## *POLYBROMINATED DIPHENYL ETHERS*

***First draft prepared by***

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## 1. *EXPLANATION*

### 1.1 *Introduction*

Polybrominated diphenyl ethers (PBDEs) are anthropogenic chemicals that are added to a wide variety of consumer/commercial products (e.g. plastics, polyurethane foam, textiles) in order to improve their fire resistance. PBDEs have been produced since the 1960s, primarily as three main commercial products (indicated with initial capital letters): Pentabromodiphenyl Oxide or Ether (Penta-BDE), Octabromodiphenyl Oxide or Ether (OctaBDE) and Decabromodiphenyl Oxide or Ether (DecaBDE). Some variability in composition is known to exist

between products from different manufacturers, but each technical product can be approximately described by its congener compositions, given in Table 1.

***Table 1. General composition of commercial PBDE flame retardants and substitution pattern of selected congeners***

| PBDE | |
|---|---|
| *Mixture* | *Congener composition (% of total)* |
| Penta | 24–38% tetraBDEs, 50–60% pentaBDEs, 4–8% hexaBDEs |
| Octa | 10–12% hexaBDEs, 44% heptaBDEs, 31–35% octaBDEs, 10–11% nonaBDEs, <1% decaBDEs |
| Deca | <3% nonaBDEs, 97–98% decaBDE |
| *Individual congeners*[a] | *Substitution pattern* |
| BDE-47 | 2,2',4,4'-tetraBDE |
| BDE-99 | 2,2',4,4',5-pentaBDE |
| BDE-153 | 2,2',4,4',5,5'-hexaBDE |
| BDE-209 | 2,2',3,3',4,4',5,5',6,6'-decaBDE |

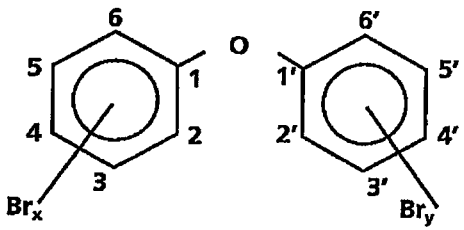
[a] See Appendix 1 for a list of common PBDE congeners.

PBDEs belong to a class of brominated aromatic compounds that are structurally similar to polychlorinated biphenyls (PCBs) and therefore share the same nomenclature, as proposed by Ballschmitter & Zell (1980) (Figure 1). Theoretically, as with PCBs, 209 distinct PBDE isomers are possible; however, each commercial mixture usually contains only a limited number of congeners from each homologue group. For example, Bromkal 70-5-DE, a commercial PentaBDE product, is 70% by weight BDE-47 and BDE-99, with approximately equal contributions from each isomer (Sjödin et al., 1998). Additional congeners detected include BDE-100 (6.8%), BDE-153 (3.9%) and BDE-154 (2.5%). For the commercial OctaBDE formulations, BDE-153, BDE-183 and BDE-203 are major congeners that have been identified (Alaee & Wenning, 2002). Earlier formulations of OctaBDE may have contained up to 12% pentaBDE isomers, in particular BDE-99, but data from more recent productions suggest that the concentration is now less than 0.5% of the total (EU, 2003).

PBDEs have not been evaluated previously by the Committee. In 1994, WHO published an Environmental Health Criteria document on brominated diphenyl ethers (IPCS, 1994), as part of an overview on the possible environmental and human health impacts of flame retardants. Recent analysis of archived samples collected over the last three to four decades has demonstrated significant increases in concentrations of PBDEs in samples from the environment and in certain samples from humans in Europe and North America. This has led to both voluntary and formal bans on the production and use of certain formulations of PBDEs. Limited national food surveys have identified diet as one of the possible main sources of human exposure. The present evaluation was undertaken in

response to a request from the Codex Committee on Food Additives and Contaminants (CCFAC), most recently at its Thirty-fifth Session (CAC, 2003), to evaluate the potential risks associated with the presence of PBDEs in food.

***Figure 1. General structural formula for PBDEs, where x + y = 1–10***




### *1.2 Uses*

Flame retardants are anthropogenic chemicals that are either physically blended (additive) or chemically bonded (reactive) to a variety of combustible products in order to improve or increase their ignition and fire resistance. Products treated with flame retardants include electronic equipment (circuit boards, computers, monitors, etc.), textiles, commercial and residential construction materials, insulation, furniture and carpets. Various reviews of the global production, applications and mechanism of action of flame retardants are available (IPCS, 1997; Rahman et al., 2001; de Wit, 2002; Alaee et al., 2003).

