily change at increasing contents of flame retardants in Dutch food. The monitoring of brominated flame retardants in Dutch food therefore remains necessary.

Brominated flame retardants are environmental contaminants which have entered the human food chain. Next to food these chemicals can also enter the human body by ingestion of housedust. Due to their persistent behaviour brominated flame retardants leave the human body very slowly. Brominated flame retardants therefore have bioaccumulating properties.

In order to determine the health risk of brominated flame retardants these chemicals have been investigated in Dutch food product and, as a measure of the amount in the body, in Dutch breast milk. In Dutch food twelve flame retardants were found, eleven of which also occurred in breast milk. Contrary to results in Sweden the content of flame retardants in Dutch breast milk did not decline between 1998 and 2003.

For health risk assessment a maximal allowed intake level is needed. Such an intake level is only available for the flame retardant PolyBromoDiphenylEther-99 (PBDE-99). At the moment the exposure to PBDE-99 from food equals its maximal intake level. So, though the exposure to PBDE-99 does not pose an immediate health risk, this may easily change when the content of brominated flame retardants in Dutch food would increase. The continuous monitoring of brominated flame retardants in Dutch food therefore remains necessary.

Key words: brominated flame retardants, food, dietary intake, risk assessment

Rapport in het kort

Gebromeerde vlamvertragers: voorkomen, inname via de voeding en risicoevaluatie

Gebromeerde vlamvertragers zijn tot de voedselketen van de mens doorgedrongen. De aanwezigheid van deze stoffen in voedsel vormt vooralsnog geen risico voor de gezondheid. Dit is wel het geval wanneer het gehalte in voedingsmiddelen toe zou nemen.
Het in kaart brengen van gebromeerde vlamvertragers in voeding blijft daarom nodig.

Vlamvertragers met broom zijn vanuit het milieu in het voedsel terechtgekomen. Vanuit voedsel, maar ook uit bijvoorbeeld huisstof, worden deze stoffen in het lichaam opgenomen. Door hun scheikundige eigenschappen verlaten zij het lichaam maar heel langzaam. Hierdoor slaat het lichaam vlamvertragers in feite op.

Om vast te stellen of blootstelling aan vlamvertragers schadelijk is zijn voedingsmiddelen op aanwezigheid van vlamvertragers onderzocht. Daarnaast is, als maat voor de hoeveelheid in het lichaam, ook moedermelk onderzocht.
In Nederlandse voedingsmiddelen konden twaalf vlamvertragers aangetoond worden. Hiervan bleken er elf ook in moedermelk voor te komen. Het moedermelkonderzoek liet verder zien dat de hoeveelheid vlamvertragers in het lichaam tussen 1998 en 2003 niet afgenomen is.

Om vast te stellen of de blootstelling aan vlamvertragers ook risicovol is, moet gewerkt worden met de maximaal dagelijks toelaatbare inname van deze stoffen. Zo'n maximale inname is voor één vlamvertrager beschikbaar. Tussen de blootstelling aan deze vlamvertrager via de voeding en zijn maximaal toelaatbare inname bestaat slechts een zeer kleine marge. Hoewel er op dit moment nog geen nadelige effect op de gezondheid is, kan dit snel veranderen wanneer het gehalte van vlamvertragers in voedingsmiddelen toe zou nemen. Monitoringsonderzoek naar vlamvertagers in voeding blijft nodig. Daarnaast zou de blootstelling via huisstof beter in kaart gebracht moeten worden.

Trefwoorden: gebromeerde vlamvertragers, blootstelling, voeding, risicoschatting

Contents

Summary

The study recorded in this report considers the risk assessment and the temporal trends of the three predominant brominated flame retardants (BFRs): hexabromocyclododecane (HBCDD), tetrabromobisphenol-A (TBBP-A) and polybrominated diphenyl ethers (PBDEs). It also overviews the concentrations of the BFRs recently measured in food and food products in the Netherlands, including estimates of the dietary intake.

Time trend in environment and humans

BFRs have widely spread in the environment, with European levels being orders of magnitude lower than those in North-America. In Europe environmental levels are declining or levelling off. Comparison of trends in the environmental concentrations with concentrations in breast milk in Sweden indicates a lag-time of at least a decade before a positive environmental effect in the form of decreasing levels of PBDEs was passed on to the human population. As reflected by PBDE levels in breast milk, this has already led to a decreasing trend in effective PBDE exposure (amount residing in the body) in Sweden (time period: decline from 2000 onwards). In the Netherlands such a decreasing trend has not been observed
(period: 1998–2003)

Exposure via food and house dust

Information on the occurrence of BFRs in Dutch food products is limited to two monitoring campaigns in 2001/2002 and in 2003/2004. Estimates of the mean dietary intake of HBCDD and TBBP-A by the Dutch population are from the 2001/2002 study and amount to 2.9 and 0.04 ng/kg body weight, respectively. The most recent dietary intake estimate of PBDEs in the Netherlands (2003/2004) reports a long-term median dietary intake of the sum of PBDEs of 1.7 ng/kg bw /day (95^{th} percentile 3.0 ng/kg bw/day).
Measurements of PBDEs in housedust from European homes have shown that the ingestion of soil/dust is an important route of exposure, in particular for toddlers and children. Though ingestion of PBDEs via soil/dust may lead to significant exposure, the contribution of soil/dust ingestion to the accumulation of PBDEs in the body remains to be clarified, in particular the extent to which PBDEs from soil/dust are absorbed from the gastrointestinal tract.

Risk assessment

For PBDE-99 a maximal allowed intake level of 0.26 ng/ kg-bw per day was calculated. This is equal to the 99-percentile of the PBDE-99 intake from food in the Dutch population (0.24 ng/kg-bw per day). The relative small margin between the human exposure to PBDE-99 from food and its maximal allowed intake level indicates the intake of of this flame retardant to be of relevant health concern.

Recommendations

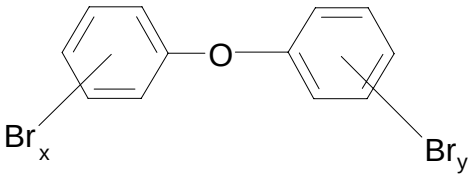
Monitoring of BFRs in food and breast milk
As only limited data are available of the occurrence of BFRs in Dutch food products, it is not possible to present, at the moment, a time trend. It is therefore recommended to monitor the PBDE, HBCDD and TBBP-A concentrations in food products and/or human milk regularly (yearly for a period of 5 years) in order to determine the time trend of the BFR exposure of the Dutch population from food and the effective BFR exposure, i.e. the amount of BFRs which has accumulated in the body. Measurements in pooled samples of different food categories and/or milk samples following the specific procedure used to sample 2004 RIVM food data (De Mul et al. 2005) or breast milk (Zeilmaker et al., 2002; Zeilmaker, 2005) is recommended. In view of the large variations in concentrations, multiple samples should be analysed per food category. Concentration variability may further be reduced by improvement of measurement accuracy.

Exposure to PBDEs from house dust
In order to clarify the extent to which PBDEs from soil/dust contribute to the accumulation of PBDEs in the body, the absorption of these compounds from the gastrointestinal tract should be determined. In this context an in vitro digestion system is recommended (Oomen et al., 2003; Versantfoort et al., 2005). In this in vitro test system the processes which occur in the human gastrointestinal tract after ingestion of PBDEs from food or soil-dust are simulated, resulting in a estimate of the absorption of PBDEs from soil/dust relative to food.

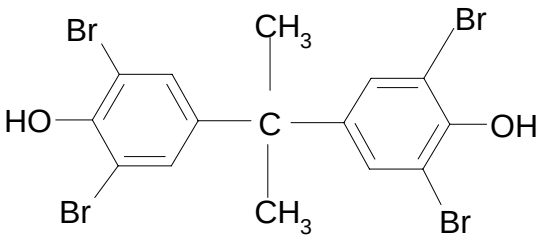
Risk assessment
To date PBDE-99 is the only BFR for which a quantitative risk assessment can be performed. For the other bioaccumulating BFRs, i.e. the other PBDEs and HBCDD, a corresponding risk assessment can only be carried if suitable results of toxicity and toxicokinetic studies will become available. As the research on BFRs is fully under way the regular reviewing of its progress over the next coming years is necessary in order to keep the risk assessment presented in this report up to date.

1. Introduction

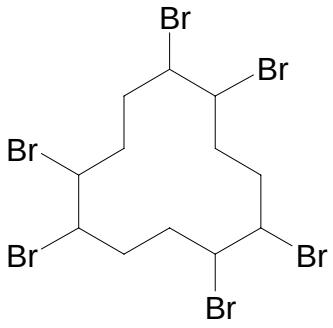
Brominated flame retardants (BFRs) are widely used in electronic household equipment (e.g. personal computers and television sets), plastics, textile and polyurethane foam in furniture and cars for safety reasons. BFRs have been produced since the 1970s. The annual world market demand of brominated flame retardants in 2001 was about 204,000 tons, of which 58 % was coming from Asia, 26 % from the two Americas, and 14 % from Europe. The most widely used BFRs are tetrabromobisphenol A (TBBP-A), hexabromocyclododecane (HBCDD) and polybrominated diphenylethers (PBDEs) (see structures below).



Polybrominated diphenyl ether
(x = 1-5, y = 1-5)



Tetrabromobisphenyl-A



Hexabromocyclododecane

Figure 1. The chemical structure of some brominated flame retardants

Potential routes of discharging BFRs into the environment are through incineration, sewage, leaching from landfills and through volatilisation from electrical components during their lifetime (Darnerud et al., 2001).

The intake of BFRs by humans occurs via the food, the ingestion of house dust and the inhalation of (indoor) air. Just as for PCBs and dioxins, food products of animal origin with high fat content (fatty fish, meat and dairy products) are expected to be major contributors to dietary exposure. The contamination of human food products by brominated flame retardants is not well known. However in recent years a number of studies have been carried out to measure the BFR concentrations in food. There is a larger number of measurements in fish reported, but mainly as an indicator of environmental pollution and to a much less extent in fish from the food markets. There is as well a number of new studies assessing the dietary intake of brominated flame retardants by the population. These studies demonstrate that there is indeed exposure of the Dutch population to BFRs.

Because of their tendency to accumulate in fat, the environmental fate of BFRs is similar to the fate of other persistent organic pollutants, such as PCBs and dioxins. If the exposure pattern, the toxicity and the kinetics of BFRs are also similar to that of dioxins and related compounds, i.e., repeated exposure, low effect-doses and high biological half-lives, these properties may (in addition to the occurrence in food) be used for setting priorities in monitoring campaigns of BFRs.

This report regards two research questions:

1. What is the time trend of BFR concentrations in food products?
2. What is the in vivo toxicity and bioaccumulation of BFRs in test animals and humans?

To answer these questions an overview is given of the occurrence, temporal trends and toxicity of the three major classes of BFRs: TBBP-A, HBCDD and PBDEs. Information on the production and discharge into the envrironment, the toxicity and the bioaccumulation of these substances is given in chapter 2. As information on the temporal trends of BFRs in food products appeared non-available, the temporal trends of BFR concentrations in the environment are described, which could give indications on possible trends in food (chapter 3). In the same chapter, the trends in human samples are reported which reflect the long-term intake of BFR contaminated food. In chapter 4 concentrations of BFRs which are recently measured in food and food products and dietary intake estimates in the Netherlands and other countries are given. Finally, the risk assessment of PBDE-99 with the present data is given (chapter 5).

2. Background information

2.1 Production and discharge of BFRs

BFR compounds
Of the total BFRs produced in 2001, about two-third (59 %) contain tetrabromobisphenol-A (TBBP-A) and derivatives, about one-third (33 %) contain polybrominated diphenyl ethers (PBDEs) and 8 % contain hexabromocyclododecane (HBCDD) (Bromine Science and Environmental Forum, 2004). PBDEs are in production in three formulations: the penta-PBDE (DBDPO decabromodiphenyl oxide), octa-PBDE (OBDPO octabromodiphenyl oxide) and deca-PBDE (PBDPO polybrominated diphenyl oxide) mixtures, of which deca-PBDE is produced in the largest amounts (Bromine Science and Environmental Forum, 2004). Penta-PBDE, octa-PBDE and deca-PBDE commercial products contain penta-, octa- and deca-PBDEs as main components and additionally other PBDEs as well (Figure 2, PBDE congener numbering is given in Appendix 1). The commercial HBCDD product is composed of three diastereomers: λ-, β-, and γ-HBCDD.
Other main commercial BFRs are brominated polymers such as brominated epoxy, brominated polystyrene, brominated polycarbonate, poly(brominated acrylate), and brominated polyols. Polybrominated biphenyls (PBBs), the brominated counterpart of polychlorinated biphenyls (PCBs), were banned in U.S.A. and not produced any more as of 1979. In Europe PBBs were in production in Germany until 1985 and in France until 2000.
Polybrominated and mixed brominated/chlorinated dibenzo-p-dioxins and furans (PBDD/Fs and PXDD/Fs) are mainly produced as by-products of waste incineration. These substances are formed, for example, when plastics containing BFRs are heated. Given the common mechanism of action and effects of dioxin like compounds, it is reasonable to predict that their presence will incrementally add to the total dioxin body burden (Birnbaum et al., 2003).
The available information on the occurrence and toxicity of BFRs is mostly restricted to the three major ones: TBBP-A, HBCDD and various PBDE congeners.

European market
The market demand in 2001 for BFRs in Europe was estimated to be about 29,000 tons, TBBP-A, HBCDD and PBDE each accounting for about a third of the production (Table 1). Of the PBDE market demand in Europe, deca-PBDE has by far the largest part (Table 1). HBCDD is used more extensively in Europe than in North America. The total BFRs market demand in the two Americas is roughly 2 times larger than in Europe. On the other hand, the HBCDD market demand in Europe is about 3 times larger than in the Americas (Bromine Science and Environmental Forum, 2004).
The penta-PBDE technical product was voluntarily banned in the European Union last 10 years. This has led within the EU to increases in the use of HBCDD and TBBP-A. The use of penta-PBDE and octa-PBDE technical products in all applications for the European Union market is officially banned from 15 August 2004. The use of penta-PBDE, octa-PBDE and PBBs in new electrical and electronic equipment will be banned by July 2006.

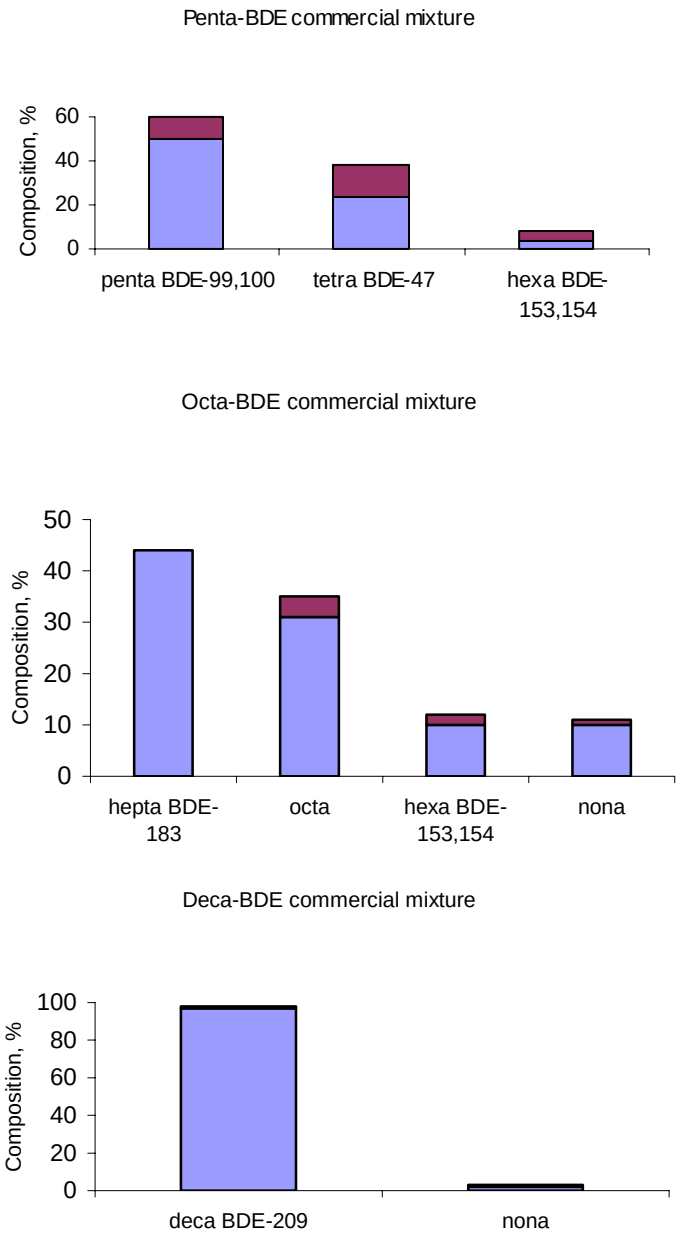


Figure 2. Composition of commercial PBDE mixtures. The different colour at the top of the bars gives the variability in the composition of the commercial mixture composition (data from De Wit, 2002).

Table 1. BFR market demand in Europe in 2001

BFR	Contribution to total market demand in Europe	Composition of market demand of PBDE
TBBP-A	39 %	
HBCDD	32 %	
PBDE	28 %	Deca-PBDE 91 % Octa-PBDE 7 % Penta-PBDE 2 %

Discharge into environment and intake by humans

PBDEs, HBCDD and PBBs are additives mixed into polymers and are not chemically bound to the plastic or textiles. Therefore, they may separate or leach from the surface of their product applications into the environment. TBBP-A is bound to the material chemically, but may not have polymerized and is released to the environment (De Wit, 2002). The waste from the products containing BFRs is either incinerated or deposited in landfills. The sources of BFRs also include industrial facilities that produce BFRs as well as consumer manufacturing facilities that use BFRs in a wide range of consumer products. The presence of BFRs in the environment has been shown in air, sewage sludge, sediments, fish, birds and mammals, including human breast milk, blood and adipose tissue (De Wit, 2002; Boon et al., 2002). The presence of PBDE in samples from living organisms and in air in the Arctic indicate long-range transport of PBDEs in air.

The intake of BFRs by humans can occur via the intake of food, the ingestion of house dust and the inhalation of (indoor) air. Just as for PCBs and dioxins, food products of animal origin with high fat content (fatty fish, meat and dairy products) are expected to be major contributors to dietary exposure. Estimates of median exposures in the UK indicate diet and inhalation to contribute 93 and 7 % respectively (Harrad et al., 2004). A Canadian/British study (Wilford et al., 2004) reported that for median inhalation exposure the maximum contribution of the inhalation pathway to the total intake (sum of both dietary and inhalation intake) is 4 %. However, a 50-fold variation between the 5^{th} and 95^{th} percentiles of inhalation exposure was shown. Consequently, the higher percentiles demonstrated a much higher contribution of the inhalation pathway to the total intake (32-34 % for the 95^{th} percentile).

House dust may contain appreciable amounts of flame retardants. In house dust of German homes average concentrations of 122, 180, 21 and 1404 ng/g dry mass were found for PBDE-47, 99, 100 and total PBDE (Knoth et al., 2003). When compared with similar measurement in American homes the latter measurements were a magnitude higher than in German homes, average PBDE-47, 99 and 100 and total PBDE concentrations amounting 1220, 1700, 274 and 5900 ng/g dry mass (Stapleton et al., 2005).

Combining measured concentrations in air, food and dust with modeling techniques Jones-Otazo et al. (2005) calculated for the Canadian population daily PBDE exposures of 1965 ng/day for the breast fed infant (0-0.5 year), 261 ng/day for toddlers (0.5–4.0 year), 209 ng/day for children (5 –11 year), 155 ng/day for teens (12-19 year) and 155 ng/day for adults (20+ years). These exposures mainly occurred from the ingestion of food and soil/house dust, the latter exposure route contributing 89 % (toddlers), 78 % (children), 61 % (Teens) and 61 % (adults) to the total exposure.

As already mentioned the concentrations of PBDEs in house dust of European origin are far less than in American or Canadian homes. Consequently, the exposure via ingestion of house dust in Europe is expected to be lower in comparison with the U.S.A. or Canada. For example, taking the (median) concentration of PBDEs in Germany as a reference (62 ng total PBDEs/g dry mass, Knoth et al., 2003), and assuming a soil/dust ingestion of 0.02 – 0.05 g/day for adults and maximally 0.2 g/day for toddlers (Oomen and Lijzen, 2004) a daily exposure of 1.2 – 3.1 ng may be calculated for adults and (maximally) 12.4 ng for toddlers. These calculations anyway indicate that, in comparison with the (median) life-long exposure in the Netherlands via food (1.73 ng/kg/day, corresponding with 121 ng/day for an adults body weigth of 70 kg, see chapter 4) the exposure to PBDEs via ingestion of soil/dust seems only a minor route of exposure when compared with the exposure via food. However, both the exposure assessment from food and housedust contain quite some uncertainty. For, neither of these exposure assessments incorporates the contribution of the decabromo congener PBDE-209. In housedust this congener may contribute up to 70 – 80 % of total PBDEs. Furthermore, the exposure via food mainly occurs by the ingestion of PBDEs in a

matrix which very well suites uptake (absorption) in the body, i.e. the food's fat fraction, however, the absorption of PBDEs originating from house dust is expected to significant less than from food. In this context the (widely made) assumption that the absorption of PBDEs from soil/house dust lies between 50 and 100 % (Otazo et al., 2005) may easily overestimate the accumulation of PBDEs originating from housedust in the body. Clearly, more research is needed to characterise the total exposure to PBDEs, i.e. by incorporating PBDE-209, and by determining the absorption of PBDEs from soil/house dust.

2.2 Toxicity and kinetics of BFRs

2.2.1 Toxicity studies

2.2.1.1 Tetrabromobisphenol-A

Tetrabromobisphenol-A (TBBP-A) was not found toxic for rodents in dose levels up to 1000 - 10000 mg/kg/day (EU RAR, 2003; see Appendix 2).

2.2.1.2 Hexabromocyclododecane

For hexabromocyclododecane (HBCDD) the thyroid and the liver appeared to be target organs. A (preliminary) 5 % Bench Mark Dose (BMD) in the range of < 10 – 37 mg/kg bw has been reported for induced hyperplasia in these organs. Based on the absence of mutagenicity and and carcinogenicity in mice it was concluded that 'there are no reasons to explore this endpoint, i.e. carcinogenicity, further'. HBCDD failed to demonstrate any fetotoxic, teratogenic or any adverse developmental effects in the rat. However, it may lead to developmental neurotoxic effects in offspring after single exposure during the neonatal period (LOAEL of 0.9 mg/kg/ day) (EU RAR, 2005; see Appendix 2).

2.2.1.3 Polybrominated flame retardants

In rodents, lower brominated PBDEs may induce developmental neurotoxicity and the disturbance of homeostasis of thyroid hormones (Appendix 2). Single doses of lower brominated PBDEs (PBDEs 47, 99 and 153), when administered during the period of pregnancy, lactation or shortly after birth, may lead to neurodevelopmental toxicity as assessed in offspring later in life. At the level of the thyroid PBDEs may interfere with the synthesis of the thyroid hormone thyroxine (T4). Furthermore PBDEs may interfere with the transport of thyroid hormones in the blood through competitive binding of PBDEs to the transthyretin transsporter (TTR). When the lower brominated PBDEs are compared on the basis of their reported NOAELs, LOAELs or 10 % Bench Mark Doses [(1)] it appears that reproductive and developmental toxicity, as measured by impaired spermatogenesis, altered mitochondrial morphology in the ovaries, increased resorption rates and external and skeletal anomalies, is the hitherto most sensitive toxic endpoint of these congeners in rodents (Kuriyama et al., 2005; Talsness et al., 2005).

The toxicity of PBDEs has recently been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2005). With regard to the disturbance of thyroid homeostasis by PBDEs the JECFA concluded that the available data were insufficient to determine the mechanism for the reported effects. With regard to the neurotoxic effects the conclusion was that 'Because of the preliminary nature of the (neurotoxicity) findings, an interpretation of significance for human health could not be made'. JECFA furthermore concluded that: 'The available data are inadequate to establish a common mechanism of

[1] NOAEL: no observed adverse effect level; LOAEL: lowest observed adverse effect level, 10 % BMD: Dose at which an effect size of 10 % is reached.

action that would allow a single congener to be used as a surrogate for total exposure or, alternativily, as the basis for establishing toxic equivalency factors'.
The JECFA did not allocate a provisional tolerable monthly/daily intake for PBDEs because the available toxicity data on PBDEs were considered not adequate for such an approach (see Appendix 2). Taking all toxicity data together the JECFA concluded: 'The limited toxicity data suggest that for the more toxic PBDE congeners adverse effects would be unlikely to occur at doses of less than approximately 100 μg/kg bw per day'. The JECFA furthermore stated that the current estimates of dietary intake were approximately 0.004 μg/kg bw per day, while intake by breast feeding infants could be up to 0.1 μg/kg bw per day for the sum of all measured PBDE congeners, including the toxic ones. In consequence, there appeared to be a large Margin of Exposure (MoE**)** between the (expected) NOAEL in animals and the actual human exposure, despite of the inadequacy of the data on toxicity and intake. This gives reassurance that intakes of PBDEs are not likely to be a significant health concern. The JECFA noted that, as with related bioaccumulative persistent contaminants (PCBs, dioxins: WHO, 2002; SCF, 2000, 2001; JECFA,2002), a more appropriate dose-metric for interspecies comparison of risk would be a measure of the accumulating potency of PBDEs ('body burden' approach). For the majority of PBDEs studied, however, the data from experimental animals or on concentrations in human tissues were considered insufficient to allow a comparison with external dose. Notwithstanding this conclusion the JECFA 'considered that continuing studies of PBDEs in samples from humans, including human milk, would be useful in assessing the overall exposure to PBDEs in foods and other possible sources'.

2.2.2 Bioaccumulation of BFRs

Regarding the extent of bioaccumulation, knowledge on the (terminal) half–life, an aggregate measure for the rate of removal of the parent compound and its metabolites from the body, is crucial (WHO, 2002; SCF, 2000, 2001; JECFA, 2002). When the exposure to a compound occurs daily via the intake of food, half-lives in humans of the order of magnitude of months-years lead to the bioaccumulation of the substance: as the duration of exposure increases, more and more of the substance will accumulate in the body until the concentration in the body ('body burden', BB) reaches a constant level ('steady state'). For example, the dioxin 2,3,7,8-TCDD has a terminal half-life of about 20 days in rodents and more than 7 years in man. A near 'steady state' situation in humans will be reached after 28-35 years. As shown in Table 2 (provisional) estimates of the terminal half-life of TBBP-A, PBDEs and HBCDD in rats and in humans are yet available. As with 2,3,7,8-TCDD the estimated half-lives in humans tend to be far greater than in rats, with half-lives of tetra, penta, and hexabrominated PBDEs being in the order of that of 2,3,7,8-TCDD. TBPP-A did not indicate bioaccumulating properties in the rat nor in humans, whereas HBCDD has been found to have clear bioaccumulating properties in the rat (Chengelis, 2001, as cited in EU RAR, 2005).

Table 2. Terminal half-lives of TBPPA, HBCDD and PBDEs in rats and in humans (Geyer et al. 2004; Hagmar et al., 2000; Jakobsson et al., 2003).

Compound	Half-life	
	Rat [1](days)	Humans[2] (years)
TBBP-A	2.8	-
HBCDD	8/20[3]	0.17
PBDE-47 (tetrabromo)	21.4	1.8
PBDE-99 (pentabromo)	33.0	2.9
PBDE-100 (pentabromo)	21.2	1.6
PBDE-154 (hexabromo)	35.4	0.74 ; 3.3
PBDE-153 (hexabromo)	59.3	1.9 ; 6.5
PBDE-183 (heptabromo)	-	0.24 ; 0.30
PBDE-209 (decabromo)	-	0.019

[1] As measured in adipose tissue; [2] Total body half-life in non-occupationally exposed humans as assessed with a linear one-compartment pharmacokinetic model; [3]Chengelis, 2001, as cited in EU RAR, 2005

3. Temporal trends of BFRs in environment and humans

Unlike several of the 'classical' persistent organic pollutants such as PCBs, dioxins and furans, whose levels have been decreasing markedly during the last 20 years, several studies have reported rising trends in environmental concentrations of PBDEs. There is therefore a serious question as to whether levels of PBDEs (and other BFRs) will continue to increase in the environment and humans.
There is a large difference in levels of BFRs between North America and Europe, due to different production and use. For example, North America consumes half of the world's production of PBDEs and 98 % of the penta-PBDE mixture (Hale et al., 2003). Furthermore, while penta-PBDE has been restricted for over ten years and has been banned within Europe since 2004, the production and use of this mixture continue to rise in North America (Alcock et al., 2003). As a consequence, levels of BFRs in North America are higher than in Europe. For example PBDE concentrations in U.S.A. and Canadian sewage sludge as well as in human milk and serum in women from North America appear to be at least 10-fold greater than European levels.

3.1 Diet

There is no information on the trends of BFRs in the diet, however, two studies analysed a few historic diet samples.
Australian historic butter samples originating from around 1944 were analysed (Müller et al., 2003). The PBDE concentrations in the butter samples were consistently below the limit of detection and the sum of 8 PBDEs was less than 0.20 ng/g lw (lipid weight).
PBDE levels were measured in four vegetable oils (olive and peanut) from the Middle East, two of which were produced in the 1940s and two were present day samples. PBDE-28, -47, -49, -99, -100, -153, -154, -183 were below detection limit in all of the oil samples, the sum of 8 PBDEs was less than 0.05 ng/g lw.

3.2 Meta-analysis of PBDE concentrations in environment and humans

Hites (2004a) acquired and classified most of the literature on PBDEs in the environment or in humans published before August 2003, and made a meta-analysis of concentrations. The present section gives a summary of this meta-analysis with regard to temporal trends.

3.2.1 Marine mammals

Current PBDE concentrations in marine mammals from the Canadian Arctic are very low (see Figure 3) at about 5 ng/g lw, but they have increased exponentially with a doubling time of about 7 years. Marine mammals from the rest of the world (Europe and U.S.A.) have current PBDE levels of about 1000 ng/g lw, and these concentrations have also increased exponentially with a doubling time of about 5 years.

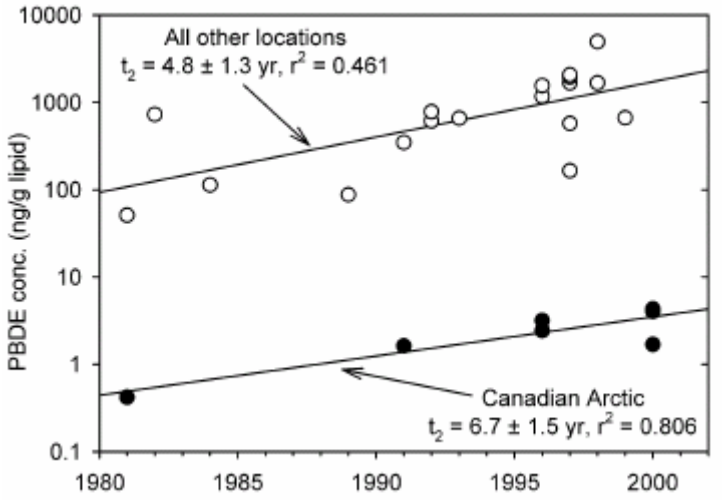


Figure 3. Sum of PBDEs concentrations in marine mammals shown as a function of the year in which the samples were collected (figure taken from Hites, 2004a).

3.2.2 Human samples

Hites (2004a,b) reviewed PBDE concentrations measured in human samples: ambient human tissue (from people not occupationally exposed), blood (usually serum) and human milk. A plot of all these concentrations versus sampling year (see Figure 4) shows an exponential increase with a doubling time of about 5 years. In general, the PBDE concentrations in people have increased by a factor of about 100 during the last 30 years. The North American samples are always above the regression line (in recent years by a factor of >10), the Japanese samples are usually below the regression line (by a factor of about 5). This indicates again that people in the United States are exposed to higher levels of PBDEs than are Europeans and that the Japanese are exposed to less than the Europeans. The concentrations of PBDEs are about 20 times higher in people from the U.S. (~35 ng/g lw) as compared to people from Europe (~2 ng/g lw).

3.3 North America

The environment and the people in North America are much more contaminated with PBDEs than in Europe. PBDE concentrations in the North American environment (sediments, fish, birds and marine mammals) and in human samples (blood, breast milk and fetal liver) increase exponentially with time doubling every 4-6 years and there are no indications of levelling off. PBDE concentrations in Canada and especially the Canadian Arctic are lower than in the U.S.A. and the trends are somewhat slower.

The concentrations of PBB-153, which was a main component of hexabromobiphenyl banned in the 1970s, generally remained the same in U.S.A. Great Lakes fishes. On the other hand, they are decreasing in the serum of the U.S.A. general population.

A detailed review on the environmental and human temporal trends of BFRs in North America can be found in Appendix 3.

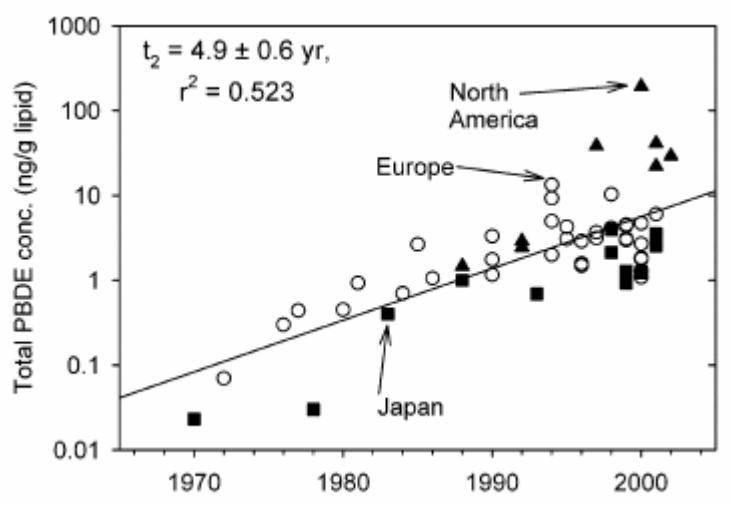


Figure 4. Total PBDE concentrations in human blood, milk, and tissue shown as a function of the year in which the samples were taken (figure taken from Hites, 2004b). The three symbol types indicate the location from which the samples were collected. The overall regression is shown.

3.4 Japan

In Japan, PBDE concentrations in the environment (sediments and fish) increased exponentially up to early 1990s. This was followed by a decrease, due to the reduction of the commercial tetra-PBDEs consumption in Japan after 1990. The time-trend of total PBDEs in Japanese breast milk, which began levelling off after 1998, and the PBDE levels therein are not remarkably different from those in Swedish breast milk.
The historical trends of polybrominated dibenzo-p-dioxins and furans (PBDD/F) in Japanese sediment cores of Tokyo Bay were similar to those of PBDEs.
A detailed review on environmental and human temporal trends of BFRs in Japan can be found in Appendix 3.

3.5 Europe

In Europe the temporal trend of BFRs in environmental samples appears to be dependent on the region and the type of sample, as is illustrated below. Note that the use of the technical PentaPBDE product in the European Union has been drastically reduced in the last 10 years and has been banned from August 2004, while HBCDD continues to be used.

3.5.1 Fish and mussels

Concentrations in fish are highly variable depending on the type of fish and the location from which they were collected. These variations are likely due to the proximity of the fish feeding grounds to PBDE sources. In general, fish from Europe have about 10 times lower PBDE concentrations than fish from North America. The mean and median of the sum of PBDEs are 120 and 49 ng/g lw, respectively, for the European fish (Hites, 2004a).
Pike are collected yearly from Lake Bolmen in southern Sweden and the PBDE congeners PBDE-47, -99, -100, -153 and -154 were analysed for most years between 1967 and 2000 (Kierkegaard et al., 2004). The temporal trends for all PBDE congeners show increasing

concentrations from the 1970s to the mid-1980s (Figure 5). The concentration of PBDE-47 showed a 30-fold increase between 1968 and 1983 (doubling time of 4-5 years). PBDE congeners reached their maximum concentrations in the mid- to late 1980s and then leveled off or decreased. The trend may be indicative of decreasing use and production of lower brominated PBDE products.

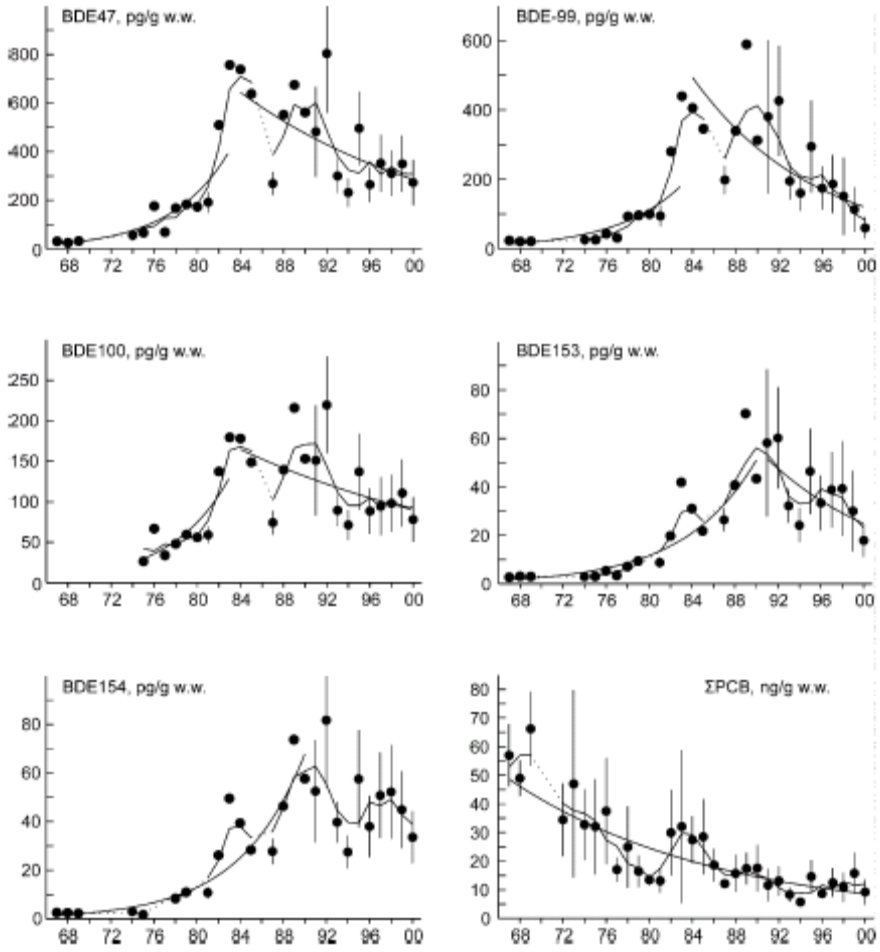


Figure 5. Temporal trends of tetra- to hexa-PBDEs and the sum of PCB (on wet weight basis) in pike fromLlake Bolmen. The line represents a three-point running mean smoother, the dots the arithmetic means with the 95% confidence interval indicated. The curves represent the log-linear regression for selected time periods (figure taken from Kierkegaard et al., 2004).

No significant trend was detected for PBDE-47, -99 and-100 in roach from Lake Krankesjön in Sweden between 1980 and 1996 (De Wit, 2002; Kierkegaard et al., 1999). This is in agreement with the more or less constant levels found in pike from Lake Bolmen between 1982 and 1996 (De Wit, 2002; Kierkegaard et al., 1999).
Eel samples from the Rhine and Meuse Rivers revealed decreasing PBDE levels during 1983-1993, whereas PBDE levels increased in the River Roer eel during the same time period (Darnerud et al., 2001; De Boer, 1995). However, decreasing PBDE concentrations were observed in yellow eel from the River Roer over the period 1977-1999 and Haringvliet-east (1983-1999) in the Netherlands (Kierkegaard et al., 2004; De Boer and Allchin, 2001).

The concentrations of PBDE-47, -99 and -100 have increased exponentially in mussels from the Seine estuary between 1981 and 1999/2001 (Johansson et al. 2004). The concentration of these congeners was constant between 1999 and 2001, whereas in 2002 and 2003 the concentrations of PBDE-47 and –99 decreased significantly (Figure 6). The levels of PBDE-47 and –99 in mussels from the Seine estuary are comparable to the levels observed in mussels from the Netherlands.

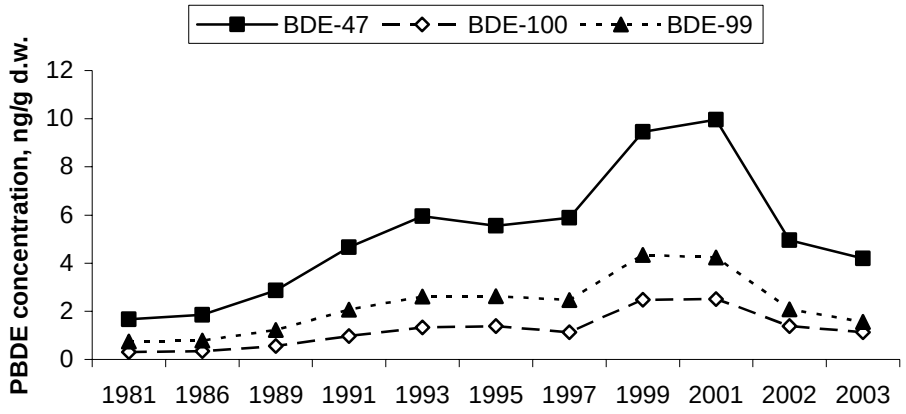


Figure 6. The concentrations of PBDE-47, -99 and -100 in mussels from the Seine estuary between 1981 and 2003 (figure from Johansson et al., 2004).

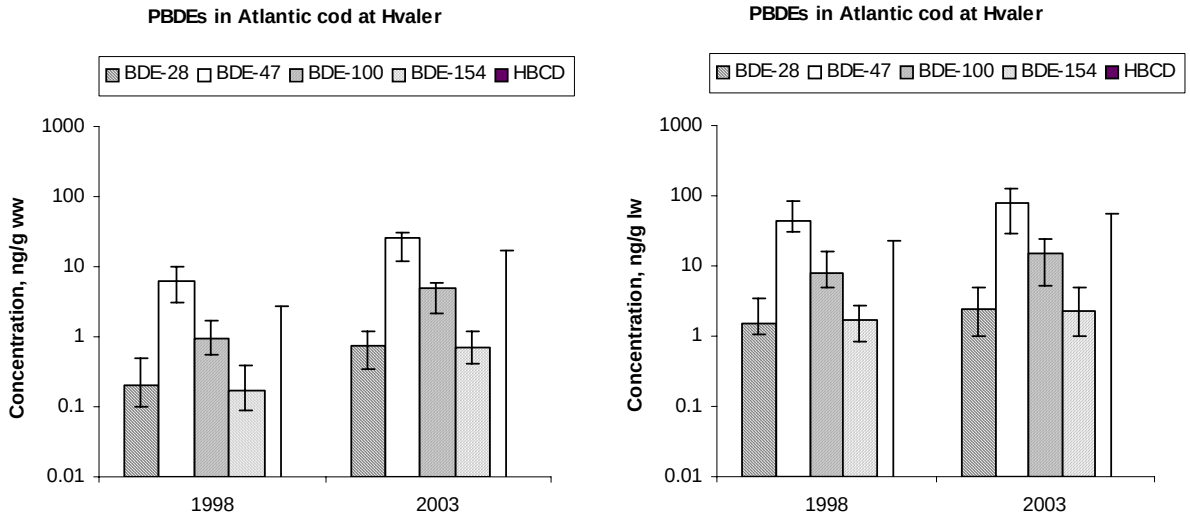


Figure 7. Temporal trends of BFRs in Atlantic cod at Hvaler in 1998 and 2003 (data from Bytingsvik et al., 2004, ww – wet weight, lw – lipid weight). Error bars represent the data ranges.

An increase of 3-4 times was seen in wet weight concentrations of all PBDE congeners, when comparing Atlantic cod from Hvaler (outer Oslo fjord) in 1998 and 2003 (Bytingsvik et al., 2004). The concentration of HBCDD was about 8 times higher in 2003 as compared to 1998 (see Figure 7). When expressed on a lipid weight basis, the increase was more modest, with levels 1.5 times higher for all PBDEs, whereas HBCDD showed an increase of 3-4 times. This study indicates that there has been an increase in concentrations of both PBDEs and especially HBCDD, in the Hvaler, outer Oslo fjord area during the last five years. However,

only one site and two time points are considered here. This study points out that the concentration of HBCDD, in particular, has been increasing the last years, and that HBCDD is now present in relatively high concentrations even in remote areas like Bear Island, Barends Sea.

3.5.2 Dated sediment cores

The analysis of a sediment core from the Baltic Sea, close to the south coast of Sweden, provided a retrospective trend from 1939 to 1987 and showed that the PBDE levels have increased, especially after 1980 (see De Wit, 2002).
Zegers et al. (2000) measured 14 PBDEs in sediment cores from three locations in Western Europe. Starting from the beginning of the 1970s, the pentaPBDE-mixture is clearly present in the sediment cores, while the deca-mix formulation is only present since the late 1970s, in agreement with the production figures for the commercial formulations. The sediment cores from Drammenfjord, Norway indicate a continuous increase in PBDEs from the early 1970s up to the most recent sediments from 1999. Analysis by Hites (2004a) shows that at this location, the PBDE concentrations increased with a doubling time of about 3 years until the mid-1980s, at which time the concentrations seem to have levelled off (the doubling time increased to about 8 years). In sediment cores taken from Lake Woserin, Germany and the Dutch Wadden Sea the penta- brominated congeners were levelling off in the most recent sediment layers representing 1995 and 1997. PBDE-209 decreased in the most recent layer of all three locations. These differences may reflect differences in exposure routes. Lake Woserin receives its input of contaminants from long range transport through air. The Wadden Sea and the Drammenfjord are both areas in close contact with major industrial areas via water currents. A PBDE input from local sources via the dissolved phase or suspended particles is much more likely for these two areas.

3.5.3 Birds

A decreasing trend for the lower brominated PBDE congeners has been found in eggs from guillemots (Dutch: zeekoeten) from the Baltic Sea since the voluntary withdrawal of use in a number of countries, but levels of HBCDD are still increasing (Sellström et al., 2003). The PBDE-47, PBDE-99 and PBDE-100 concentrations increased from the 1970s to the 1980s, peaking around the mid- to the late 1980s, then followed by a rapid decrease during the rest of the study period (Figure 8). In 2000-2001 the concentrations of the major PBDE congener were less than 10 % of its peak values. The concentrations of HBCDD show an increasing tendency from 1969 to 1997 (Figure 8). After a peak in the middle of the 1970s followed by a decrease, the concentrations increased during the latter part of the 1980s. During 1993-2001 the annual mean concentrations are more or less stable at a higher level as compared to the beginning of the study period in 1969.