PBDEs are primarily used as additive flame retardants, specific to applications as defined by their physical-chemical properties. Commercial PentaBDE mixtures are mainly used in polyester and flexible polyurethane foam formulations in amounts that can result in the finished material being composed of up to 30% by weight of flame retardant. The main use of OctaBDE is in a variety of thermoplastic resins, in particular ABS (acrylonitrile–butadiene–styrene) plastic, which can contain up to 12% by weight OctaBDE. DecaBDE is used in various plastic polymers such as polyvinyl chloride, polycarbonates and high-impact polystyrene, as well as back coating for textiles (commercial furniture, automobile fabrics, carpets, etc.).

### *1.3 General considerations on exposure sources of PBDEs*

The worldwide demand for PBDEs in 2001 was estimated to be almost 70 000 tonnes (BSEF, 2003), with DecaBDE accounting for almost 80% of the total market. This is in comparison with an estimated production figure of 40 000 tonnes in 1990 (cited in de Wit, 2002). The major commercial product currently in use, as noted above, is the DecaBDE formulation, which accounts for over 80% of the total market demand. From a regional perspective, the Western Hemisphere and Asia represent the largest users of PBDEs (85% of market), with almost 95%

of the PentaBDE total of 7500 tonnes used in the Americas. The Organisation for Economic Co-operation and Development (OECD) classifies PBDEs as high production volume chemicals (annual production of greater than 1000 tonnes). Main sources of PBDE input to the environment include emissions from manufacturing and production facilities (air and surface waters) and release during the life cycle of consumer products treated with PBDEs (degradation, recycling, disposal). For example, it has been estimated that up to 43 tonnes of PentaBDE per year are released to the environment in Europe by volatilization from polyurethane foam used in a variety of consumer products (Prevedouros et al., 2004). Airborne emissions of lower brominated PBDE congeners (up to hexa-substituted) are expected to exist in both the vapour and particulate phases and therefore be subject to long-range atmospheric transport processes. An additional source of PBDEs entering the environment is the use of municipal sewage treatment sludge as fertilizer (Hale et al., 2001; Öberg et al., 2002). Based on their low vapour pressure and high log octanol–water partition coefficients (log $K_{ow}$ range of 5.0–9.9), PBDEs are expected to strongly adsorb to soil and suspended organic material in the water column, facilitating their transfer to aquatic organisms. Current abiotic and biotic PBDE residues, including those detected in food and human tissues, are typically dominated by a limited number of congeners, namely BDE-47, BDE-99, BDE-153 and BDE-100. Environmental monitoring programmes have documented the ubiquitous nature of PBDE contamination, including increased temporal trends in sediments, biota and humans (Hites, 2004).

## 2. BIOLOGICAL DATA

### 2.1 Biochemical aspects

#### 2.1.1 Absorption, distribution, metabolism and excretion

*(a) Introduction*

A large amount of information is available on the occurrence of PBDEs in wildlife and human biological matrices, such as blood and milk. However, specific information about uptake, distribution, metabolism and excretion of PBDEs in experimental animals is significantly less than what is known about structurally related chlorinated biphenyls (PCBs) and dibenzo-*p*-dioxins (PCDDs). Nevertheless, the number of experimental studies done with rodents and PBDEs allows us to draw some conclusions regarding the fundamental toxicokinetic and metabolic aspects of this type of flame retardant. Recently, several detailed review papers dealing with these aspects have been published, and this section contains much information that has already been presented in these publications (Darnerud et al., 2001; de Wit, 2002; Hakk & Letcher, 2003; Gill et al., 2004). In addition, this information has been cross-checked with the very recent European Union (EU) risk assessment reports for octaBDE and decaBDE (EU, 2001, 2003, 2004) and, if applicable, adjusted and updated. Although several PBDEs accumulate in wildlife, including fish and invertebrates, and can enter the human food-chain through this pathway, this section deals only with the mammalian toxicokinetics and metabolism of these compounds, mainly derived from laboratory studies.

*(b) Uptake*

The toxicokinetics and metabolism of one of the most persistent PBDEs, BDE-47, have been studied in rats and mice (Örn, 1997; Örn & Klasson-Wehler, 1998).

A significant part (86%) of the oral administered dose in rats was retained in the body of male Sprague-Dawley rats 5 days after administration of a single gavage dose of 14.4 mg/kg bw. The highest concentration was found in adipose tissue and consisted mainly of the parent compound. In addition, only the parent compound could be detected in most other lipid-rich tissues, with the exception of liver and plasma, in which trace amounts of hydroxylated metabolites were also found (Örn & Klasson-Wehler, 1998). A similar absorption value was seen when female C57BL/6J mice ($n$ = 4–6) were given a single oral dose (gavage) of BDE-47 (0, 0.1, 1.0, 10.0 or 100 mg/kg bw). Based on excreta analysis 1 day following dosing, over 80% of BDE-47 was shown to be absorbed (Staskal et al., 2005).

In adult male Sprague-Dawley rats ($n$ = 3–4) exposed to a single oral dose of BDE-99 (15 µmol/kg bw or 8.5 mg/kg bw), analysis of urine and faeces indicated that approximately 82% of the original dose was retained after 24 h (Klasson-Wehler et al., 2001).

Except for decaBDE, no toxicokinetic studies have been performed with individual PBDEs that allow identification of the absorption rate from the gastrointestinal tract. However, a few studies have been done with technical mixtures that identified the absorption of either total PBDEs or a distinct isomeric group. In two studies, the gastrointestinal absorption of various PBDEs present in the technical mixtures DE-71, a commercial pentaBDE product dominated by BDE-47 and BDE-99), and DE-79 (dominated by hexa- through nonaBDE congeners) was determined in male Sprague-Dawley rats that were fed for 21 days with 33 ng/day each. Based on tissue analysis at day 21, the minimal absorption of the PBDE mixture in DE-71 and DE-79 was estimated to be 36.7% and 32.3% of the dose, respectively (Hakk et al., 2001; Huwe et al., 2002).

Several experimental studies with rodents have addressed the bioavailability of decaBDE. Absorption of the fully brominated congener from the gastrointestinal tract appears to be very low compared with that of the lower brominated PBDEs, as was estimated from analysis of excretions (urine and faeces), which ranged between 90% and >99% a few days after oral dosing (Norris et al., 1975a; NTP, 1986; el Dareer et al., 1987; Mörck & Klasson-Wehler, 2001). In addition to its low bioavailability, it was also observed that intestinal absorption of decaBDE in male rats did not depend on the dietary concentration over 2 orders of magnitude (0.025–5.0%) (NTP, 1986; el Dareer et al., 1987). In contrast with these earlier studies, very recent rat studies by Mörck et al. (2003) have specifically addressed the bioavailability and metabolism of decaBDE. In these experiments, different solvents were used to maximize the solubility of this compound in the test vehicle. Solvents were dimethyl sulfoxide/peanut oil (50:50 mixture), anisole/peanut oil (30:70 mixture) and a solution of soya phospholipone/Lutrol (16:34 w/w) in water (concentration 0.11 g/l). Approximately 90% of the [$^{14}$C]decaBDE dose (3 µmol/kg bw or 2.9 mg/kg bw) was excreted by male Sprague-Dawley rats via the faeces

within 3 days. These specific experiments showed that absorption of decaBDE can be at least 10%. In additional experiments, it was suggested that this bioavailability could be even higher (Sandholm, 2003; Sandholm et al., 2003), and 26% was recently suggested for risk assessment purposes (EU, 2001, 2004). Oral administration of a single dose of BDE-209 (2 µmol/kg bw) in a combination dimethylamide/polyethylene glycol/water (4:4:1) vehicle to male Sprague-Dawley rats indicated that a maximum plasma concentration of 264 pmol/ml was reached approximately 6 h after dosing. The estimated bioavailability was 26% (Sandholm et al., 2003). The question remains if these special vehicle formulations in the latter experiments are representative of the real-life uptake situation of decaBDE for humans, when compared with the much lower absorptions found in earlier animal studies using administration through the diet.

The majority of results from these experiments suggest that intestinal uptake of decaBDE is not efficient when administered in the diet; consequently, this congener is expected to have a low bioaccumulation potential (Darnerud et al., 2001; Hakk & Letcher, 2003). However, these experiments also showed that absorption from the intestinal tract after oral exposure may display a dosing vehicle dependency. The bioavailability of representative PBDEs, as a function of excretion, is given in Table 2 (Hakk & Letcher, 2003).

Besides uptake from the gastrointestinal tract, percutaneous absorption has also been addressed in two recent EU risk assessment studies for octa- and decaBDE (EU, 2001, 2003, 2004). Although no information is available about the percutanous absorption of penta-, octa- or decaBDE, the authors refer to the physicochemical properties of PCBs, which are assumed to be similar to those of PBDEs. For these types of lipophilic compounds, it is assumed that the stratum corneum is the crucial barrier and the rate-limiting step in the uptake. This will determine i) diffusion into and through the lipid-rich intercellular matrix of the stratum corneum or ii) diffusion out of the stratum corneum into and through the relatively aqueous viable epidermis below. This process depends on the lipophilicity or lipid solubility of the compound (Jackson et al., 1993). In view of these considerations and given the physicochemical properties of octaBDE — a high log $K_{ow}$ (6.29), poor water solubility (<0.5 µg/l) and high relative molecular mass (801) — the dermal absorption is expected to be low and estimated to be 4.5%. Using a similar approach for decaBDE and data from studies with PCBs (Garner & Matthews, 1998), a percutaneous absorption of a maximum of 1% is estimated for this compound. However, in spite of the low estimated percutaneous absorption for octa- and decaBDE, the EU risk assessment studies (EU, 2001, 2003, 2004) suggested that the percutaneous absorption may be associated with a likely trend towards accumulation in the stratum corneum, which by itself might behave as a storage site (Leung & Paustenbach, 1994). Analogous with PCBs, it is postulated that this could lead to a slow systemic release over time (EU, 2001, 2003). With respect to this suggested role of the stratum corneum, it should, however, be noted that at present, there is no indication that this actually occurs for either the octa- or decaBDE congeners in humans.