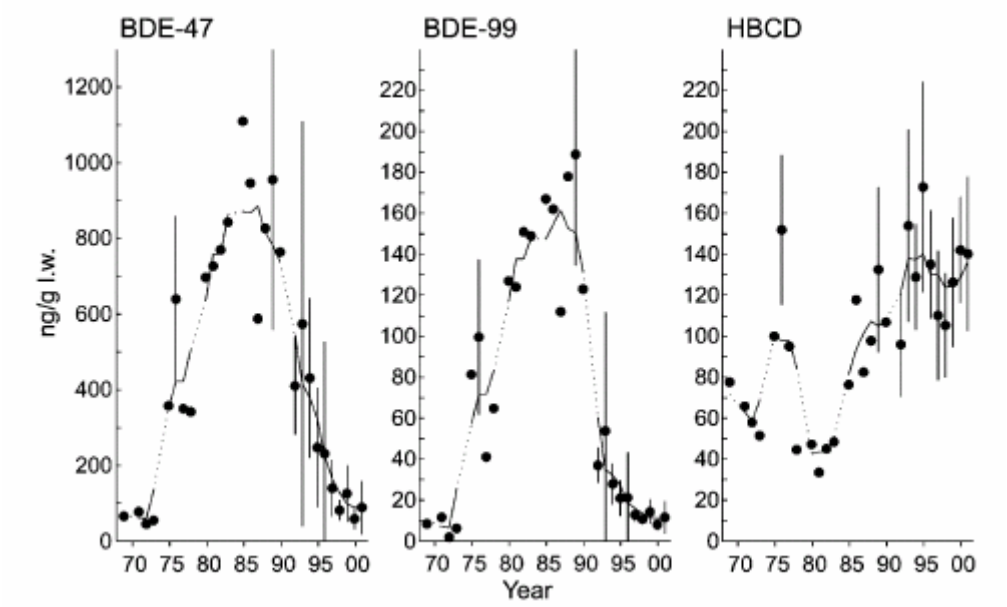


Figure 8. Temporal trends of PBDE-47, PBDE-99, and HBCDD in guillemot egg from Stora Karlsö, Sweden (figure taken from Sellström et al., 2003).

This significant decrease in PBDE concentrations after the late 1980s is in disagreement with other Swedish trend studies covering the same time period. Pike from the Swedish Lake Bolmen showed the same increase in concentrations, but after the late 1980s the concentrations have decreased slowly or levelled out (Kierkegaard et al., 1999; 2004, see section 3.5.1). Reductions in the emissions from the European production and downstream use of lower PBDEs could be the explanation for decreasing concentrations in guillemot eggs from the Baltic Sea. The slow decrease or levelling off in concentrations in pike may indicate a local source of PBDE to that lake, while the increasing concentrations in humans may reflect a continuous direct exposure from flame retarded products. The trends in guillemot eggs indicate that the environmental concentration declined rather quickly after emissions have decreased in a region.
The deca-PBDE (PBDE-209) trend was studied in peregrine falcon eggs (1973-2002) and sparrow hawk muscle tissue samples (1975-2001) from the UK (De Boer et al., 2004; Law et al., 2004). A statistically significant increase of concentrations of PBDE-209 in peregrine falcon eggs over the period 1975 to 1995 was observed, as well as a significant decrease from 1995 to 2001. This may suggest a correlation with the consumption of the Deca-PBDE mixture in the UK, with a peak in 1989 and a decrease since that time. Data for sparrow hawks did not show any significant trend, but more positive samples were observed in samples from later years. The HBCDD concentrations found in the peregrine falcon eggs and sparrow hawk were generally very low, and no time trend could be established.

3.5.4 Human samples

PBDE and HBCDD levels in blood from Dutch mothers and infants are reported by Weiss et al. (2004). The mean PBDE-47 concentrations were 3.2 and 3.7 ng/g lw in maternal serum and cord blood (infant level), respectively. This is lower than reported mean levels in the U.S.A. of respectively 28 and 25 ng/g lw (Mazdai et al., 2003), and comparable to levels found in Swedish blood reported in 2001. Notably the mean PBDE-153 concentration was the highest concentration of all PBDEs in maternal serum, PBDE-47 being the most abundant congener in the past. In cord blood PBDE-47 levels were higher than PBDE-153 levels. HBCDD mean concentration was 1.1 and 2.4 ng/g lw in maternal serum and cord blood,

respectively, which is similar to serum sample concentrations from Swedish women. This indicates that the exposure of Dutch women to HBCDD has resulted in a considerable accumulation in the body.
The sum of the six PBDEs (PBDE-28, -47, -99, -100, -153, -154) in serum from Norway increased from 0.44 ng/g lw in 1977 to 3.3 ng/g lw in 1999 (Figure 9, left side, Thomsen et al., 2002).
On average, the PBDE content in Norwegian breast milk has increased by more than 300 % from 1986 to 2001 and by 58 % from 1993 to 2001 (Thomsen et al., 2003). The mean PBDE level in 2001 of 3038 pg/g lw agrees well with the level of 2800 pg/g lw reported in Swedish breast milk. The levels in serum and breast milk are quite consistent and the PBDE level seems to peak around 1998 (see Figure 9, right side) which supports the recent trend found in Swedish breast milk (Lind et al., 2003).
The flame retardant TBBP-A is industrially the most important individual BFR used. However, reports on TBBP-A in human samples and in the environment in general are scarce. TBBP-A was not identified in the Norwegian serum pools from 1977 and 1981, but a slight increase of TBBP-A concentration in serum was observed from 1986 to 1999 (Thomsen et al., 2002, Figure 9).

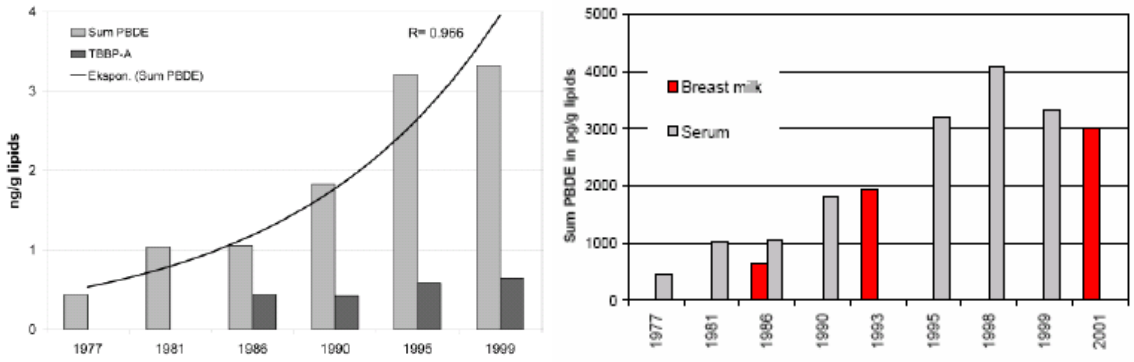


Figure 9. The concentration of TBBP-A and total PBDE concentration in pooled serum samples from 40 to 50 year old Norwegian men (left; figure taken from Thomsen et al., 2002). The mean PBDE levels in Norwegean breast milk compared to levels in Norwegian serum (right; figure taken from Thomsen et al., 2003).

The median total PBDE concentration in European human milk of most reported studies are summarised in Table 3 (Ryan, 2004).
PBDE levels in the human breast milk from Stockholm, Sweden increase exponentially between 1972 and 1997, doubling every five years (Meironyté et al., 1999; Noren and Meironyté, 2000). However, PBDE levels in human milk showed a decreasing trend from 1998 to 2000. An increase in mean values of both the sum of PBDEs and PBDE-47 in individual breast milk samples from Uppsala county, Sweden was seen from 1996 to 1998, after which the levels decreased up to year 2001 (Lind et al., 2003). These changes in levels are similar to what has been reported in pooled samples from Stockholm (Figure 10), although a large within-year variation was found in individual concentrations (Lind et al., 2003).
Comparison of trends in guillemot eggs, with a decrease starting the mid-1980s, and in breast milk from Sweden, with a decrease starting 1998, indicates a potential lag-time of a decade

before a positive effect in the environment was translated to decreasing levels in the human population (Sjödin, 2003).

Table 3. PBDEs in human milk from Europe (data from Ryan, 2004).

Country	Collection year	Median total PBDEs (ng/g lw)
Sweden	1972 1984-1985 1994 1997 2000-2001	0.1 0.7 2.2 4.0 2.1
Sweden	1996-1999 2000-2001	3.2 2.9
Germany	1992 2000 2002	1.7 1.8 6.6
Finland	1994-1998	1.6
UK	2001-2002	6.6
Norway	1993, 2001 2001	1.9, 2.9 2.8
Belgium	2000-2001	2.9

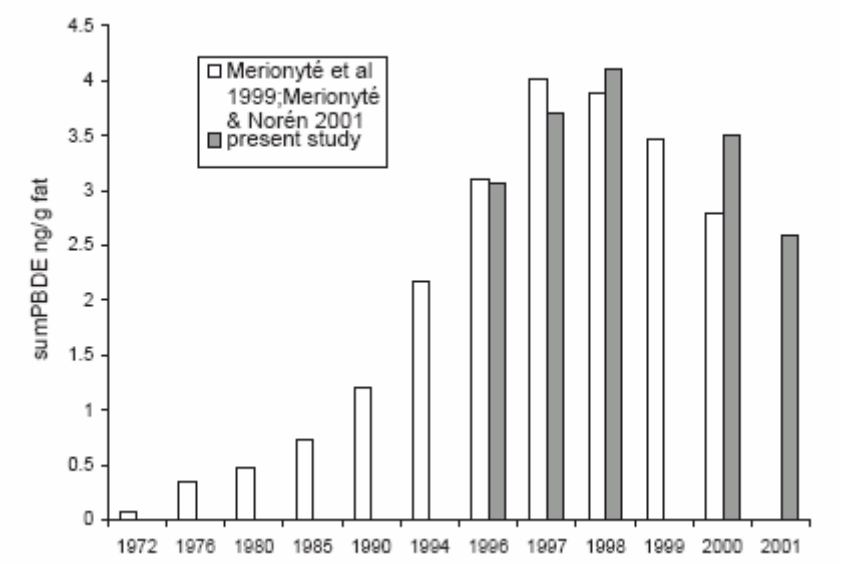


Figure 10. A comparison between data on PBDE levels in pooled breast milk from Stockholm, Sweden (white bars) and mean values of individual breast milk samples from Uppsala county, Sweden (grey bars) (Figure from Lind et al., 2003).

A steep increase of PBDE concentrations is shown in human milk from the Faroe Islands from 1987 to 1999 (Fängström et al., 2004, Figure 11). The Faroe Islands are situated between the Norwegian Sea and the North Atlantic Ocean, about one-half of the way from Iceland to Norway. The Faroe Islands are located quite far from the European continent and from industrial sources of PBDEs. The range of PBDE concentrations in Faroe human milk is similar to those observed in the UK and Germany, with average total PBDE concentrations of about 6-7 ng/g lw, which is up to 3-fold higher than observed in Sweden and Japan. The PBDE pattern in Faroe breast milk is different from the one reported in studies elsewhere, with PBDE-153 as the dominant congener, rather than PBDE-47 otherwise being the most

prevalent congener. The PBDE-47 trend is in accordance with findings from Sweden (see Figure 11). However, the PBDE-153 profile is different from Swedish data, with considerably higher concentrations and a steeply increasing trend.

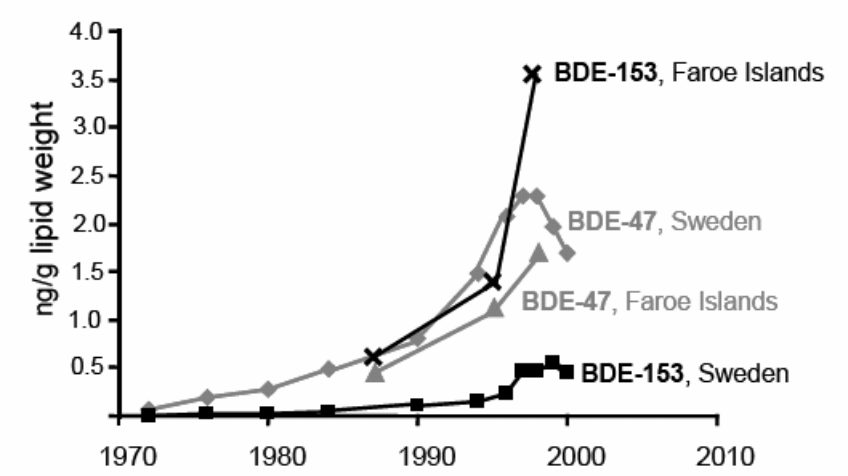


Figure 11. A time trend comparison between Sweden and Faroe Islands (figure from Fängström et al., 2004).

In the Netherlands the occurrence of PBDEs in breast milk was investigated in 1988, 1998 and 2003 (Zeilmaker, 2002; 2005). In 1988 a pilot-study, comprising 10 individual breast milk samples, revealed the presence of PBDE-28, -47, -99 and -153 in Dutch breast milk (Figure 12, top). More extended monitoring campaigns were performed in 1998 (103 invidual samples) and 2003 (99 individual samples). In comparison with the 1988 samples additionally PBDE-100 and -183 were found in breast milk, together with an increase in the sum of PBDEs. PBDE-47 and -153 were found the predominant congeners, followed in decreasing amounts by PBDE-99, -100, -183 and -28 (Figure 12, middle and bottom). Qualitatively, the occurrence of PBDEs in Dutch breast milk correlated well with the occurence of these compounds in serum of Dutch women during week 20 and 35 of pregnancy (78 samples, Weiss et al., 2004). As in serum PBDE- 47, -99, -100, -153 were found in breast milk (PBDE-28 was found in breast milk but not in serum, whereas PBDE-154 was found in serum but not in breast milk). As in serum PBDE-47 and -153 appeared the most abundant congeners in breast milk. The amounts of the PBDEs found in breast milk were lower than in serum (mean serum concentrations were 3.2 ng/g lw for PBDE-47, 0.69 ng/g lw for PBDE-100, 0.98 ng/g lw for PBDE-99, 1.4 ng/g lw for PBDE-154 and 4.5 ng/g lw for PBDE-153). Similarly, the sum of PBDEs in breast milk of 4-5 ng/g lw (Figure 12, middle and bottom) is lower than the sum of PBDEs found in serum of 10.8 ng/g lw.
Next to PBDEs also HBCDD was found in serum (mean concentration: 1.1 ng/g fat), indicating that the exposure of Dutch women to this compound has resulted in a considerable accumulation in the body (note that, as HBCDD was not investigated in breast milk, a comparison of the amount of HBCDD in serum and breast milk cannot be made).
The PBDE congener concentrations as well as the sum of PBDEs in Dutch breast milk increased in time or stayed about the same for all congeners, except PBDE-183. No substantial difference in the sum of PBDEs was found between the 1998 and the 2003 samples, even a small increase was found, therefore there are no indications on decrease of PBDEs in Dutch breast milk in this period.

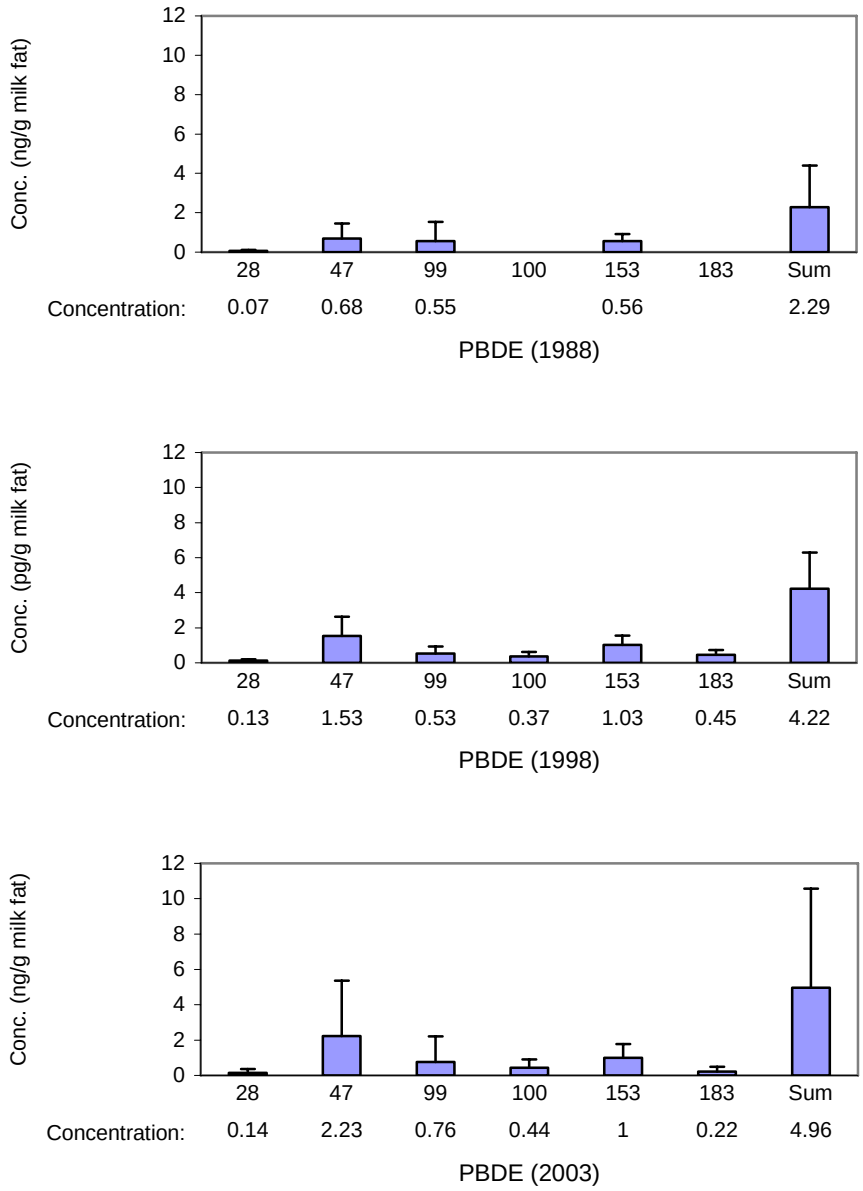


Figure 12. The content of PBDE in Dutch breast milk. Top - 1988 (10 samples), middle - 1998 (103 samples), bottom - 2003 (99 samples). Indicated: mean content ± SD (ng/g milk fat).

4. Brominated flame retardants in the diet

4.1 Brominated flame retardants concentrations in food products

Food products sampled in the Netherlands
The Netherlands Institute for Fisheries Research (RIVO) investigated the background concentrations of brominated flame retardants in food products (total 84 samples of poultry, pork, beef, cow fat, pig fat, cheese, milk, whipped cream, eggs, vegetable oil, fish, crustaceans) sampled in 2001/2002 (Leonards et al., 2002). The RIVO measured concentrations of polybrominated diphenyl ethers (PBDEs), hexabromocyclododecane (HBCDD), tetrabromobisphenol-A (TBBP-A) and polybrominated biphenyls (PBBs). The PBBs and PBDE congeners PBDE-71, -77, -190 were not detected in any of the samples. The PBDE-209 is found only in beef fat sample and needs further confirmation. The congeners PBDE-28, -47, -99, -100, -153 and -154 were reported by RIVO; the RIVO total PBDE concentration also includes these congeners.
RIVM investigated the background concentrations of PBDEs in food products sampled in 2003/2004. A sampling programme was designed to obtain representative data on levels of lipophilic components like PBDEs in foods consumed by the general population in the Netherlands. The sampling strategy is based on the assumption that these substances are almost entirely present in the fat fraction of the foodstuffs. For the selection of foods, the database of the Dutch National Food Survey 1998 (Kistemaker et al., 1998) was used. This survey describes the consumption pattern of the Dutch population and includes information on the daily consumption over two consecutive days and a record of age, sex and body weight of 6250 individuals (Kistemaker et al., 1998). Relevant food categories (butter, cheese, milk, eggs, vegetable oils and fats, industrial oils and fats, cereals, fruit, beef, pork, poultry, mixed meat, cow fat, pig fat, chicken fat) were sampled in 2004 and analysed at the Laboratory of Analytical Chemistry of the RIVM in addition to the three fish categories (lean fish, fatty fish, crustaceans) which were sampled in 2003, and analysed by RIVO. For further details see De Mul et al. (2005).

Comparison of different studies
Figure 13 contains a comparison of the total lower bound PBDE concentrations found in European food products. A extensive overview of the Dutch residue data in food products, including comments, and a comparison with the measurements from the literature is given in Appendix 4. Measurements in fish from the literature are only included if they are relevant for fish consumption and reported as concentration per wet weight as RIVO data
(not per g lipids). TBBP-A is not included in the comparison because we did not find any literature on this compound.
The largest total PBDE residues are found in fatty fish, followed by lean fish, vegetable oil and fats, meat, diary products and eggs. It is also clear that there is a large variation in concentrations, which can significantly influence the dietary intake estimates. Some variation can be explained by different congeners measured in different studies and by different food products included in the food groups in different studies. But the large variation cannot be totally explained by the reasons mentioned. Note that the same congeners are measured with the same measurement method in the RIVM samples of 2004 and in the samples of the FIRE project (Flame retardant Integrated Risk assessment for Endocrine Effects, an EU-project

which aims at improving the risk assessment of BFRs for human health and wildlife) at the RIVM.

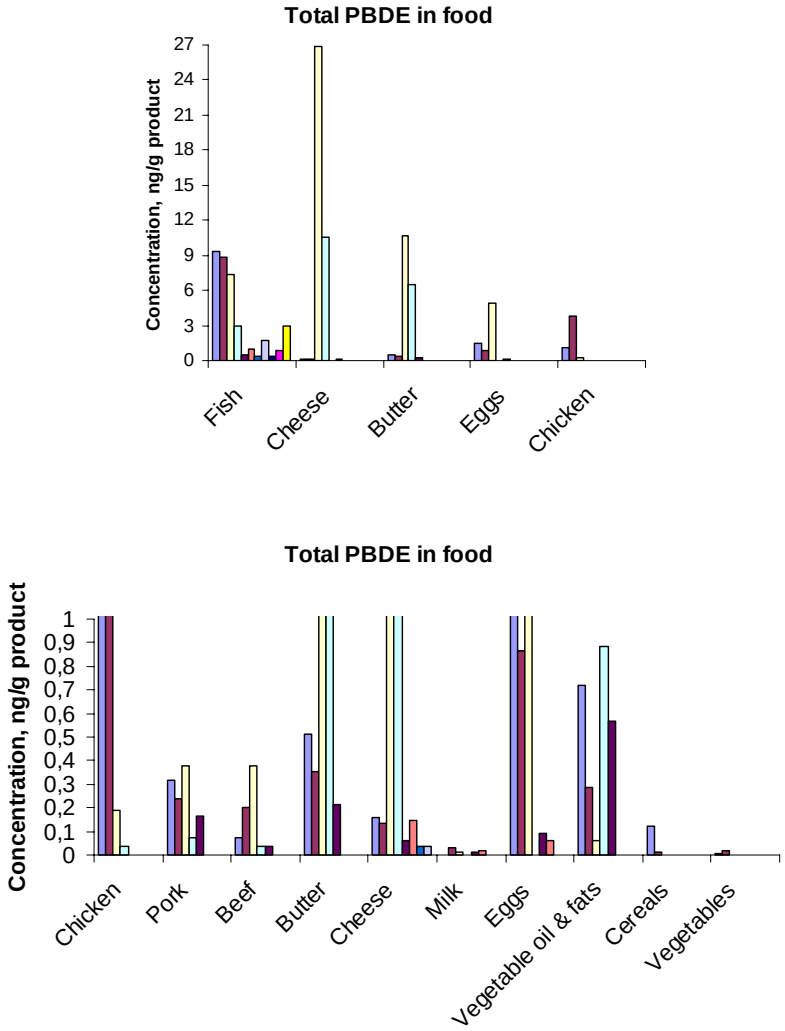


Figure 13. Total PBDE residues in European food products (lower bound measurements, <LOD=0 in pooled samples). Residues larger than 1 ng/g are shown in the top figure, residues lower than 1 ng/g are shown in the bottom figure.

From left to right:

Fish (Netherlands FIRE 1999 fatty fish, Netherlands FIRE 1999 fatty fish, Netherlands 2001/2 fatty fish mean, Netherlands 2003 fatty fish mean, Netherlands FIRE 1999 lean fish, Netherlands FIRE 1999 lean fish, Netherlands 2001/2 lean fish mean, Netherlands 2003 lean fish mean, Spain 2000 Bocio et al. 2003, Finland 1997-1999 Kiviranta et al. 2004, EU supermarket salmon Hites et al. 2004);

Cheese (Netherlands FIRE 1991, Netherlands FIRE 1991, Netherlands FIRE 1999, Netherlands FIRE 1999, Netherlands 2001/2 mean, Netherlands 2004, Spain 2000 yogurt and cheese, Finland 1997-1999);

Butter (Netherlands FIRE 1991, Netherlands FIRE 1991, Netherlands FIRE 1999, Netherlands FIRE 1999, Netherlands 2004);

Eggs (Netherlands FIRE 1991, Netherlands FIRE 1991, Netherlands FIRE 1999, Netherlands 2001/2 mean, Netherlands 2004, Spain 2000);

Chicken, pork, beef, vegetable oils and fats (Netherlands FIRE 1999, Netherlands FIRE 1999, Netherlands 2001/2 mean, Netherlands 2004, Spain 2000);

Milk (Netherlands 2001/2 mean, Netherlands 2004, Spain 2000, Finland 1997-1999 milk, sour milk, yogurt, UK D'Silva et al. 2003, France mean Tritscher et al. 2003);

Cereals (Netherlands FIRE 1991 mean, Netherlands 2004);

Vegetables (Spain 2000, Finland 1997-1999).

Time trend
In conclusion, there is a large variation in reported concentrations in food products in Europe. Furthermore, consistent information on the temporal trend is lacking. Therefore, it is important to continue the monitoring of PBDE and HBCDD time trends in food products in the future. Therefore regular measurements in pooled samples of different food categories following the procedure used to sample the RIVM data of 2004 (De Mul et al. 2005) is recommended. In view of the large variations in concentrations, a number of samples should be analysed per food category. It is important as well to achieve a good measurement accuracy, as otherwise an unnecessary measurement variability is introduced.

4.2 Dietary intake estimates of brominated flame retardants from data 2001/2002

The dietary intake in the Netherlands was estimated in 2001 using the RIVO contamination data and the consumption data of the third Dutch National Food Consumption Survey (DNFCS, in Dutch VCP3) (De Winter-Sorkina et al., 2003). The mean dietary intakes of brominated flame retardants by the Dutch population were calculated by multiplication of the mean compound concentration with the mean consumption per food group and summing over food groups. In the middle estimate, for samples with a BFR level lower than the limit of detection (LOD), a value of 0.5 × LOD was assumed. The RIVO determined a LOD for every analysis separately (Leonards et al., 2002). When a compound or a congener could not be detected at all in a food group, the food group was omitted for that compound or congener. In the lower estimate the concentrations of non-detects were set to zero. The reason to perform two calculations was that for some samples RIVO reported very high detection limits. For example, one pork sample has a detection limit for PBDE-153 of 8.2 ng/g, while the maximum measured PBDE-153 concentration in pork equals 0.2 ng/g. Thus, in this case the assigned non-detect concentration dominates the calculation of the intake.
In addition to the separate compounds, we calculated the intake of the sum of the PBDEs. The PBDE congeners having only non-detects in a food group were assumed to have a concentration of zero. If one or more samples of a congener in a food group was positive, for this congener the rest of the samples in this group got a value of 0.5 × LOD for the middle estimate or zero for the lower estimate. In comparison with previous calculations (De Winter-Sorkina et al., 2003) the present report contains corrected intakes of the sum of PBDEs.

Table 4 shows the mean dietary intakes of BFRs by the Dutch population.The dietary intake of HBCDD is comparable to the dietary intake of the sum of PBDEs, while that of TBBP-A is much lower. The relative contribution of food categories to the mean intake of the sum of PBDEs and HBCDD by the Dutch population are shown in Figures 14 and 15. The major contribution to the dietary intake of the sum of PBDEs and of HBCDD comes from meat and meat products. For the sum of PBDEs the contribution of fish and fish products is also relatively high.

Table 4. Mean dietary intake of BFRs by the Dutch population estimated from 2001/2002 data.

Compound	Middle dietary intake estimate (ng/kg-bw/day)	Lower dietary intake estimate (ng/kg-bw/day)
PBDE-28	0.009	0.009
PBDE-47	0.7	0.5
PBDE-99	0.5	0.3
PBDE-100	0.2	0.1
PBDE-153	1.0	0.1
PBDE-154	0.5	0.2
Sum PBDEs	2.9	1.2
HBCDD	2.9	1.5
TBBP-A	0.04	0.04

LOD – limit of detection, bw – body weight, the mean body weight of DNFCS participants was 65.8 kg.

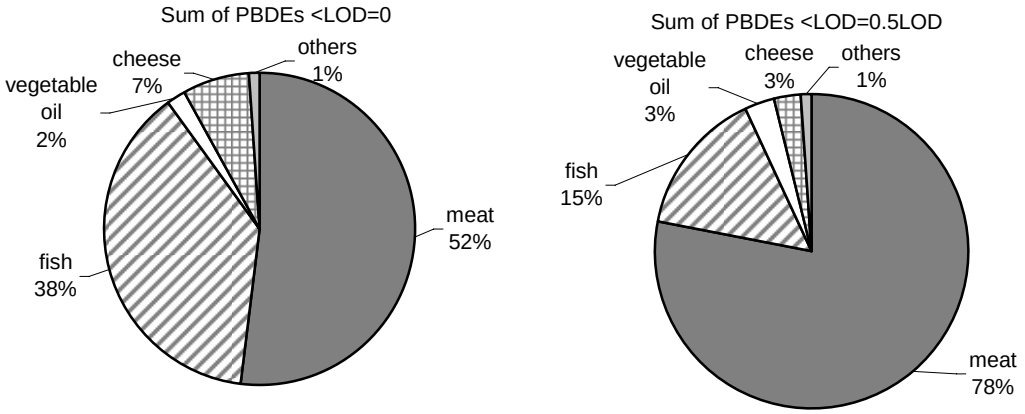


Figure 14. The relative contribution of food categories and food products to the mean intake of the sum of PBDEs by the Dutch population, according to lower bound (left) and middle (right) estimates. Only food products with contributions ≥2 % are included.

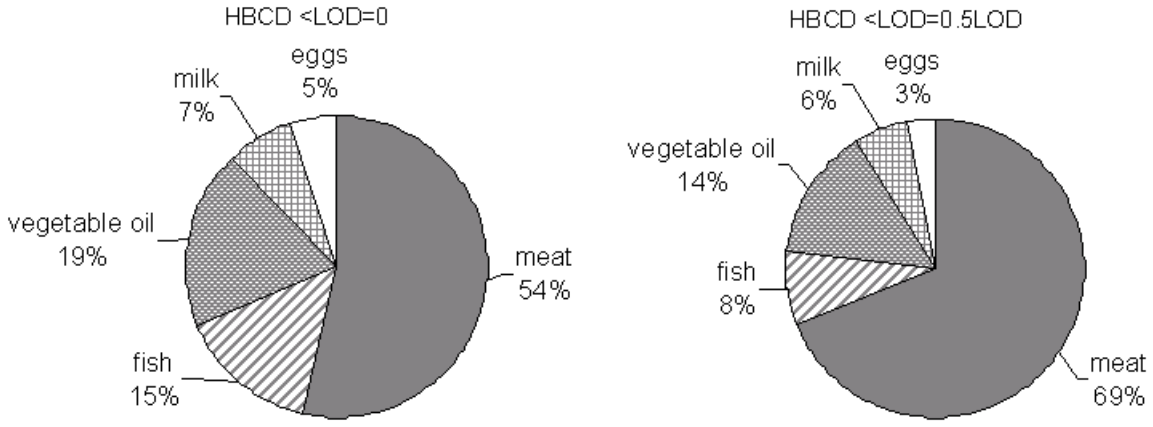


Figure 15. The relative contribution of food categories and food products to the mean intake of HBCDD by the Dutch population, according to lower bound (left) and middle (right) estimates. Only food products with contributions ≥2 % are included.

4.3 Dietary intake estimates of PBDEs from data 2003/2004

Recently the dietary intake of PBDEs in the Netherlands was estimated using the most recent RIVM and RIVO food contamination measurements from 2004/2003, and the food consumption data of the third Dutch National Food Consumption Survey (DNFCS, in Dutch: VCP 3) performed in 1997/1998. Lower and middle dietary intake estimates have been made for PBDE congeners PBDE-47, PBDE-99, PBDE-100, sum of PBDE-153 and PBDE-154, PBDE-183, and the sum of PBDEs (based on PBDE-28, -47, -66, -85, -99, -100, -138, -153, -154, -183 congener concentrations). Just as in the previous estimate of the dietary intake of PBDEs (section 4.2), a lower and a middle estimate were calculated, assigning a value of 0 or 0.5 × LOD for the non-detects respectively. The LOD concentration level was determined separately for every analysis.

Appendix 5 shows the principal flow scheme which has been employed to analyse human dietary intake of PBDEs in the Netherlands. The dietary intake estimation method is extensively described in Freijer et al., 2001. The DNFCS distinguishes 1207 different food products. For 495 of these products it was assumed that they did not contain PBDEs. The conversion of the measured PBDE concentrations to concentrations in 712 NEVO food products is made using the RIKILT Conversion Programme for Agricultural Products (CPAP) model (Van Dooren et al., 1995).

Daily intakes for all individuals that participated in the survey were calculated for the two consecutive days considered in the survey. This was performed by multiplying for each individual the consumed food products with the contaminant concentration and summing up all intakes of one day. A frequency distribution of the intakes of all individuals 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. A distribution of life-long averaged intakes would be considerably narrower than the distribution of daily intakes, because within-subjects variations level out. Slob (1993a, 1993b) developed a statistical model for the description of dietary intake of chemicals with long-term effects (like dioxins, PCBs and brominated flame retardants): the STatistical Exposure Model (STEM). STEM performs a regression analysis of the log-intake on age, obtains the between-subjects variation and returns the percentiles of the long-term (usual) intake. Further details on the procedure and an extensive evaluation of the assumptions can be found in Slob (1993a, 1993b).

Table 5 gives the medians and the 90, 95, 97.5 and 99 percentiles of the lower and the middle estimate of the long-term daily dietary intake distributions of the sum of PBDEs for ages 2, 10, 40 years and life-long exposure. The dietary intake for children (per unit body weight) is higher than for adults. The results for PBDE congeners PBDE-47, PBDE-99, PBDE-100, the sum of PBDE-153 and PBDE-154, PBDE-183 are shown in Appendix 6.

Table 5. Percentiles of the long-term daily dietary intake distribution of the sum of PBDEs in the Dutch population estimated from 2003/2004 data.

Age (yrs)	Lower dietary intake estimate (ng/kg-bw/day)					Middle dietary intake estimate (ng/kg-bw/day)				
	Sum of PBDEs									
	P50	P90	P95	P97.5	P99	P50	P90	P95	P97.5	P99
2	2.54	4.27	4.95	5.63	6.54	4.37	6.71	7.57	8.41	9.51
10	1.27	2.15	2.49	2.83	3.28	2.26	3.46	3.91	4.34	4.91
40	0.78	1.31	1.52	1.73	2.00	1.38	2.12	2.40	2.66	3.01
Averaged life-long	0.98	1.66	1.92	2.19	2.54	1.73	2.65	3.00	3.33	3.76

A summary for median averaged life-long daily dietary intakes of individual and total PBDEs is shown in Table 6. Most surprising result is a large intake of PBDE-183 which is about equal to the intake of PBDE-47 congener. PBDE-47, a part of the penta-PBDE commercial product, was voluntarily banned in EU the last 10 years. PBDE-183 is a main compound in octa-PBDE commercial product. However, for PBDE-183 the reproducibility of the measurements was less. PBDE-183 shows a relatively large variation (Relative Standard Deviation: 65 %, other PBDE congeners: 16 %).

Table 6. Median of the averaged life-long daily dietary intakes of PBDEs by the Dutch population estimates from 2003/2004 data.

Compound	Lower dietary intake estimate (ng/kg-bw/day)	Middle dietary intake estimate (ng/kg-bw/day)
PBDE - 47	0.38	0.40
PBDE - 99	0.08	0.11
PBDE - 100	0.012	0.080
PBDE -153 + PBDE - 154	0.0018	0.119
PBDE - 183	0.34	0.42
Sum of PBDEs (-28, -47, -66, -85, -99, -100, -138, -153, -154, -183)	0.98	1.73

The model uncertainty can be estimated when a different model for the same purpose is used. The PBDE intake calculation was also performed by RIKILT using the Monte Carlo Risk Assessment (MCRA) programme release 3.4 developed at RIKILT in collaboration with Biometris Wageningen UR (De Mul et al., 2005). The middle intake estimates from both STEM and MCRA models are shown in Table 7. It is clear that the median exposure levels calculated with MCRA were similar to those calculated with the STEM model. This was true for all congeners and the sum of PBDEs. The 97.5 percentiles of exposure from MCRA tended however to be higher than the levels calculated with STEM. Differences ranged from 17 % higher for the sum of PBDE-153 and PBDE-154 to 121 % higher for PBDE-100 (De Mul et al., 2005).

Table 7. Medians and 97.5 percentiles of long-term dietary intakes of PBDEs by the Dutch population, according to middle estimate from 2003/2004 data by STEM and MCRA models.

Compound	Median intakes ng/kg bw/d		P97.5 intakes ng/kg bw/d	
	STEM	MCRA	STEM	MCRA
PBDE - 47	0.40	0.40	1.09	1.59
PBDE - 99	0.11	0.12	0.21	0.35
PBDE - 100	0.08	0.08	0.14	0.31
PBDE -153 + PBDE - 154	0.12	0.12	0.23	0.27
PBDE - 183	0.42	0.50	1.19	1.45
Sum of PBDEs (-28, -47, -66, -85, -99, -100, -138, -153, -154, -183)	1.73	1.72	3.33	4.62

Figure 16 gives contributions of different food subcategories to the middle estimate of the total PBDE intake as calculated by the MCRA model. The largest contributions are from oils and fats (25 %) and from milk, fish and meat (19, 13 and 11 % respectively). For the middle estimate of the PBDE-47 intake the contribution of milk dominates with 49 %, and for PBDE-183 the contribution of oils and fats dominates with 62 % (De Mul et al. 2005).

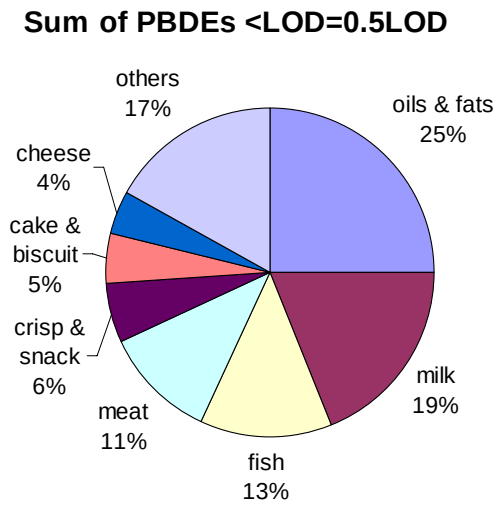


Figure 16. The relative contribution of food categories and food products to the middle estimate of the sum of PBDEs by the Dutch population (from De Mul et al., 2005).

4.4 Comparison of different studies

Figure 17 shows a comparison of the mean PBDE dietary intakes estimated from 2003/2004 data and the previous Dutch study based on RIVO measurements from 2001/2002 (De Winter-Sorkina et al., 2003). The comparison shows that the mean PBDE-47 intake is about the same for both studies, while the mean intakes of PBDE-99 and PBDE-100 are smaller from the 2003/2004 data. The mean intake of the sum of PBDE-153 and PBDE-154 is much smaller for the 2003/2004 data. In the 2001/2002 study the PBDE-153 and PBDE-154 concentrations found in beef and pork showed the highest contribution to the mean intake. In the 2003/2004 study PBDE-153 and PBDE-154 was found mainly in fish, there were no

residues found in meat above the detection limit. The mean total PBDE intake is about the same for both studies.

PBDE residues measured in RIVM 2004 pork, beef and chicken samples are lower than those in 1999 FIRE and RIVO 2001/2002 samples (see Figures 18 and 13). The accuracy of RIVO 2001/2002 measurements is low as can be seen from the high levels of detection. In the previous study with RIVO 2001/2002 data beef, pork and chicken contributed 52 % to the mean lower bound and 78 % to the mean middle estimate total PBDE intake, while in the current study with RIVM 2003/2004 data they contribute respectively only 13 % and 15 % to the sum of the same PBDE congeners intakes as in previous study.

The difference between the lower and the middle estimate PBDE intake in the current study is smaller than in the previous study, which indicates the better accuracy of the measurements (see Figure 17). It should be noted that more congeners are included in the current study. Especially PBDE-183, which was not included in the previous study, is contibuting about a third to the sum of PBDEs intake. Omitting the PBDE-183 intake, the lower and the middle mean intakes of the sum of congeners PBDE-47, -99, -100, -153 and -154 from the current study (0.7 and 1.0 ng/kg-bw/day) are lower than estimated from the 2001/2002 data (1.2 and 2.9 ng/kg-bw/day). The higher mean dietary intake from 2001/2002 data is mainly due to higher PBDE concentrations found in meat. If the lower mean intake of the sum of PBDE-47, -99, -100, -153 and -154 based on 2003/2004 data than the one based on 2001/2002 data can be explained by reduced concentrations in the environment is not clear, since only a small amount of samples was taken in the studies and the variation in the samples can be large. To be able to discern a time trend, succesive studies are needed.

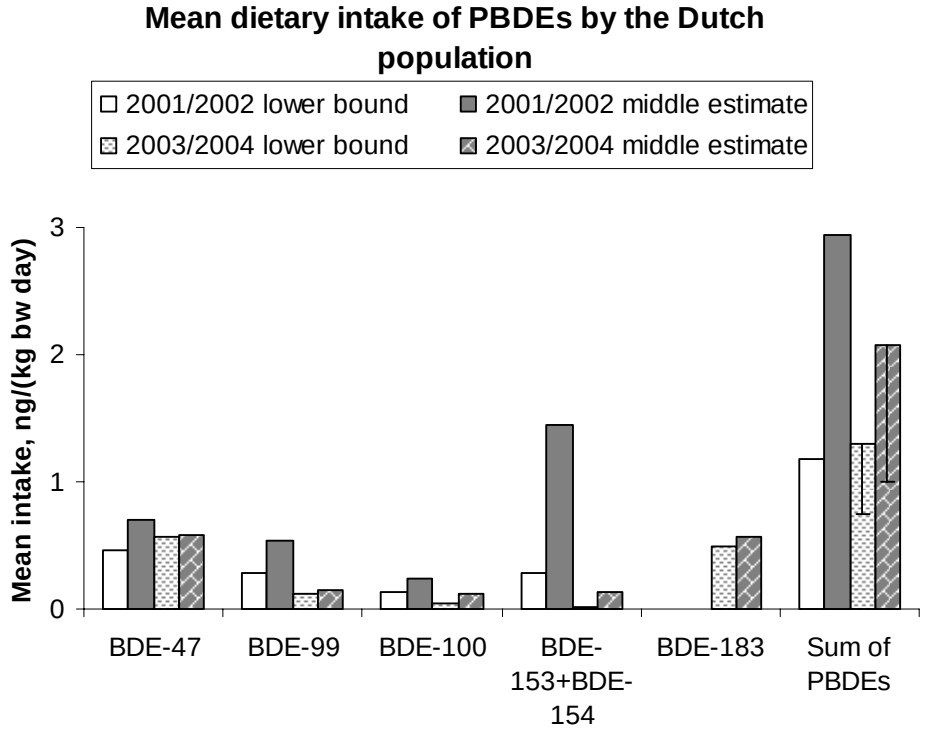


Figure 17. Comparison of the mean short-term dietary intakes of PBDEs by the Dutch population based on data from 2003/2004 and 2001/2002. The error bars show the contribution of PBDE 183, which was not included in the 2001/2002 study.

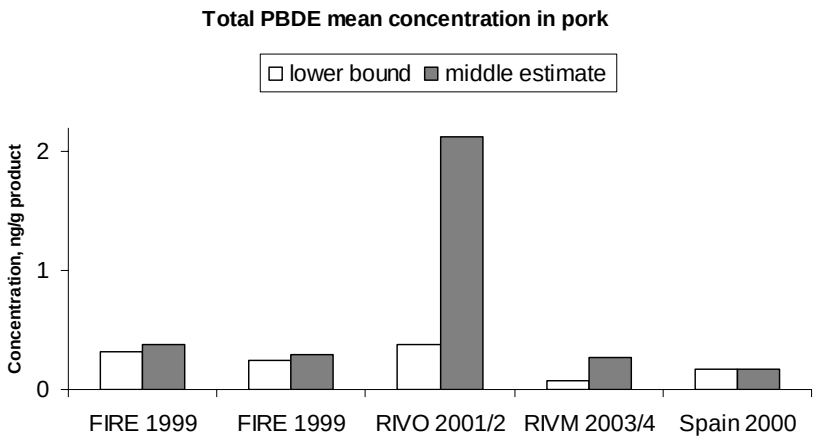


Figure 18. Total PBDE mean concentration in pork from different studies.

A comparison of mean short-term lower bound and middle dietary intake estimates of the sum of PBDEs with other studies from different countries is shown in Figure 19 and in Appendix 7. In this figure intakes are presented in ng/day instead of ng/kg body weight/day, since most studies report the mean short-term intakes in this way. The mean total PBDE dietary intake by the Dutch population is higher than that by the population of Sweden, Canada and Finland, is similar to that in Spain and lower than in the UK. However, different congeners contribute to the total PBDE intake in these studies (see Appendix 7). All studies measured the PBDE congeners PBDE-47, -99, -100, -153 and -154. Therefore, corrections indicated with error bars in Figure 19 to exclude other congeners are made, except for the middle estimate of the Spanish study. The mean intake of the sum of the same congeners as in other studies can be seen below the error bars. The lower bound mean dietary intake of the sum of PBDE-47, -99, -100, -153 and -154 by the Dutch population (2003/2004) appears to be similar to that in Canada, Sweden and Finland, and lower than that in Spain and the UK. The middle estimate mean intake appears to be higher than in Finland and Sweden, and again lower than that in Spain and the UK.

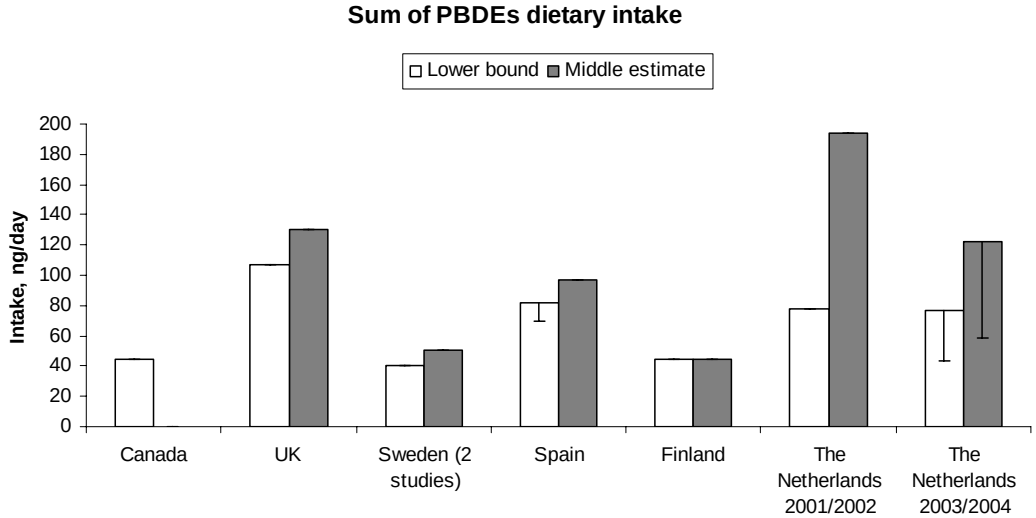


Figure 19. Comparison of short-term mean dietary intakes of the sum of PBDEs from different studies. Error bars show the correction, mainly for PBDE-183, which allows to compare the sum of the same congeners PBDE-47, -99, -100, -153, -154. These congeners are shown below the error bars.

5. Risk assessment of PBDE-99

The difference of the half-lives of tetra-, penta- and hexa-brominated flame retardants between rats and humans (see Table 2) indicates that, as with dioxins, these compounds display much more bioaccumulating potency in humans than in rats. Consequently, a toxic evaluation based on daily intake may lead to imprecise toxic risk assessment. Alternatively, a risk assessment of brominated flame retardants therefore should, as with dioxins, be based on their bioaccumulating properties (section 2.2.2; WHO, 2002; SCF, 2000 and 2001; JECFA, 2002). At the moment such a risk assessment can be performed for PBDE-99. For this flame retardant a rodent study (Kuriyama et al., 2005) is available which is almost similar in experimental design and toxicological outcome in comparison with one of the studies which has been used for the derivation of the human Provisional Tolerable Monthly Intake (PTMI) of the dioxin 2,3,7,8-TCDD (Ohsako et al., 2001; JECFA, 2002). Taking the risk assessment of 2,3,7,8-TCDD as a reference, the approach taken with this chemical will be illustrated below for PBDE-99.

Regarding PBDE-99 toxicity in the rat, the hitherto most sensitive effect of PBDE toxicity appeared after a single p.o. exposure of rat dams with PBDE-99 at the sixth day of pregnancy, i.e. Gestational Day 6 (GD6). This exposure led to the disturbance of spermatid- and sperm-production in male offspring as assessed on postnatal day 140 (Kuriyama et al., 2005). For this effect a LOAEL of 60 μg/kg bw was reported. Impaired spermatid- and sperm-production is amongst the most sensitive toxic endpoints of 2,3,7,8-TCDD and is (one of) the toxic endpoint(s) on which the PTMI of this compound was based (Ohsako et al., 2001; JECFA, 2002; see also Appendix 2). Taking the bioaccumulating potential of 2,3,7,8-TCDD as the starting point of the risk assessment and kinetic modeling as the method for the interspecies scaling of this property for 2,3,7,8,-TCDD a PTMI of 70 pg/kg bw per month was derived (equivalent with a Tolerable Daily Intake (TDI) of 2.3 pg/kg bw per day, JECFA, 2002). As PBDE-99 resembles 2,3,7,8-TCDD in persistency and reproductive toxicity and the Ohsako and the Kuriyama study were of similar experimental design the risk assessment procedure applied on 2,3,7,8-TCDD may be applied on PBDE-99 as well. The procedure (for details see Appendix 2) consists of the following steps:

1 The determination of a relevant NOAEL or LOAEL in experimental animals. In the case of PBDE-99 this consists of a LOAEL of 60 μg/kg administered as a single dose p.o. to rat dams on GD 6 of pregnancy. This (prenatal) exposure resulted in impaired (postnatal) spermatid- and sperm-production in male offspring.
2. The calculation of the dam's body burden at GD_{16}, i.e. the time-window at which male offspring is thought to be most sensitive for the induction of impaired spermatid- and sperm production.
3. The calculation of the corresponding dam's body burden at GD_{16} after chronic exposure to PBDE-99.
4. The calculation of the chronic human exposure which leads to the same body burden in women.

This procedure (fully described in Appendix 2) resulted in a maximal allowed intake level of 0.26 ng PBDE-99/kg bw/day. This maximal allowed intake lies just above the 99th percentile of the long-term daily intake of PBDE 99 from food in the Dutch population (0.24 ng/kg bw/day). This indicates that, at the moment, a negligible fraction of the Dutch population exceeds the maximal allowed intake level. However, an increase of the PBDE-99

content of Dutch food products may easily lead to a significant fraction of the population exceeding the maximal intake level.

6. Conclusions and recommendations

Time trends
PBDE concentrations in the environment and in humans in Europe and North America increased exponentially with doubling times of 4-6 years since the 1970s. European PBDE levels in humans are at least one order of magnitude lower than in North America. Moreover, while in North America the concentrations are still increasing, in the European environment lower PBDEs may level off or decreasing due to the (voluntary) ban on penta-PBDE. The time period between a ban on PBDEs and a decrease in the environment depends on the amount of PBDEs used as well as on the local and regional PBDE sources.
From the environment PBDEs have penetrated the human food chain. Once taken up from food PBDEs tend, as dioxins, to be excreted form the body only very slowly. Consequently a time lag is expected before a decrease in environmental and food levels is expressed in a decrease in the amount of PBDEs residing in the human body. As a substitute for the latter amount PBDE levels in breast milk may be used. PBDE time-trend studies in Swedish breast milk indicate a decrease of PBDE concentrations after 1998. However, studies in Dutch breast milk (1998, 2003) indicate that such a decrease is not (yet?) observed in the Netherlands. The comparison of the PBDE trends in the environment and in breast milk from Sweden, indeed indicate a time lag of at least a decade before a decrease in environmental levels is passed on to decreasing levels in the human body.
In Europe the concentrations of HBCDD show an increasing tendency from 1969 to 2001 and its use in the EU will continue. Therefore a decrease of HBCDD concentrations in humans and in the environment is not expected.
Reports on TBBP-A, as well as on other BFRs in human samples and in the environment in general are scarce. TBBP-A is the most important BFR in Europe, but its bioaccumulating properties, if at all, seem to be negligible when compared with other BFRs.

Dietary intake
The most recent (and also the most complete) dietary intake estimate of PBDEs in the Netherlands reports a long-term median dietary intake of the sum of PBDEs of
1.7 ng/kg bw /day (97.5th percentile: 3.3 ng/kg bw/day). This is similar to estimated intakes in Canada, Sweden and Finland, and lower than that in Spain and the UK.

Risk assessment of PBDE-99
As PBDE-99 resembles 2,3,7,8-TCDD in persistency and reproductive toxicity the risk assessment procedure applied to 2,3,7,8-TCDD was applied to PBDE-99. This resulted in a maximal allowed intake level of 0.26 ng/ kg-bw/day for PBDE-99.
When compared with the long-term daily intake of PBDE-99 from food in the Dutch population the calculated intake level equals the 99th percentile values of long-term intake of the Dutch population to this congener (0.24 ng/kg-bw/day).
In this context the relative small margin between the human exposure to PBDE-99 from food and the maximal allowed intake level for this compound does not corraborate JECFA's recent conclusion that intakes of PBDEs from food are of unlikely health concern[2]. To the contrary, this margin merely indicates the intake of PBDEs from food to be of relevant health concern.

[2] JECFA's conclusion was based on the margin between a (postulated) NOAEL for PBDE toxicity in the rat greater than 100 µg/kg bw per day and human PBDE exposure from food of 4 ng/kg-bw/day (see section 2.2.2).

Recommendations

The two sets of PBDE concentration measurements in Dutch food products performed in the Netherlands were within a relatively short period of time (2001/2002; 2003/2004). Moreover, a high concentration variability was found in the food products. Therefore, conclusions concerning the real time-trend of BFRs in food products cannot be drawn from these studies. To be able to monitor PBDE, HBCDD and TBBP-A time trends in food products, measurements in pooled samples of different food categories following the procedure used to sample 2004 RIVM data (De Mul et al., 2005) is recommended. A number of samples per food product should be analysed in order to address the concentration variability. Concentration variability may further be reduced by improvement of measurement accuracy.
Additionally the annual or biannual monitoring of PBDEs, HBCDD and TBBP-A in human breast milk would reveal the relationship between levels in food and levels which actually determine toxic risk, i.e. the amounts of BFRs which have accumulated in the body.

Measurements of PBDEs in housedust have shown that the ingestion of soil/dust may be a relevant route of exposure of PBDEs, in particular for toddlers and children. Though ingestion of PBDEs via soil/dust may be a relevant route of exposure the contribution of soil/dust ingestion of PBDEs to the accumulation of these compounds in the body remains to be clarified. In particular the uncertainty in the fraction of the ingested amount of PBDEs from soil/dust which may be absorbed should be clarified. In this context the determination of the bioavailibility of PBDEs from food and housedust (fraction of PBDEs in a product which enters the blood after absorption and so contributes to bioaccumulation) by means of an in vitro digestion system is recommended (Oomen et al., 2003; Versantvoort et al., 2005). In this in vitro test system the processes which occur in the human gastrointestinal tract after ingestion of PBDEs from food or soildust are simulated, resulting in a estimate of the bioavailibility of PBDEs from soil/dust relative to food.

To date PBDE-99 is the only BFR for which a proper quantitative risk assessment can be performed. For the other bioaccumulating BFRs, i.e. the other PBDEs and HBCDD, a corresponding risk assessment can only be carried if suitable results of toxicity studies will become available. As the toxicological (and toxicokinetic) research on BFRs is fully under way the continuous monitoring of its progress over the next coming years is necessary to keep the conclusions drawn in this report up to date.

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Appendix 1. PBDEs analysed by RIVO and RIVM

Name	IUPAC-nr	Structure
PBDE	17	2,4,2'-tri
	28	2,4,4'-tri
	47	2,4,2',4'-tetra
	66	2,3,4,4'-tetra
	71	2,6,3',4'-tetra
	75	2,4,6,4'-tetra
	77	3,4,3',4'-tetra
	85	2,3,4,2',4'-penta
	99	2,4,5,2',4'-penta
	100	2,4,6,2',4'-penta
	119	2,4,6,3',4'-penta
	138	2,3,4,2',4',5'-hexa
	153	2,4,5,2',4',5'-hexa
	154	2,4,5,2',4',6'-hexa
	183	2,3,4,6,2',4',5'-hepta
	190	2,3,4,5,6,3',4'-hepta
	209	2,3,4,5,6,2',3',4',5',6'-deca

Appendix 2. Toxicity, kinetics and bioaccumulation of BFRs

Toxicity and kinetics of BFRs

Toxicity studies
In a number of toxicological studies in rodents (sub-chronic toxicity, 2-generation toxicity study, developmental toxicity study) tetrabromobisphenol-A (TBBP-A) did not induce toxic effects in dose levels up to 1000 - 10000 mg/kg/day (EU RAR, 2003).

After repeated daily exposure the thyroid (hyperplasia) and the liver (increase in weight, without pathological findings) appeared to be target organs for HBCDD. At relative short exposure periods, i.e. a 28 day exposure period, these effects were reversible. Studies which are still in progress indicate a 5 % Bench Mark Dose for these effects in the range of < 10 – 37 mg/kg bw. Based on the absence of mutagenicity of HBCDD and its negative response in a brief report on long-term carcinogenicity it was concluded that 'there are no reasons to explore this endpoint further'. HBCDD failed to demonstrate any fetotoxic, teratogenic or any adverse developmental effects in the rat. However, as with PBDEs (see below), single exposure during the neonatal period (day 10 of pregnancy) may lead to developmental neurotoxic effects in offspring (changes in spontaneous behaviour, learning and memory effects at the age of three months). For this effect an indicative LOAEL of 0.9 mg/kg/ day can be deduced (EU RAR, 2005).

In rodents lower chlorinated PBDEs may induce developmental toxicity, developmental neurotoxicity and the disturbance of homeostasis of thyroid hormones. The (hitherto) most sensitive toxic effect described of lower brominated PBDEs in rodents (LOAEL: 0.06 mg/kg bw) consists of the disturbance of spermatid and sperm production (exposure of dams to a single dose 2,2',4,4',5-penta-PBDE 99 at gestational day (GD) 6, effects assessed at postnatal day (PND) 140, Kuriyama et al. 2005). Single doses of lower brominated PBDEs (PBDEs 47, 99 and 153), when administered during the period of pregnancy /lactation or shortly after birth, may lead to neurodevelopmental toxicity (disturbance of cognitive and learning ability) as assessed in offspring later in life (NOAEL < 0.06 mg/kg, Erikssson, 2001 and 2002; Branchi, 2002; Viberg, 2003b; Kuriyama et al., 2004a; Viberg, 2004; Sand, 2004). At the level of the thyroid PBDEs may interfere with the synthesis of the thyroid hormone thyroxine (T4). In the thyroid this hormone is synthesized and subsequently deiodinated into the more effective triiodo-thyronine (T3). Both T3 and T4 appear in the blood from which they may be cleared by the liver into the bile (T4 glucuronidation by the enzyme uridine-diphospho-glucuronosyl-transferase (UDPGT)). Thyroid hormone homeostasis is controlled by a sensitive feedback mechanism (hypothalamus-pituitary-thyroid axis). The pituitary hormone thyroid stimulating hormone (TSH) induces the synthesis of T4. The rate of TSH release is controlled by the hypothalamic hormone thyrotropin-releasing hormone (TRH) as well as by the amounts of circulating T4 and T3.
In the rat PBDEs may interfere with thyroid hormone homeostasis by increasing the catabolism of T4 and T3 through induction of hepatic UDPGT. This induction may lead to enhanced excretion into the bile, thereby lowering the circulating amounts of the hormones in the blood (Zhou et al., 2001, 2004; Birnbaum and Staskal, 2004).
Furthermore PBDEs may interfere with the transport of thyroid hormones in the blood through competitive binding of PBDEs (or even better their hydroxylated metabolites) to the

transthyretin transsporter (TTR). TTR is the protein involved in the transport of T4 in the blood and into the developing organs (Halgren and Darnedud, 2002; Birnbaum and Staskal, 2004). Disturbance of thyroid hormone homeostasis proved to be a sensitive endpoint for PBDE toxicity, with reported NOAELs amounting as low as 140 µg/kg (Andrade et al., 2004; Kuriyama et al., 2004b).

When the toxicity endpoints of the lower brominated PDBEs are compared on the basis of their NOELs, LOAELs or 10% bench mark doses (BMDs)(see Table A2.1), it appears that reproductive toxicity (as measured by impaired spermatogenesis), is the hitherto most sensitive toxic effect (Kuriyami et al., 2005). For PDBE-99, the congener that has been studied rather extensively, the LOAEL for this effect is 60 µg/kg bw/day, which is 5-8 times lower than the lowest reported NOAEL and BMD for developmental neurotoxicity: 400 µg/kg bw/day (Viberg et al., 2004) and 310 µg/kg bw/day (Sand et al., 2004), respectively. It is also 10 times lower than the LOAEL of 600 µg/kg bw/day reported for developmental neuro-toxocity (Branchi et al., 2002), and about 2 times lower than the LOAEL of 140 µg/kg bw/day for thryoid hormone disturbance (Andrade et al., 2004; Kuriyami et al., 2004b).

Table A2.1. Toxicity endpoints for PDBE-99 (in µg/kg bw/day)

Toxicity endpoint	**NOAEL**	**BMD_{10}**	**LOAEL**
reproductive toxicity	-	-	60
developmental neurotoxicity	400	310	600
thyroid hormone disturbance	-	-	140

Kinetics

After oral exposure TBBPA is well absorbed in rats, metabolized in to liver and excreted in the bile. In the GI tract the biliary TBBPA metabolites are deconjugated by the intestinal flora, rendering the parent compound (Hakk and Letcher, 2003). In the rat TBBPA has a (terminal) whole-body half-life of less than 3 days (Brady, 1979), indicating the rapid removal from the body by metabolism. Recently, the serum half-life of TBBPA was determined at 2.2 days in workers at an electronics dismantling plant (Hagmar et al., 2000).

Though limited kinetic data are available HBCDD seems to be well absorbed, metabolised and excreted from the rat body, mainly via the faeces (Hakk and Letcher, 2003). After repeated daily exposure of rats HBCDD showed clear bioaccumulating properties in adipose tissue of the rat, with highest concentrations in adipose tissue being reached at the end of the 89-day exposure period (Chengelis, 2001, as cited in EU RAR, 2005).

As a general rule the absorption of PBDEs decreases with increasing extent of bromination. So, intestinal absorption of decaPBDE may be less than 10 %, whereas that of tetra- or penta-PBDEs may be greater than 70 % (Hakk et al. 2004; JECFA, 2005). As with dioxinlike compounds the distribution in the body is mainly determined by organ lipid content, with adipose tissue, lungs, skin, muscle and the liver [(3)] showing the highest concentrations (Hakk et al., 2004; Staskal et al., 2004). In rats PBDEs may be metabolized by oxydation, methylation and/or debromation, with the excretion of metabolites mainly occurring via the faeces (Hakk et al., 2003; Hakk et al., 2004; Staskal et al., 2004). The urinary excretion of PBDEs via water soluble metabolites is only a minor excretion route (Hakk et al., 2003, 2004). The rate of metabolism is rather small, which adds to the bioaccumulating properties

[3] In contrast to dioxins PBDEs do not show preferential accumulation in the liver by specific binding to cytochromome P450 1A2 (Chen and Bunce, 2003; Hakk *et al.* 2004; Staskal *et al.* 2004; Peters *et al.* 2004).

(see below). Furthermore, significant species differences may exist. For example, whereas in the rat PBDE 47 is hardly excreted in the urine, in mice the excretion of the unmetabolized parent compound may amount up to 40 % of the administered dose (Staskal et al., 2004).

JECFA evaluation 2005

JECFA did not allocate a provisional tolerable monthly intake or provisional tolerable weekly intake for PBDEs based on the NOEL for the most sensitive adverse effect because the available data on PBDEs were considered not adequate for such an approach:

- 'PBDEs represent a complex group of related chemicals and the pattern of PBDE congeners in food is not clearly defined by a single commercial mixture'
- 'The available data are inadequate to establish a common mechanism of action that would allow a single congener to be used as a surrogate for total exposure or, alternativily, as the basis for establishing toxic equivalency factors'
- 'There is no systematic database on toxicity including long-term studies on the main congeners present in the diet, using standardized testing protocols that could be used to define a NOEL for individual PBDEs of importance' [4]
- 'Several of the reported effects are biological outcomes for which the toxicological significance remains unclear' [5]
- 'Studies with purified PBDE congeners in vitro have shown a lack of Ah receptor activation [6]; however, many of the adverse effects reported are similar to those found with dioxin-like contaminants, suggesting that some toxicity data may be confounded by the presence of traces of impurities that are potent Ah receptor agonists'

Risk assessment of 2,3,7,8-TCDD

Risk assessments of 2,3,7,8-TCDD which are based on the bioaccumulating properties of this compound have been performed by WHO (2002), the Scientific Committee on Food of the European Union (2000, 2001) and, most recently, by the Joint Expert Committee on Food Additives (JECFA, 2002). As JECFA's assessment extends earlier SCF ones, JECFA's approach is presented here.

Critical studies

First two rodent studies showing the lowest No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) were identified, i.e. the study of Ohsako et al. (2001, single dose study) and Faqi et al. (1998, multiple dose study). In the Ohsako study pregnant rats were given one single oral dose of 2,3,7,8-TCDD (0 – 800 ng/kg b.w.) on day 15 of gestation (GD 15), and male offspring was examined on day 49 and 120 after parturition. In this study a **NOAEL of 12.5 ng/kg bw** was found (higher doses induced effects on the urogenital complex). In the Faqi study dams were treated subcutaneously before mating and throughout mating, pregnancy and lactation. They received an initial loading dose of 25, 60 or 300 ng 2,3,7,8-TCDD/kg bw 2 weeks prior to mating, followed by weekly maintenance doses of 5, 12 or 60 ng/kg bw. Effects on male reproduction were studied on Postnatal Days (PND) 70 and 170. Even at the lowest dose combination tested disturbed sperm production was found (**LOAEL initial 25 ng/kg bw, maintenance 5 ng/kg bw**).

[4] Only in the case of decaPBDE a long-term toxicity study is available,
[5] In particular the effects on thyroid hormone homeostasis en neurodevelopmental toxicity
[6] Ah receptor activation is considered as the key stage in the common mechanism of action of dioxin like compounds.

Calculation of maternal body burden in the rat after repeated exposure

In the rat GD 15 marks the onset of the sensitive phase of sexual differentiation in rats and represents a critical time of fetal exposure. The determinant of the reproductive (and urogenital) effects is the fetal concentration on GD 15-16. These concentrations may be calculated using linear relationships between the administered dose at GD 15 – 16 and the resulting maternal and fetal concentrations. These relationships, which are available for single as well as repeated exposure of dams to 2,3,7,8-TCDD [7], indicate that a single bolus dose and a repeated low dose which lead to the same maternal body burden lead to a different fetal concentration, with fetal exposure after a single bolus dose being higher than after repeated exposure. Consequently, in order to lead to the same fetal exposure the maternal body burden after repeated exposure may be higher than after exposure to a single bolus. Given the relationships mentioned above, a factor of 1.7 was calculated to correct a maternal body burden after single bolus dose to a maternal body burden after repeated dose which lead to the same fetal concentration on GD 15 – 16 [8].

Ohsako study: When, together with an absorption fraction of 0.61 [9] the mentioned correction factor is applied on the p.o. NOAEL of 12.5 ng/kg bw of the Ohsako study an equivalent maternal body burden after repeated dosing of $12.5 \cdot 0.61 \cdot 1.7 = 12.96$, rounded 13 ng/kg**,** is calculated [10].

Faqi study: In the Faqi study a more complex dosing schedule was applied: 25 ng/kg bw fourteen days before mating, followed by 5 ng/kg bw seven days before mating, at mating and at GD 7 and 14. Given a one compartment model, complete absorption of the adminisitered doses and a half-life of 21 days the remainings of these doses at GD 14 are: 9.67 ng/kg from the loading dose of 25 ng/kg ($25 \cdot e^{-\frac{\ln 2 \cdot 29}{21}}$) and 2.43, 3.03 and 3.86 from the 5 ng/kg maintenance doses at 7 days before mating, at mating and at GD7 ($5 \cdot e^{-\frac{\ln 2 \cdot 22}{21}}, 5 \cdot e^{-\frac{\ln 2 \cdot 15}{21}}, 5 \cdot e^{-\frac{\ln 2 \cdot 8}{21}}$), together adding up to 18.99 ng/kg. JECFA rounded this maternal body burden to 20 ng/kg. Adding to this the maintenance dose of 5 ng/kg administered at GD 14 a maternal body burden of 25 ng/kg is calculated for GD 15. Taking an absorption fraction of 1 for the subcutaneous route of adminstration and a factor of 0.0534 for the conversion of a maternal to a fetal body burden after repeated exposure this corresponds with a fetal body burden of $25 \cdot 0.0534 = 1.34$ ng/kg. The fetal body burden corresponds with a maternal body burden of 25 ng/kg (note that, by change, the maternal body burdens at GD_{15} and after repeated exposure, are equal).

As animal feed usually contains trace amounts of 2,3,7,8-TCDD both maternal body burden were augmented with a background body burden of 3 ng/kg, resulting in a maternal body burden after repeated exposure of 16 ng/kg for the Ohsako study and 28 for the Faqi study.

[7] JECFA, 2002, pp. 583 – 586, dose range: 50 – 1000 ng/kg b.w.; 0.71 – 21 ng/kg b.w./day
[8] When a non-linear relationship is used a factor of 2.6 was obtained (for fetal concentration up to 15.2 ng/kg b.w.)
[9] 0.609, JECFA, 2002, pp. 583
[10] JECFA, 2002, pp. 591, Table 34

Equivalent Human Montly Intake (EHMI, linear model)
The maternal (rat) body burdens of the Ohsako and the Faqi study were extrapolated to man by means of a one-compartment 'steady state' kinetic model:

$$I_d = \frac{BB_{ss} \cdot \ln 2}{t_{1/2} \cdot F_{abs}}$$

with:

BB_{ss}	'steady state' Body Burden (ng/kg)
$t_{1/2}$	Half-life of 2,3,7,8-TCDD (days)
I_d	Daily intake of 2,3,7,8-TCDD (ng/kg/day)
F_{abs}	Absorption fraction of the daily intake

Substituting 7.6 years for the half-life of 2,3,7,8-TCDD in humans, an absorption fraction of 0.5 for the uptake from human food and 16 and 28 ng/kg as the human maternal body burden (eqally to the body burden in the rat in the study of Ohsako et al. (2001) and Faqi et al. (1998)) one arrives at corresponding daily intakes of 8.0 pg/kg/day and 14 pg/kg/day respectivily. These intakes correspond with monthly intakes of 240 and 420 pg/kg/month.

Application of uncertainty factors
The calculated EHMI values relate on a NOAEL (Ohsako study) and a LOAEL (Faqi study). To extrapolate a LOAEL to a NOAEL a factor of 3 was applied on the Faqi study (resulting in an estimated NOAEL of 140 pg/kg/month).

As the use of body burdens to scale doses from animal studies to equivalent human levels removes the need for uncertainty factors for toxicokinetic differences between animals and man such an uncertainty factor was omitted. JECFA furthermore concluded that humans may be less sensitive than rats for some effects of 2,3,7,8-TCDD, but the conclusion is less certain for other dioxins, and it cannot be excluded that the most sensitive humans might be as sensitive to the adverse effects of 2,3,7,8-TCDD as rats were in both the critical toxicity studies. JECFA therefore concluded that no uncertainty factor in either direction needs to be applied for differences in toxicodynamics among humans.
So, JECFA did not apply an uncertainty factors (of 3.2) for interspecies and intrahuman differences in toxicodynamics.

In order to allow for intrahuman differences in kinetics a factor of 3.2 was applied on both the Ohsako and the Faqi study.

Provisional Tolerable Monthly Intake (PTMI)
Applying uncertainty factors on the EHMI values results in a Provisional Tolerable Monthly Intake (PTMI) of 240/3.2 = 75 pg/kg/month for the Ohsako study and 420/9.6 = 44 pg/kg/month for the Faqi study, using the linear model.

In the same way a range for PTMI was obtained using the non-linear model for the relationship between dose and maternal and fetal body burdens. In this case PTMI values of 103 and 66 were calculated for the Ohsako and the Faqi study.

JECFA concluded that 'the range of PTMIs derived from the two studies, with either the linear or the power model, for extrapolating the maternal body burden after single or multiple

doses, is 40 - 100 pg/kg bw per month. The midpoint of this range, 70 pg/kg bw per month was chosen as the PTMI for use in risk assessment' [11]

Risk Assessment of 2,3,7,8-TCDD as applied to PBDE-99

Bioaccumulating potential of PBDEs

The kinetic properties of PBDEs indicate that this compound has dioxinlike, bioaccumulating, properties in mammals. For example, for PBDE-99 a terminal half-life of 33 days was determined in the rat by directly following the decline of this compound in adipose tissue (males: 24.3 days; females: 41.6 days, Hufnagel, as referenced in Geyer et al., 2004). In humans such a direct way of determining the half-life of PBDE-99 is not (yet) possible. Here the half-life may be estimated from a (more or less constant) intake which has, when sustained long enough, led to a 'steady state' of PBDE-99 in the body (note that the constant levels of PBDEs in Dutch breast milk which has been collected between 1998 and 2003 suggests Dutch women to be in such a 'steady state' situation). As calculated in this report the (median) human exposure to PBDE-99 from food amounts 0.11 ng/kg/day, equivalent to 7.7 ng/day for a 70 kg adult. Next to food housedust may significantly contribute to the human exposure to PBDE-99. For example, given a (median) concentration of 23.9 ng/g of PBDE-99 in (German) housedust (Knoth et al., 2003, Organohalogen Compounds, 61, 207 - 210) the daily intake of 50 - 100 mg dust may lead to an exposure of 1.2 – 2.4 ng/day. Considering PBDE-99 in the body to arise from the combined exposure from food and housedust and assuming this compound to mainly distribute in the body's fat mass the terminal half-life at 'steady state' then is:

$$t_{1/2} = \frac{\ln 2 \cdot c_{fat} \cdot m_{fat}}{I_{a,f} \cdot F_{abs,f} + I_{a,d} \cdot F_{abs,d}}$$

with:

$t_{1/2}$	Terminal half-life in the body (days or years)
c_{fat}	The concentration in body fat (as reflected in blood, adipose or milk fat, pg or ng/g fat)
m_{fat}	Body fat mass (g)
$I_{a,f}$	Actual, long-term, daily intake from food (pg or ng/day)[12]
$I_{a,d}$	Actual, long-term, daily intake from housedust (pg or ng/day)[13]
$F_{abs,f}$	Fraction of the intake from human food which is absorbed
$F_{abs,d}$	Fraction of the intake from housedust which is absorbed

[11] JECFA, 2002, pp. 591
[12] Constant intake from food as averaged over the period between the onset of the exposure and the reaching of the 'steady state' situation
[13] as 12

In calculating the half-life of PBDE-99 Swedish data on the actual intake of PBDE-99 from food (9.1 ng/day), the concentration in the body's fat fraction (0.872 ng/g), the body's fat mass (13.5 kg at a body weight of 70 kg) and the absorption faction from food (0.89) may be used (Geyer et al., 2004). The actual intake from housedust may be estimated on 1.8 ng/day (see above). No data on the absorption of PBDE-99 from housedust are available. However, this fraction may be assumed to vary between zero and the absorption fraction from food. Alternative to the Swedish data data from the Netherlands may be used. In Dutch breast milk, which was collected in 2003, a (median) concentration of 0.44 ng PBDE-99 /g milk fat was found (Zeilmaker, personal communication). Together with a body fat mass of 19.5 kg (30 % body fat at a female body weight of 70 kg) and a (median) daily intake of 7.7 ng/day (this report) these data may be used to calculate a half-life as well.
Substituting these values into the equation shown above and leaving the only parameter unknown, i.e. the absorption factor from house dust, variable then results in estimates of the half-life of PBDE-99 as a function of (the uncertainty in) the absorption factor from housedust. The result of this calculation, which is shown below, indicates that 1. the half-life calculation is quite insensitive for the absorption fraction from housedust and 2. that half-lives as calculated from Swedish and Dutch data are quite similar (Swedish data: max 2.8 years; min: 2.3 years; Dutch data: max: 2.4 years, min: 1.9 years).

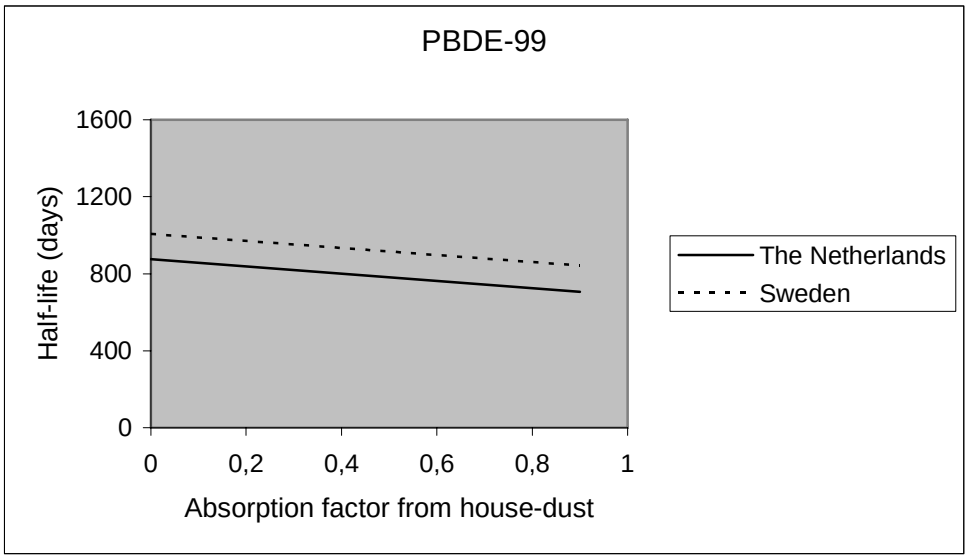


Figure A2.1. The half-life of PBDE-99 as calculated from Swedish and Dutch food/ 'body burden' data and variable absorption from housedust.

The calculations shown in Figure 1 can also be made for PBDE- 47, 99, 100, 153 and 154 (data not shown). As for PBDE-99 the half-lives of these congeners, which are summarized in Table 1, do not depend much on the absorption from house dust. Again half-lives as calculated from Swedish and Dutch data corresponded quite well, with half-lives based on Dutch data being roughly 20 % lower than half-lives based on Swedish data (see Figure 2).

Table A2.2 Minimum and maximum estimates of the half-lives of PBDEs as obtained from Swedish and Dutch food/'body burden'data.Minimum estimate: $F_{abs,d} = F_{abs,f}$ *; Maximum estimate:* $F_{abs,d} = 0$

	Half-time (years)			
Congener	Sweden		The Netherlands	
	min	max[1]	min	max
PBDE-47	1.9	2.0	2.1	2.2
PBDE-99	2.3	2.8	1.9	2.4
PBDE-100	1.6	1.7	2.0	2.1
PBDE-153 + 154	5.3	5.7	3.8	4.1

[1]as already mentioned in Geyer *et al.* (2004)

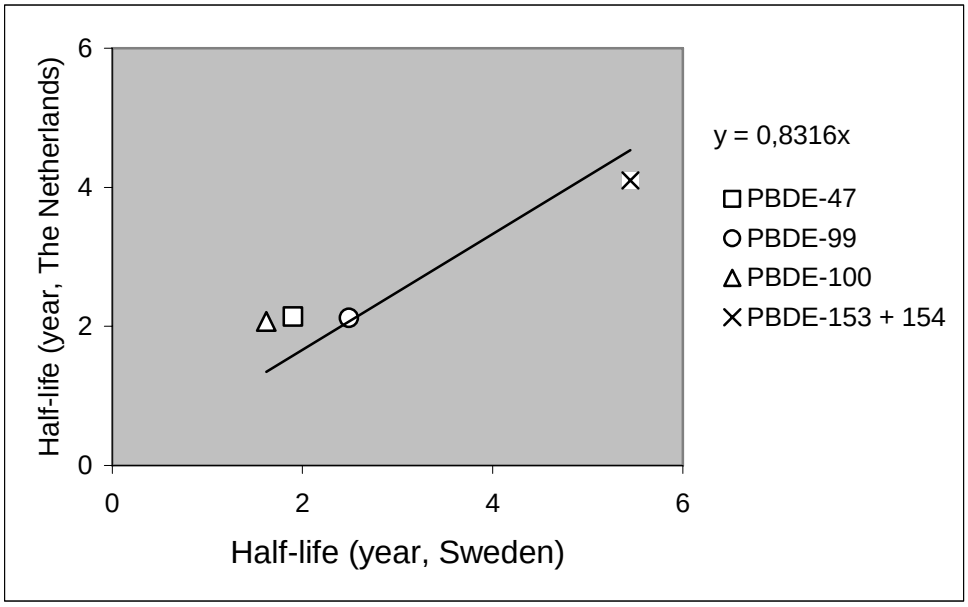


Figure A2.2. The correlation between half-life estimates of PBDEs as obtained from breast milk/food intake data in the Netherlands or adipose/blood/breast milk/food data from Sweden. Absorption fraction from housedust: 0.5.

Taken all data together it can be concluded that the terminal half-life of tetra-, penta- and hexa-bromodiphenylethers have half-lives in humans of several years. Consequently, these compounds will have clear bioaccumulating properties in humans.

Calculation of the maximal allowed daily intake of PBDE-99

Once it is concluded that lower brominated PBDEs have bioaccumulating potential in humans it follows that bioaccumulation is to be taken as the starting point for the risk assessment of these compounds. For, for persistent chemicals the amount which has accumulated in the body ('body burden'), merely than the exposure itself, determines the toxic risk (WHO, 2002a,b; SCF, 2000 and 2001; JECFA, 2002). For dioxinlike compounds like 2,3,7,8-TCDD this approach has repeatedly been applied to derive maximal allowed daily intakes.
Furthermore, 2,3,7,8-TCDD and PBDE-99 resemble each other in toxicity. For, the hitherto most sensitive effect of PBDE-99 toxicity appeared to be a single p.o. exposure of rat dams at GD6 of pregnancy. This exposure led to the disturbance of spermatid- and sperm-production in male offspring as assessed on postnatal day 140 (Kuriyama et al., 2005). Similar impaired spermatid- and sperm-production has also been found as the most sensitive endpoint for 2,3,7,8-TCDD toxicity. Hence this endpoint was used to derive the Provisional Tolerable Monthly Intake (PTMI) for this compound (Faqi et al., 1998; Ohsako et al., 2001; JECFA, 2002).
In this context the risk assessment procedure applied on the dioxin 2,3,7,8-TCDD may thus directly be applied on PDDE-99 (for details, see JECFA, 2002).

The risk assessment procedure of PBDE-99 then is as follows:

1. The determination of a relevant No Observed Adverse Effect Level (NOAEL) or LOAEL in experimental animals.
2. The calculation of the dam's body burden at the time-window at which male offspring is thought to be most sensitive for the induction of impaired spermatid- and sperm-production, i.e. the 16th day of gestation (GD16).
3 The calculation of the (chronic) human exposure which leads to the same body burden in women.
4. The application of uncertainty factors

Ad 1. In the case of PBDE-99 a LOAEL of 60 µg/kg administered as a single dose p.o. to rat dams on GD 6 of pregnancy was determined (Kuriyama et al., 2005).

Ad 2. The maternal body burden in the rat remaining at GD 16 from the PBDE-99 dose administered at GD 6 is given by means of a one-compartment kinetic model analysis (half-life of PBDE-99: 33 days, fraction absorbed as for p.o. administration of 2,3,7,8-TCDD in the rat: 0.6; JECFA, 2002):

$$BB_{GD_{16},rat} = 0.6 \cdot 60 \cdot e^{-\frac{\ln 2 \cdot 10}{33}} = 29.2 \text{ µg/kg}$$

(a background body burden from feed in the animal experiment is ignored).

Ad. 3/4. Next, the daily PBDE-99 intake (from food and housedust) which leads to this body burden in man is calculated with the aid of the one-compartment 'steady state' kinetic model:

$$I_{max} \cdot F_{abs(f,d)} = \frac{BB_{ss} \cdot \ln 2}{F_u \cdot t_{1/2}}$$

with:

BB_{ss} 'steady state' body burden (ng/kg-bw, obtained from the animal experiment)
$t_{1/2}$ Half-life of PBDE-99 in humans (days)
I_{max} Maximal (total) allowed daily human intake (sum of intake from food and housedust)
$F_{abs(f,d)}$ Absorption fraction (composite parameter weighing the absorption from food and housedust)
F_u Uncertainty factor (comprising inter- and intra-spedies differences in toxicokinetics and toxicodynamics, i.e. toxicity)

Substituting the equation for the half-life and considering the exposure from housedust as background exposure, i.e. $F_{abs(f,d)} \cdot I_{max} = I_{max,f} \cdot F_{abs,f} + I_{a,d} \cdot F_{abs,d}$, then gives:

$$I_{max,f} \cdot F_{abs,f} = \frac{BB_{ss} \cdot (I_{a,f} \cdot F_{abs,f} + I_{a,d} \cdot F_{abs,d})}{F_u \cdot c_{fat} \cdot m_{fat}} - \frac{I_{a,d} \cdot F_{abs,d}}{BW}$$

with:

$I_{max,f}$ Maximal allowed daily intake from food (ng/day)

As the Kuriyama study yielded a LOAEL, an uncertainty factor of 3 is applied to allow for LOAEL => NOAEL extrapolation (JECFA, 2002). Similarly an uncertainty factor of 3.2 is applied for intra-human differences in kinetics and both interspecies and intraspecies differences in sensitivity for PBDE-99 toxicity, i.e. toxicodynamics (JECFA, 2002). So in this way a total uncertainty factor of $3 \cdot 3.2 \cdot 3.2 \cdot 3.2 = 98$ is obtained

All parameters being known the (range of the) maximal allowed daily intake then can easily be calculated for the two extreme case $F_{abs,d} = 0$ and $F_{abs,d} = F_{abs,f}$.

For Swedish data (BB_{ss} = 29.2 ng/kg, $I_{a,f}$ = 9.1 ng/day, $F_{abs,f}$ = 0.89, $I_{a,d}$ = 1.8 ng/day, $F_{abs,d}$ = 0 or 0.89, F_u = 98, c_{fat} = 0.872 ng/g, m_{fat} = 13.5 kg, BW = 70 kg) one obtains a maximum allowed intake of 0.23 – 0.25 ng/kg/day.
When using Dutch data $I_{a,f}$ = 7.7 ng/day, c_{fat} = 0.44 ng/g and m_{fat} = 19.5 kg results in a maximal allowed intake of 0.27 – 0.30 ng/kg/day.

Taken all data together 0.26 ng/kg/day seems to be a fair estimate of the maximal allowed daily human intake of PBDE-99.

Appendix 3. Temporal trends of BFRs in environment and humans: North America and Japan

A.3.1 North America

A.3.1.1 Fish

The mean and median of the sum of PBDEs are 1050 and 310 ng/g lw, respectively, for the North American fishes (Hites, 2004a).

The total PBDE concentrations in the Great Lakes fish (trout from Lakes Superior, Michigan, Huron and Ontario, and walleye from Lake Erie) increased exponentially with time between 1980 and 2000 (Figure A3.1), doubling every 3-4 years (Zhu et al., 2004; De Wit, 2002; Luross et al., 2000). The concentrations of PBB-153, which was a component of a flame retardant banned in the 1970s, generally remained the same in these lake fishes.

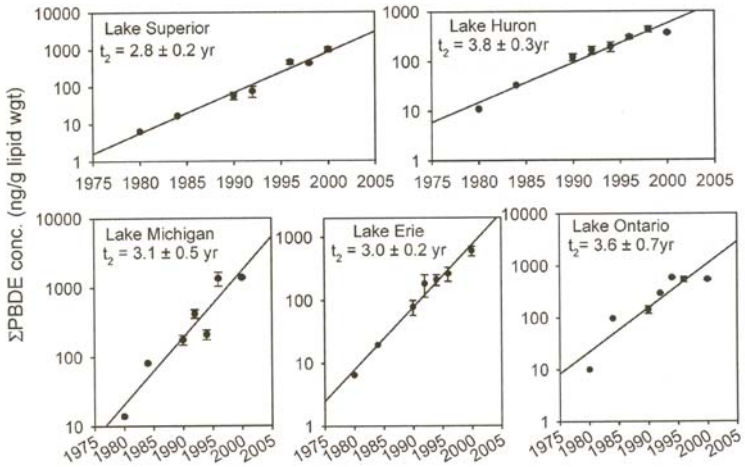


Figure A3.1 Temporal trend of the sum of PBDE concentrations in fishes from the Great Lakes (Zhu and Hites, 2004).

A.3.1.2 Dated sediment cores

The PBDEs concentrations in sediment cores from Lake Superior generally show a significant increase in recent years (Song et al., 2004). The concentrations of PBDE-209 was found about an order of magnitude higher than other congeners, and counts for about 90 % of the total PBDE inventory in the sediments. This finding agrees with the fact that PBDE-209 counts for more than 70 % of the total PBDE production in North America.

The concentrations of PBDE-209 in sediments of Canadian lakes increased during the last decades (Muir et al., 2003).

A.3.1.3 Birds and marine mammals

In North America, temporal trends in herring gull eggs from the Great Lakes (Norstrom et al., 2002), ringed seal from Canadian Arctic (Ikonomou et al., 2002), harbour seals from California (She et al., 2002) and beluga from St. Lawrence estuary, Canada and Canadian Arctic (Lebeuf et al., 2004; Law et al., 2003) - all indicate steady and continuing increases in PBDE concentrations, with no indications of levelling off. The sum of PBDEs in herring gull

eggs from the Great Lakes increased 20-75-fold through the 1981-2000 period. The concentrations of total PBDEs in the ringed seals from Canadian Arctic have been doubling every 4-5 years between 1981 and 2000 (an increase of more than 10-fold), correlating well with the production of the commercial penta-PBDE mixture over the same time period (Ikonomou et al., 2002) while in contrast, levels in human milk from Sweden have decreased since 1997 (Figure A3.2). Penta- and hexa-PBDEs in ringed seals are increasing at approximately the same rate as the sum of PBDEs and more rapidly than tetra-PBDEs and tri-PBDEs. An almost 100-fold increase was reported in the concentration of PBDEs in harbour seals from California between 1989 and 1999.

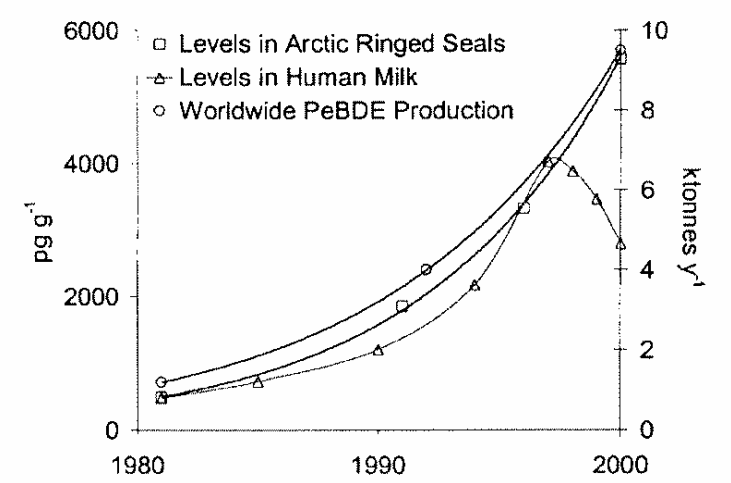


Figure A3.2 Comparison of PBDE levels in ringed seals from the Canadian Arctic, PBDE levels in human milk from Sweden and world-wide commercial penta-PBDE production (Ikonomou et al. 2002).

A.3.1.4 Human samples

The level of PBDEs in blood serum from Dallas, Texas was 0.77 ng/g lw in 1973 and 62 ng/g lw in 2003 (Schecter et al., 2004), which is a 80-fold increase over 30 years period.
PBDEs (triPBDEs to hexaPBDEs), a PBB (BB-153) and a PCB (CB-153) were measured in archived human serum pools covering the years 1985 to 2002 (Sjödin et al., 2003). The human serum concentrations in time are plotted in Figure A1.3 on a lipid weight basis together with the data on PBDEs and CB-153 from a Swedish retrospective time trend study using human milk. PBDE-47 and the sum of PBDE are both higher in the United States than in Sweden. When recently an indication of a decrease has been noted in the Swedish trend, in the U.S. the average of PBDE-47 in 2002 is 4.4 times higher than the measurement made in 1992, indicating a doubling in concentration in about 5 years for this period.
Brominated biphenyl BB-153 was the main constituent of commercially produced hexabromobiphenyl. This product has not been commercially produced in the U.S. since the mid-1970s following an accident in Michigan in which cattle feed was contaminated with this product. The concentration of BB-153 seems to be decreasing in serum from U.S. general population samples. This decrease is similar to that for CB-153, which has not been commercially used since the mid-1970s.
PBDE residues in Canadian human fetal liver and placenta were measured yearly between 1998-2003 and 2000-2003, respectively (Doucet et al., 2004). The tissue concentrations demonstrate a notable increase during the time period, especially for the fetal liver which increased approximately 10 fold from 1998 to 2003. At present, the amounts of PBDEs in

human fetal liver appear to be greater than in human milk, maternal blood and fetal blood on a fat weight basis.

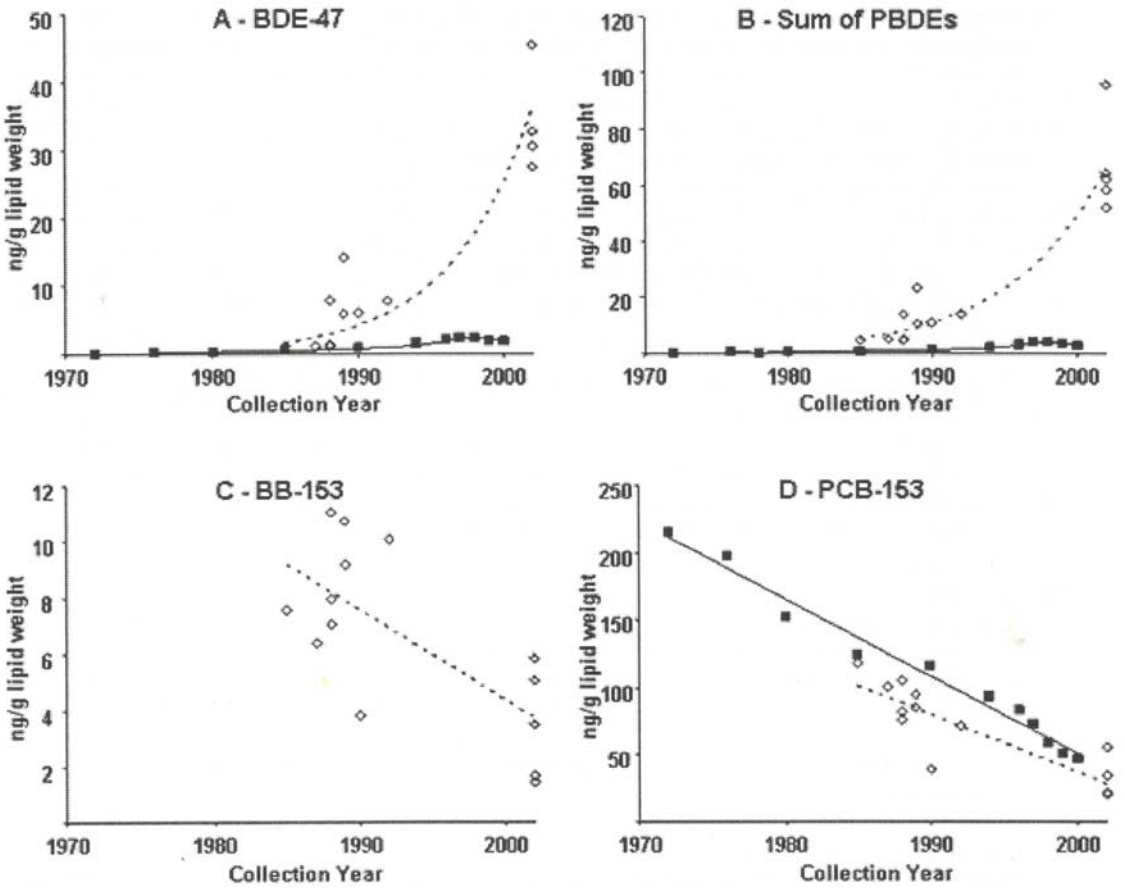


Figure A3.3 Concentrations in human serum pools of PBDE-47 (A), the sum of quantified PBDEs (B), PBB-153 (C) and PCB-153 (D) plotted against time of sample collection from 1972 to 2002. Also given are results from a Swedish retrospective time trend study of PBDEs and PCB-153 (Sjödin et al., 2003).

Ryan (2004) compared the PBDE levels in breast milk from different studies in North America and Japan with the levels in Europe. Table A3.1 shows the median total PBDE concentrations in human milk from USA and Canada. The PBDE levels in U.S. breast milk are 10-100 times greater than human milk levels in Europe and Japan.
Temporal trends in human milk in North America appear to be rising exponentially, doubling every 2 years up to 2000 (Watanabe and Sakai, 2003). PBDEs in human milk from Vancouver, Canada (Ryan et al., 2002) increased by more than one order of magnitude in about 10 years.

Table A3.1. PBDEs in human milk from North America (Ryan, 2004).

Country	Collection year	Median total PBDEs (ng/g lw)
USA; New York	1997	147
USA	2000	196
USA; Texas	2002	34
USA	2002-2003	58
USA; west coast	2003	50
Canada	1982 1986 1992 2001-2002	<0.2 0.6 3.0 22
Canadian Arctic (Nunavik)	1989-1991 1996-2000	1.7 6.8

A.3.2 Japan

A.3.2.1 Fish

PBDE levels in Japanese sea bass and grey mullet, collected at Osaka bay, were reported to show an increasing trend from 1986 to 1989, and then a drastically decreasing trend after 1990. PBDE levels in a sample taken in 1999 had decreased to only about 5% of that found in 1989 (Watanabe and Sakai, 2003; Ohta et al., 2001).

A.3.2.2 Dated sediment cores

In Japan, an increasing trend for PBDEs was reported for a sediment core at Osaka Bay from 1960-2000 (Sakai et al. 2002).

Concentrations of PBDEs and PBDD/Fs in sediment cores from Tokyo Bay between 1904 and 1999 were studied by Choi et al. (2003). Background levels of PBDEs were found during 1904-1941. The concentrations increased rapidly from 1946-48 to the surface layers in 1998-1999 and peaked in 1992-93. The major congener during the whole period was PBDE-209. Comparing the historical use and the temporal trends of PBDEs in the sediment cores indicate a lag of about 10 years between peak use and deposition in the sediments.

The levels of PBDD/F increased significantly from late 1960s to the mid-1990s, and then generally levelled off. The historical trends of PBDD/Fs were similar to those of PBDEs.

A.3.2.3 Marine mammals

In whales from Japan, PBDE levels in 2001 were significantly higher than in 1982, showing an about 10–fold increase (Kajiwara et al., 2004). Similarly, finless porpoise from China showed a 5-fold increase between 1990 and 2000.

A.3.2.4 Human samples

PBDE levels in adipose tissue in Japan from 1970 and 2000 revealed a significant increase from 29 pg/g lw to 1290 pg/g lw (Watanabe and Sakai, 2003).

The total PBDE concentrations in pooled human milk samples from Osaka, Japan

(1973-2000) continuously increased (Figure A3.4) during the period between 1973 (<0.01 ng/g lw) and 1988 (1.6 ng/g lw). After a decrease at the beginning of the 1990s, the total PBDE concentration seemed to increase again and began levelling off (Akutsu et al., 2003). The levels and time-trend of total PBDEs in Japanese mothers' milk were not remarkably different from those in Swedish mothers' milk.

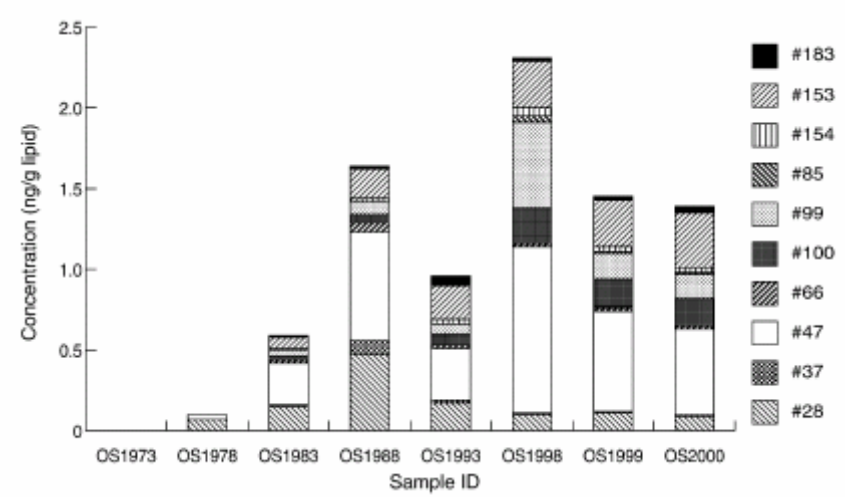


Figure A3.4 Time-trend of PBDE concentrations in pooled human milk samples collected from mothers living in Osaka between 1973 and 2000 (Akutsu et al., 2003).

Appendix 4. Comparison of BFR concentrations in food products

Product	the Netherlands		Other studies
	2003/ 2004 (ng/g product)	2001/ 2002 (ng/g product)	Concentration (ng/g product)
PBDE28			
Beef	0.0035^{+} (0*)	0.27^{+}(0*)	nd (grain fed), 0.036 (free range), USA, Luksemburg *et al.,* 2004
Beef fat	0.02^{+}(0*)	0.18^{+}(0*)	PBDE-28/33, range nd, mean 0.0013^{+}(0*), USA, Huwe, 2004
Pig fat	0.02^{+}(0*)	0.2^{+}(0*)	Pork fat, PBDE-28/33, range nd-0.0023, mean 0.0033^{+}(0.0021*), bacon (about 34% fat), PBDE-28/33, range nd-0.0046, mean 0.0017^{+}(0.0007*), USA, Huwe, 2004
Chicken	0.002^{+} (0*)	0.11^{+}(0*)	Chicken fat, PBDE-28/33, range nd-0.006, mean 0.0017^{+}(0.0005*), USA, Huwe, 2004 Nd - nd (free range), USA, Luksemburg *et al.* 2004
Fish Salmon Mackerel Herring	0.15^{+} (0.12) 0.08^{+} (0.05*) 0.05^{+}(0*) 0.14^{+} (0.13*)	0.17^{+} (0.16*) 0.1 0.14 0.25	Nd -0.099, USA, Luksemburg *et al.* 2004 Atlantic salmon, range 0.05-0.24, mean 0.12, mackerel 0.08-0.1, mean 0.09, herring, 0.06-0.08, mean 0.07, Norway, Bethune *et al.,* 2004
PBDE47			
Beef	0.018^{+}*	0.16^{+} (0.10*)	0.01 (grain fed)-0.045 (free range), USA, Luksemburg *et al.*, 2004
Beef fat	0.19^{+}*	0.18^{+} (0*)	Range nd-0.178, mean 0.05^{+}(0.028*), USA, Huwe, 2004
Pig fat	0.079^{+}*	0.21^{+} (0.12*)	Mean background level 1.9 (assuming 82% lipid), contaminated samples 106.6 (2002 mean), 2788 (1998), Australia, Burniston *et al.,* 2003. Pork fat, range nd-3.9, mean 0.518^{+}(0.513*), Bacon (about 34% fat), range nd-0.454, mean 0.083^{+}(0.062*), USA, Huwe, 2004
Chicken	0.017^{+}*	0.08^{+} (0.04*)	Chicken fat, 0.56-10.58 (possible local source of contamination), USA, 1997, Huwe *et al.* 2002 Chicken fat, range nd-2.8, mean 0.424^{+}(0.419*), USA, Huwe, 2004 0.012 - 0.037 (free range), USA, Luksemburg *et al.*, 2004
Meat products	nd-0.037	0.16^{+} (0.08*)	Meat and meat products (beef, pork, chicken, lamb) 0.024^{+}(0.023*), tetraPBDE (47-77), Spain, Bocio *et al.,* 2003
Eggs	0.02^{+}*	0.01^{+} (0*)	0.017^{+}(0.017*), tetraPBDE (47-77), Spain, Bocio *et al.* 2003
Cow's milk	0.028^{+}*	0.01^{+} (0*)	0.01 (assuming 5% fat), UK, D'Silva *et al.,* 2003 0.008^{+}(0.008*), tetraPBDE (47-77), Spain, Bocio *et al.*, 2003
Cheese	0.065^{+}*	0.05^{+} (0.02*)	Diary products (yogurt, cheese), 0.011^{+}(0.011*), tetraPBDE (47-77), Spain, Bocio *et al.*, 2003
Vegetable oil	0.01^{+} (0*)	0.26^{+} (0*)	Fats (margarine) and oils, 0.17^{+}(0.17*), tetraPBDE (47-77), Spain, Bocio *et al.,* 2003
Vegetables			Lettuce, tomato, green beans, cauliflower, 0.004^{+}(0.0039*), tetraPBDE (47-77), Spain, Bocio *et al.,* 2003
Tubers			Potato, 0.0005^{+}(0*), tetraPBDE (47-77), Spain, Bocio *et al.*, 2003
Pulses			Lentils, beans, 0.0023^{+}(0.0020*), tetraPBDE (47-77), Spain, Bocio *et al.*, 2003

Cereals	0.0098[+]*		Bread, pasta, rice, 0.0022[+](0*), tetraPBDE (47-77), Spain, Bocio *et al.*, 2003
Fruits	0.004[+]*		Apple, orange, pear, 0.0004[+](0*), tetraPBDE (47-77), Spain, Bocio *et al.*, 2003
Fish	1.09[+] (1.07*)	5.56[+] (5.56*)	
Salmon	0.8	2.1	0.16[+](0.16*), tetraPBDE (47-77), Spain, Bocio *et al.*, 2003
Mackerel	0.7[+] (0.5*)	3	0.006 –3.24 , USA, Luksemburg *et al.*, 2004 Atlantic salmon, range 0.67-3.09, mean 1.66,
Herring	2.9	7.75	mackerel 0.76-1.07, mean 0.86,
Eel	2.5[+] (2.4*)	4.4	herring, 1.23-1.81, mean 1.23, Norway, Bethune *et al.*, 2004 nd-81 (freshwater eel), 2003, the Netherlands, Van Leeuwen *et al.*, 2004
Mussels	0.5	0.2	0.03-0.12, mean 0.08, Norway, Bethune *et al.*, 2004
PBDE99			
Beef	0.02[+]*	0.18[+] (0.11*)	0.075 (grain fed)-0.017 (free range), USA, Luksemburg *et al*., 2004
Beef fat	0.183[+]*	0.49[+] (0.40*)	Range nd-0.279, mean 0.071[+](0.053*), USA, Huwe, 2004
Pig fat	0.158[+]*	0.35[+] (0*)	Mean background level 1.9 (assuming 82% lipid), contaminated samples 59 (2002 mean), 4264 (1998), Australia, Burniston *et al.*, 2003. Bacon (about 34% fat), range nd-0.624, mean 0.105[+](0.088*), pork fat, range nd-2.97, mean 0.51[+](0.508*), USA, Huwe, 2004
Chicken	0.019[+]*	0.08[+] (0.04*)	0.42-16.97 (possible local source of contamination), 13 samples, USA, 1997, Huwe *et al.*, 2002 Chicken fat, range 0.06-4.4, mean 0.74[+](0.74*), USA, Huwe, 2004 0.053 - 0.021(free range), USA, Luksemburg *et al.*, 2004
Fish	0.54[+] (0.51*)	0.83[+] (0.83*)	0.0067 – 0.395, USA, Luksemburg *et al.*, 2004
Salmon	0.4[+]*	0.4	Atlantic salmon, range 0.15-0.47, mean 0.27,
Mackerel	0.5[+]*	1.3	mackerel 0.20-0.33, mean 0.26,
Herring	0.7[+]*	2.5	herring, 0.08-0.29, mean 0.18, Norway, Bethune *et al.*, 2004
Eel	0.3[+]*	0.3	nd-7 (eel), 2003, the Netherlands, Van Leeuwen *et al.*, 2004
Mussels	0.2[+]*	0.065	0.01-0.07, mean 0.04, Norway, Bethune *et al.*, 2004
PBDE100			
Beef	0.01[+](0*)	0.09[+] (0.03*)	nd (grain fed)-0.034 (free range), USA, Luksemburg *et al.*, 2004
Beef fat	0.05[+](0*)	0.1[+](0*)	Range nd-0.048, mean 0.011[+](0.01*), USA, Huwe, 2004
Pig fat	0.05[+](0*)	0.14[+] (0.07*)	Mean background level 0.28 (assuming 82% lipid), contaminated samples 19.7 (2002 mean), 984 (1998), Australia, Burniston *et al.*, 2003. Bacon (about 34% fat), range nd-0.085, mean 0.014[+](0.013*), pork fat, range 0.009-0.559, mean 0.086[+](0.086*), USA, Huwe, 2004
Chicken	0.005[+] (0*)	0.06[+] (0.02*)	Chicken fat, 0.07-2.31 (possible local source of contamination), USA, 1997; Huwe *et al.*, 2002 Chicken fat, range 0.01-0.859, mean 0.152[+](0.151*), USA, Huwe, 2004 0.005-0.013 (free range), USA, Luksemburg *et al.*, 2004
Fish	0.3[+]*	1.14[+] (1.14*)	0.0018 – 0.279, USA, Luksemburg *et al.*, 2004
Salmon	0.2[+]*	0.3	Atlantic salmon, range 0.12-0.52, mean 0.30,
Mackerel	0.13[+]*	0.19	mackerel 0.14-0.20, mean 0.16,
Herring	0.93[+]*	1.95	herring, 0.01-1.39, mean 0.36, Norway, Bethune *et al.*, 2004
Eel	0.88[+]*	0.6	nd-61 (freshwater eel), 2003, the Netherlands, Van Leeuwen *et al.*, 2004
Mussels	0.2[+]*	0.05	Nd-0.04, mean 0.02, Norway, Bethune *et al.*, 2004
PBDE153			
Beef	0.005[+] (0*)	0.11[+] (0.05*)	nd (grain fed)-0.0028 (free range), USA, Luksemburg *et al.*, 2004
Beef fat	0.04[+] (0*)	0.25[+] (0.18*)	Range nd-0.042, mean 0.014[+](0.013*), USA, Huwe, 2004

Chicken	0.004^{+} (0*)	0.06^{+} (0.02*)	Chicken fat, 0.1-4.63 (possible local source of contamination), USA, 1997, Huwe *et al.*, 2002 Chicken fat, range 0.017-0.576, mean 0.126^{+}(0.126*), USA, Huwe, 2004 0.033 (grain fed)-0.0034 (free range), USA, Luksemburg *et al.,* 2004
Pig fat	0.004^{+} (0*)	0.55^{+} (0.5*)	Mean background level 0.3 (assuming 82% lipid), contaminated samples 15.6 (2002 mean), 1312 (1998), Australia, Burniston *et al.,* 2003. Bacon (about 34% fat), range nd-0.14, mean 0.027^{+}(0.026*), pork fat, range 0.008-0.178, mean 0.062^{+}(0.062*), USA, Huwe, 2004
Cow's milk	0.0005^{+} (0*)	0.01^{+} (0*)	0.004 (assuming 5% fat), UK, D'Silva *et al.,* 2003
Fish Salmon Mackerel Herring		0.25^{+} (0.24*) 0.3 0.2 0.15	Nd – 0.047, USA, Luksemburg *et al.,* 2004 Atlantic salmon, range <0.03-0.07, mean 0.05, mackerel <0.03-0.05, mean 0.04, herring, <0.02-0.04, mean 0.03, Norway, Bethune *et al.,* 2004
Mussels		0.09^{+}(0)	<0.01-0.03, mean 0.02, Norway, Bethune *et al.,* 2004
PBDE154			
Beef	0.01^{+}(0*)	0.12^{+} (0.09*)	nd (grain fed)-0.0012 (free range), USA, Luksemburg *et al.,* 2004
Beef fat	0.05^{+}(0*)	0.1^{+}(0*)	Range nd-0.024, mean 0.0075^{+}(0.0063*), USA, Huwe, 2004
Pig fat	0.045^{+} (0*)	0.13^{+} (0.07*)	Mean background level 0.2 (assuming 82% lipid), contaminated samples 12.3 (2002 mean), 984 (1998), Australia, Burniston *et al.,* 2003. Bacon (about 34% fat), range nd-0.085, mean 0.0148^{+}(0.0135*), pork fat, range nd-0.137, mean 0.043^{+}(0.043*), USA, Huwe, 2004
Chicken	0.0045^{+} (0*)	0.07^{+} (0.05*)	Chicken fat, range nd-0.126, mean 0.039^{+}(0.038*), USA, Huwe, 2004 0.0078-0.0019 (free range), USA, Luksemburg *et al,*. 2004
Fish Salmon Mackerel Herring		0.29^{+} (0.29*) 0.2 0.2 0.25	0.00084 – 0.164, USA, Luksemburg *et al.,* 2004 Atlantic salmon, range 0.05-0.16, mean 0.11, mackerel 0.05-0.08, mean 0.06, herring, 0.03-0.09, mean 0.05, Norway, Bethune *et al.,* 2004
Mussels		0.025^{+} (0.005*)	<0.01-0.04, mean 0.02, Norway, Bethune *et al.,* 2004
Total PBDE (2001/2: sum of PBDE-28, -47, -99, -100, -153, -154; 2003/4: added PBDE-66, -85, -138, -183)			
Beef	0.152^{+} (0.038*)	nd-2.2, 0.66^{+} (0.38*)	0.18^{+}(0.14*) FIRE, 1999, same congeners as RIVM 2003/2004, RIVM, the Netherlands 0.0162, Japan, Ohta *et al.,* 2002 0.042^{+}(0.036*), tetra- to octaPBDE, Spain, Bocio *et al.,* 2003 0.12 (grain fed)-0.035 (free range), same congeners as RIVO, 0.154 (grain fed)-0.177 (free range), sum of PBDE-7, -13, -15, -17, -25, -28, -35, -47, -49, -66, -75, -85, -99, -100, -126, -138, -153, -154, -155, -181, -183, -197, -203, -207, -209, USA, Luksemburg *et al.,* 2004a 0.106-0.177 (free range), 2003/2004, USA, Luksemburg *et al.,* 2004b 0.08*, PBDE-17-209, market basket, USA, Schecter *et al.,* 2004
Beef fat	1.132^{+} (0.372*)	nd-2.3, 0.74^{+} (0.58*)	Range nd-0.586, mean 0.165^{+}(0.111*), sum of PBDE-28/33, -47, -85,-99, -100, 153, -154, -183, USA, Huwe, 2004
Pig fat	0.992^{+} (0.237*)	nd-1.5, 1.03^{+} (0.76*)	Pork fat, range 0.017-7.831, mean 1.282^{+}(1.269*), Bacon (about 34% fat), range nd-7.831, mean 0.296^{+}(0.248*), sum of PBDE-28/33, -47, -85,-99, -100, 153, -154, -183, USA, Huwe, 2004 Bacon (about 34% fat), nd-0.1, PBDE-17-209, market basket, USA, Schecter *et al.,* 2004 4.6^{+} (2.7*) (assuming 82% lipid), Australia, Burniston *et al.,* 2003
Pork	0.273^{+} (0.073*)	nd-1.5, 2.13^{+} (0.38*)	0.0636, Japan, Ohta *et al.* 2002 0.172^{+}(0.166*), tetra- to octaPBDE, Spain, Bocio *et al.,* 2003 0.04*, PBDE-17-209, market basket, USA, Schecter *et al.,* 2004

Chicken	0.12^{+} (0.035*)	nd-1.3, 0.34^{+} (0.19*)	0.00625, Japan, Ohta *et al.,* 2002 Chicken fat, 1.2-35.3 (possible local source of contamination), same congeners as RIVO, 1.8-39.4, PBDE-17 to 209, USA, 1997, Huwe *et al.,* 2002 0.010^{+}(0*), tetra- to octaPBDE, Spain, Bocio *et al.,* 2003 Chicken fat, sum of PBDE-28/33, -47, -85,-99, -100, 153, -154, -183, range 0.086-8.965, mean 1.593^{+}(1.582*), USA, Huwe, 2004 0.144 – 0.044 (free range), same congeners as RIVO, 0.618 - 0.486 (free range), sum of PBDE-7, -13, -15, -17, -25, -28, -35, -47, -49, -66, -75, -85, -99, -100, -126, -138, -153, -154, -155, -181, -183, -197, -203, -207, -209, USA, Luksemburg *et al.,* 2004a 0.086-0.618, 2003/2004, USA, Luksemburg *et al.,* 2004b 0.28*, PBDE-17-209, individual sample, USA, Schecter *et al.,* 2004
Meat and meat products	Mixed meat 0.195^{+} (0*)	nd-2.2, 0.98^{+} (0.46*)	Beef, pork, chicken, lamb, 0.109^{+}(0.102*), tetra- to octaPBDE, 0.062^{+}(0.061*), tetra- to hexaPBDE (47-154), Spain, Bocio *et al.,* 2003 Nd-1.373, median 0.283*, PBDE-17-209, market basket, USA, Schecter *et al.,* 2004
Eggs	0.112^{+} (0.09*)	nd, 0.08^{+} (0*)	1.21^{+}(1.19*), FIRE, same congeners as RIVM 2003/2004, the Netherlands, RIVM, 1991 4.98^{+}(4.94*), FIRE, same congeners as RIVM 2003/2004, the Netherlands, RIVM, 1999 0.065^{+}(0.058*), tetra- to octaPBDE, 0.055^{+}(0.055*), tetra- to hexaPBDE (47-154), Spain, Bocio *et al.,*2003 0.074, PBDE-17-209, market basket, USA, Schecter *et al.,* 2004b
Meat and eggs			0.015^{++}(0.013*), Finland, Kiviranta *et al.,* 2004 0.0647, Japan, 2002-2003, Ashizuka *et al.,*. 2004
Cow's milk	0.038^{+} (0.028*)	nd , 0.04^{+} (0*)	0.125-0.225 (assuming 5% fat), Germany, Krüger, 1988 0.01 (assuming 5% fat), UK, D'Silva *et al.,* 2003 0.006-0.03, France, Tritscher *et al,* . 2003 0.014^{+}(0.013*), tetra- to hexaPBDE (47-154), 0.017^{+}(0.013*), tetra- to octaPBDE, Spain, Bocio *et al.,* 2003 Liquid milk products, 0.002^{++}(0.00082*), Finland, Kiviranta *et al.,* 2004 0.02-0.03*, PBDE-17-209, market basket, USA, Schecter *et al.*, 2004
Cheese	0.226^{+} (0.146*)	nd-0.24, 0.14^{+} (0.06*)	0.27^{+}(0.15*), FIRE, same congeners as RIVM 2003/2004, the Netherlands, RIVM, 1991 18.77^{+}(18.73*), FIRE, same congeners as RIVM 2003/2004, the Netherlands, RIVM, 1999 Yogurt, cheese, 0.036^{+}(0.034*), tetra- to hexaPBDE (47-154), 0.048^{+}(0.034*), tetra- to octaPBDE, Spain, Bocio *et al.,* 2003 Solid milk products, 0.04^{++}(0.034*), Finland, Kiviranta *et al.,* 2004 0.69*, PBDE-17-209, market basket, USA, Schecter *et al.*, 2004
Dairy products			Cheese, butter, milk, ice cream, yogurt, milk, margarine, range 0.009-0.679, median 0.0315*, PBDE-17-209, market basket, USA, Schecter *et al,* 2004 Milk and milk products 0.0086, Japan, 2002-2003, Ashizuka *et al.,* 2004
Vegetable oil	1.024^{+} (0.884*)	nd-0.5, 0.24^{+} (0.06*)	nd, <0.05ng/g lw, olive and peanut oil, Egypt present, Palestine 1940's, Jacobs *et al,* 2003 vegetable oil and fats, 0.467^{+}(0.465*), tetra- to hexaPBDE (47-154), 0.588^{+}(0.569*), tetra- to octaPBDE, Spain, Bocio *et al.,* 2003 Fats, 0.22^{++}(0.18*), Finland, Kiviranta *et al.,* 2004 0.122, Japan, 2002-2003, Ashizuka *et al.,* 2004

Fish	excluding wild eel, nd-10.4, 2.45^{+} (2.22*), fatty fish 3.24^{+} (2.95*), lean fish 1.87^{+} (1.68*)	excluding wild eel, 0.4-15.9, 6.70^{+} (6.68*), fatty fish 7.39^{+} (7.37*) lean fish 0.42^{+} (0.42*)	Fatty fish 9.13^{+}(9.10*), lean fish 0.74^{+}*, FIRE, same congeners as RIVM 2003/2004, the Netherlands, RIVM, 1999 0.0085-3.078, median 1.725*, PBDE-17-209, market basket, USA, Schecter *et al.,* 2004 0.0177-1.72, Japan, Ohta *et al.,* 2002 0.334^{+}(0.325*), tetra- to octaPBDE, 0.322^{+}(0.321*), tetra- to hexaPBDE (47-154), Spain, Bocio *et al.,* 2003 0.85^{++}(0.85*), Finland, Kiviranta *et al,* 2004 0.153 – 4.955, sum of PBDE-7, -13, -15, -17, -25, -28, -35, -47, -49, -66, -75, -85, -99, -100, -126, -138, -153, -154, -155, -181, -183, -197, -203, -207, -209, USA, Luksemburg *et al.,* 2004a,b 0.01-2.88, German market, world, 2003, Paepke *et al.,* 2004 Fish 0.04-36, USA, Hayward *et al.,* 2004 nd-0.547, mean food group samples 1.259, Japan, 2002-2003, Ashizuka *et al.,* 2004 Fish muscle, 0.06-0.94, PBDE-28-209, Belgian North Sea, Voorspoels *et al.,* 2003
Salmon	nd-3.6, 2.1^{+} (1.8*)	3.4	Salmon 1.7-3, PBDE-17-209, USA, Schecter *et al.,* 2004 Atlantic salmon, 1.14-4.49, mean 2.51, Norway, Bethune *et al.,* 2004 Salmon 0.04-1.5, USA, Hayward *et al.,* 2004 Salmon median farmed EU 3, North America 3, supermarket EU 3, North America 1, wild 0.2, Hites *et al.*, 2004 Farmed trout, 0.7-1.3, congeners as RIVO 2001/2002, Switzerland, Zennegg *et al,* . 2003
Mackerel	0.8-2.8, 1.9^{+} (1.5*)	2.6-7.5, 5^{+} (5*)	Mackerel 1.26-1.78, mean 1.46,
Herring	2.5-6.5, 5.4^{+} (5.1*)	9.8-15.9 12.9^{+} (12.9*)	Herring, 1.02-3.53, mean 1.9, Norway, Bethune *et al,* . 2004
Mussels	0.3-2.1, 1.6^{+} (1.4*)	0.33-0.34, 0.36^{+} (0.34*)	0.06-0.25, mean 0.15, Norway, Bethune *et al.,* 2004
Vegetables			Lettuce, tomato, green beans, cauliflower, 0.008^{+}(0.005*), tetra- to octaPBDE, 0006.$^{+}$(0.005*), tetra- to hexaPBDE (47-154), Spain, Bocio *et al.,* 2003 Spinach, 0.134, Japan, Ohta *et al.,* 2002 Carrot, 0.0384, Japan, Ohta *et al.,* 2002 0.017^{++}(0.017*), Finland, Kiviranta *et al.,* 2004
Pulses			Lentils, beans, 0.011^{+}(0.002*), tetra- to octaPBDE, Spain, Bocio *et al.,* 2003
Potato			0.0476, Japan, Ohta *et al.,* 2002 0.007^{+}(0*), tetra- to octaPBDE, 0.002^{+}(0*), tetra- to hexaPBDE (47-154), Spain, Bocio *et al.,* 2003 Potato products, 0.0014^{++}(0.0013*), Finland, Kiviranta *et al.,* 2004
Fruits	0.015^{+} (0.004*)		Apple, orange, pear, 0.006^{+}(0*), tetra- to octaPBDE, 0.002^{+}(0*), tetra- to hexaPBDE (47-154), Spain, Bocio *et al.,* 2003 Fruits and berries, 0.0042^{++}(0.0038*), Finland, Kiviranta *et al.,* 2004
Cereal products	0.022+ (0.015*)		0.14^{+}(0.12*), rye, wheat, wheat flour, FIRE, same congeners as RIVM 2003/2004, the Netherlands, RIVM, 1991 0.015^{++}(0.015*), Finland, Kiviranta *et al.*, 2004 Bread, pasta, rice, 0.036^{+}(0*), tetra- to octaPBDE, 0.009^{+}(0*), tetra- to hexaPBDE (47-154), Spain, Bocio *et al.,* 2003
Beverages, spices, sweets			0.0055^{++}(0.0054*), Finland, Kiviranta *et al.,* 2004

		HBCDD	
Beef fat		nd-10, 3.76^{+} (2.95*)	3.3, Sweden 1999, Romberger *et al.,* 2004
Pig fat		nd-1.9, 1.02^{+} (0.80*)	0.8, Sweden 1999, Romberger *et al.*, 2004
Chicken		nd-5.1, 2.62^{+} (1.49*)	Chicken fat, 4.1, Sweden 1999, Romberger *et al.,* 2004
Lamb fat			1.2, Sweden 1999, Romberger *et al.,* 2004
Eggs		nd-1.6, 0.35^{+} (0.30*)	0.8, Sweden 1999, Romberger *et al.,* 2004
Cow's milk		nd-0.11, 0.03^{+} (0.02*)	0.07, Sweden 1999, Romberger *et al.,* 2004
Fish Eel Salmon		nd-12, 4.29^{+} (4.26*) nd-12, 3.91^{+} (3.85*) 1.6	Eel maximum 41, 1.6, 8.4 (α-,β-,γ-HBCDD), eel median 12, 0.9, 3 (α-,β-,γ-HBCDD), 2003, the Netherlands, Van Leeuwen *et al.,* 2004 Lake Ontario trout 0.4-3.8 α-HBCDD, 0.1-0.8 γ-HBCDD, Canada 2002, Tomy *et al.,* 2004 Farmed rainbow trout 1, Sweden 1996, wild salmon 4.8, Sweden 1999, Romberger *et al.,* 2004

*nd – non-detect, $^{+}$middle estimate for mean concentration (nd=0.5·LOD), LOD – limit of detection, *lower bound estimate for mean concentration (nd=0) in brackets, $^{++}$upper bound mean concentration estimate*

It should be mentioned that the PBDE contamination of beef and pork measured by the RIVO in 2001/2 is much higher than could be expected from measurements in beef fat and pig fat samples (beef fat content is 3-8.5 %, pork fat content is 3.5-21 %) by the same institute. The concentrations in the animal fat samples measured by the RIVM in 2004 were in between 0.24-0.37 ng/g fat (which is 100 % fat). This was also not equal to the fat-based concentrations in meat of 1.08-4.20 ng/g fat. Thus it is clear that to determine residues in meat, meat samples should be collected instead of animal fat samples.

The total PBDE residues in vegetable oil and fats measured by RIVM 2004 are much higher than that of RIVO 2001/2 due to the contribution of PBDE-183, which was not analysed by RIVO.

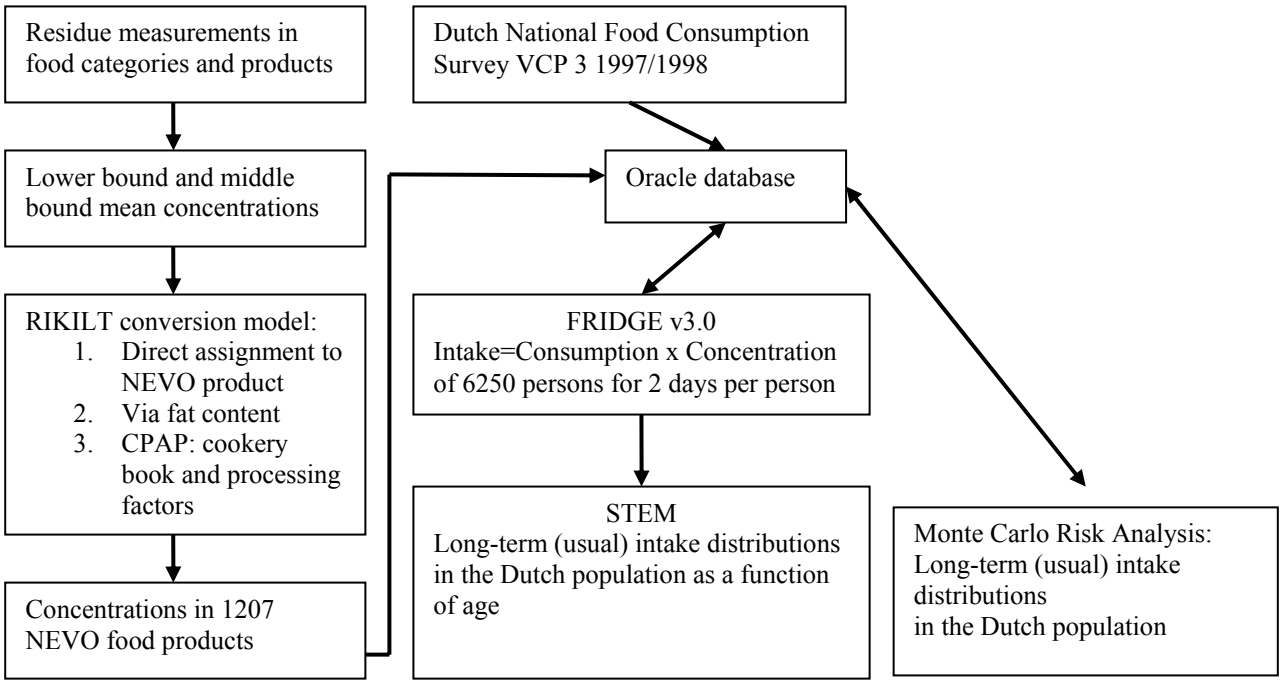
Comparison of the PBDE measurements in cow's milk and in eggs show that the limit of detection of the RIVO 2001/2 measurements was too high to determine contamination of these food products. PBDE residues are measured in milk and eggs by the RIVM in 2004, which led to relative contribution of milk to the middle estimate dietary intake of 19 % (see chapter 3.3). Notable is that measurements performed in German milk about 15 years prior to other measurements (De Wit, 2002; Krüger, 1988) show much higher total PBDE concentrations, however we do not know if these measurements concern background or contaminated samples. Measurements in eggs performed at RIVM within the FIRE project show very high total PBDE residues both for data from 1991 and 1999. Total PBDE concentrations in cheese measured in the Netherlands by the RIVO (2001/2002), the RIVM in 2004 and the RIVM in 1991 (FIRE project data) are higher than from Spain and Finland, but lower than from the U.S. Two orders of magnitude higher total PBDE residues are measured in cheese from samples of 1999 FIRE project.

PBDE residues measured in RIVM 2004 pork, beef and chicken samples are lower than those in 1999 FIRE and RIVO 2001/2 samples.

The PBDE concentration in 2001/2002 fish measured by the RIVO is in general higher than obtained in other studies world-wide. This can be explained by the high fat content of eel, herring and mackerel (12 samples from 14 fish samples analysed). However, the 2003/2004 R total PBDE residues in fatty fish measured by the RIVO are lower than that from 2001/2002 and that from 1999 FIRE project. The RIVO measured contamination of 2001/2002 salmon sample and 2003/2004 mean fatty fish residue agree well with other studies, especially with the European Union farmed and supermarket salmon (Hites et al., 2004).

Although the residue measurements for some food products are performed on a time scale of 13 years, it is difficult to make any conclusions about trends. For cheese, butter and eggs 1999 FIRE project samples have much higher PBDE residues than 1991 FIRE project samples and RIVM 2004 samples. However, on a smaller time scale, measurements in fatty fish show decreasing PBDE residue from 1999 to 2003.
HBCDD concentrations in beef fat and pig fat measured by RIVO 2001/2 are comparable with the ones from a Swedish study. Swedish measurements in eggs and milk lay within the ranges measured by RIVO. Anyway, a very limited number of HBCDD measurements in food products is available.

Appendix 5. Flow diagram of the dietary intake estimation method



Appendix 6. Percentiles of the long-term dietary intake distributions of PBDE congeners in the Dutch population estimated from 2003/2004 data

Age (yrs)	Lower bound dietary intake estimate (ng/kg bw/d)					Middle dietary intake estimate (ng/kg bw/d)				
PBDE-47										
	Median	P90	P95	P97.5	P99	Median	P90	P95	P97.5	P99
2	1.35	2.69	3.27	3.88	4.73	1.40	2.69	3.24	3.80	4.58
10	0.49	0.97	1.19	1.41	1.71	0.53	1.01	1.21	1.42	1.71
40	0.28	0.55	0.67	0.79	0.97	0.30	0.57	0.68	0.80	0.97
Life-long cumulative per day	0.38	0.76	0.92	1.09	1.33	0.40	0.77	0.93	1.09	1.32
PBDE-99										
	Median	P90	P95	P97.5	P99	Median	P90	P95	P97.5	P99
2	0.13	0.21	0.25	0.28	0.33	0.23	0.34	0.38	0.42	0.47
10	0.09	0.14	0.17	0.19	0.22	0.14	0.20	0.23	0.25	0.28
40	0.07	0.12	0.14	0.16	0.18	0.10	0.15	0.17	0.18	0.21
Life-long cumulative per day	0.08	0.13	0.15	0.17	0.20	0.11	0.17	0.19	0.21	0.24
PBDE-100										
	Median	P90	P95	P97.5	P99	Median	P90	P95	P97.5	P99
2	0.012	0.031	0.040	0.050	0.065	0.181	0.261	0.290	0.317	0.352
10	0.010	0.025	0.032	0.040	0.053	0.099	0.143	0.159	0.174	0.193
40	0.012	0.030	0.039	0.049	0.064	0.066	0.096	0.107	0.117	0.130
Life-long cumulative per day	0.012	0.031	0.040	0.050	0.064	0.080	0.115	0.128	0.140	0.155
PBDE-153 + PBDE-154										
	Median	P90	P95	P97.5	P99	Median	P90	P95	P97.5	P99
2	0.0028	0.0078	0.0104	0.0133	0.0177	0.274	0.419	0.473	0.526	0.594
10	0.0019	0.0053	0.0070	0.0090	0.0120	0.156	0.239	0.270	0.300	0.339
40	0.0016	0.0045	0.0060	0.0076	0.0102	0.098	0.150	0.169	0.188	0.213
Life-long cumulative per day	0.0018	0.0049	0.0065	0.0084	0.0111	0.119	0.182	0.205	0.228	0.258
PBDE-183										
	Median	P90	P95	P97.5	P99	Median	P90	P95	P97.5	P99
2	0.66	1.45	1.81	2.20	2.76	0.87	1.71	2.07	2.44	3.17
10	0.46	1.02	1.28	1.56	1.95	0.57	1.12	1.36	1.60	1.95
40	0.28	0.61	0.76	0.93	1.16	0.34	0.67	0.81	0.96	1.16
Life-long cumulative per day	0.34	0.75	0.94	1.15	1.44	0.42	0.83	1.01	1.19	1.45

Appendix 7. Total PBDE and HBCDD dietary intake in different countries

Country	Mean dietary intake of the sum of PBDEs ng/day	Contribution of food groups to the total mean dietary intake of sum of PBDEs (%)	Method	Reference
Canada 1998	44	Meat products 77%, Dairy products 6%, Fish 3%	"market basket", most composed food samples of animal origin, sum of congeners 28, 47, 99, 100, 153, 154	Ryan *et al.*, 2001
UK 1999/2000	130^{+} (107*)		"duplicate diet", composed samples from 10 individuals, sum of congeners 47, 99, 100, 153, 154	Harrad *et al.*, 2004
Sweden 1999	51^{+}	Fish products almost 50%, Dairy products 15%, Fat and oils 15%	"market basket", composed samples per food group: fish, meat, dairy products, eggs, fats/oils, pastry, sum of congeners 47, 99, 100, 153, 154	Darnerud *et al.*, 2001
Sweden 1998/1999	40.8* HBCDD 162*	Fish 58%, Dairy and meat products 10%	Mean for females (17-74 years), foods of animal origin, Diet National Swedish inventory, sum of congeners 47, 99, 100, 153, 154	Lind *et al.*, 2002
Spain, Catalonia 2000	97.3^{+} (81.9*) 69.4* sum of tetra- to hexaPBDE 74.6^{+} children 4-9 years old	Fish and shellfish 32^{+} (37*)%, Oils and fats 25^{+} (28*)%, Meat and meat products 21^{+} (23*)%	Total diet study, 54 samples belonging to 11 food groups, sum of tetra- to octaPBDEs, hepta- and octaPBDE 15% of the total intake	Bocio *et al.*, 2003 Bocio *et al.*, 2004
Finland 1997/1999	44^{++}(44*)	Fish 53%, fats 17%, beverages, spices, sweets 9%, cereal products 6%	Market baskets: liquid and solid milk products, fish, meat and eggs, fats, cereal products, potato products, vegetables, fruits and berries, beverages and spices and sweets, total diet basket. Sum of congeners 47, 99, 100, 153, 154	Kiviranta *et al.*, 2004
The Netherlands 2001/2002	194^{+} (78*) HBCDD 191^{+} (99*)	Meat 78^{+}(52*)%, Fish 15^{+}(38*)%, Cheese 3^{+}(7*)%, Vegetable oil 3^{+}(2*)%	84 single food product samples, sum of congeners 28, 47, 99, 100, 153, 154	De Winter-Sorkina *et al.*, 2003; this study
The Netherlands 2003/2004	122^{+}(77*) 58^{+}(44*) sum of congeners 47, 99, 100, 153, 154	Oils and fats 25^{+}%, Milk 19^{+}%, Fish 13^{+}%, Meat 11^{+}%	Pooled samples of 13 food categories, sum of congeners 28, 47, 66, 85, 99, 100, 138, 153, 154, 183	This study, De Mul *et al.*, 2005

*lower bound estimate, $^{+}$middle estimate, $^{++}$upper bound estimate