***Table 2. Excretion and bioavailability results from studies in rats administered various PBDE congeners***

| | Percentage of administered dose | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Male SD rat, 14.46 mg/kg po, 5 days, BDE-47 | Male SD rat, 8.1 mg/kg po, 72 h, BDE-99 | Male SD rat, 9.2 mg/kg po, 72 h, BDE-99 | Male SD rat, 1.09 mg/kg po, 16 days, BDE-209 | Male F344 rat, 0.0277% diet, days 1–7, 9–11 cold BDE-209, at 8 days $^{14}$C BDE-209 | Male F344 rat, 4.8% diet, days 1–7, 9–11 cold BDE-209, at 8 days $^{14}$C BDE-209 | Male F344 rat, 1.07 mg/kg iv, 72 h, BDE-209 | Male SD rat, 3.0 mg/kg po, 72 h, BDE-209 |
| *Urine* | <0.05 | 0.9 | 0.35 | <1.0 | 0.012 | 0.008 | 0.129 | <0.05 |
| *Faeces* | | | | | | | | |
| Day 1 | 5.7 | 22.3 | 52.5 | 90.6 | | | | |
| Day 2 | 5.4 | 14.8 | 30.4 | >8.4 | | | | |
| Day 3 | 1.2 | 6.0 | 3.6 | – | | | | |
| Day 4 | 0.9 | – | – | – | | | | |
| Day 5 | 0.5 | – | – | – | | | | |
| Total | 13.7 | 43.1 | 86.5 | >99 | 82.5 (0–72 h) | 85.1 (0–72 h) | 70.0 | >90 |
| *Bile* | | | | | | | | |
| Day 1 | | | 0.7 | | | | | |
| Day 2 | | | 1.8 | | | | | |
| Day 3 | | | 1.4 | | | | | |
| *Total* | | | 3.9 | | | | | 9.5 |
| References[a] | [1] | [2] | [2] | [3] | [4] | [4] | [4] | [5] |

From Hakk & Letcher (2003)

iv, intravenous; po, per os (by mouth)

[a] [1] Örn & Klasson-Wehler (1998); [2] Hakk et al. (2002); [3] Norris et al. (1975b); [4] el Dareer et al. (1987); [5] Mörck & Klasson-Wehler (2001).

*(c) Tissue distribution*

The tissue distribution of a variety of lower and higher brominated PBDEs has been studied in rats and mice. Studies with BDE-47 and rodents have shown that adipose tissue is the major storage site in the body, but concentrations on a lipid-adjusted basis were comparable for adipose tissue, liver, lung and kidney. This study also showed a marked species difference between rat and mice in tissue retention. In rats, 86% of a single oral dose (approximately 14.6 mg/kg bw) was retained in the body 5 days following dosing, while for mice, it was 47%. In addition, the radioactivity was about 3 times higher in the adipose tissue of the rat than in liver, while levels in both tissues in the mice were comparable (Örn & Klasson-Wehler, 1998). When female C57BL/6J mice were dosed by gavage with BDE-47 (single dose, 0.1–100 mg/kg bw), the tissue distribution determined 5 days later was mainly based on lipid content. Adipose tissue had the highest concentration (8–14% of dose), followed by skin, liver and muscle (0.9–2.6%) (Staskal et al., 2005).

A similar body distribution has been observed for BDE-99, with preference for the lipid-rich tissues, including adipose tissue, adrenals, gastrointestinal tract and skin, which contained more than 50% of the dose after 72 h (Hakk et al., 2002). Using whole-body autoradiography, the distribution of $^{14}$C-labelled BDE-47, BDE-85 and BDE-99 was determined in C57BL mice. Shortly after efficient uptake from the gastrointestinal tract, radioactivity for these congeners was highest in the adipose tissue, liver, adrenals, ovaries, lung and brain. In most tissues, the concentrations decreased significantly after a longer post-injection time, but radioactivity was present longest in white and brown adipose tissue. For these PBDE congeners, transfers to the fetus and to the offspring via the milk were also studied in mice. It was found that there was a low fetal uptake, with no significant differences between the three PBDEs. However, a significant maternal transfer via the milk of approximately 20% of the administered dose was found for BDE-85 and BDE-99 in the suckling offspring after 4 days. At this time, plasma levels in the neonates were more than 2 times those of the mothers (Darnerud & Risberg, 2005).

For other higher brominated PBDEs, such as octa-substituted congeners, there are no detailed toxicokinetic studies available that would allow specific conclusions about tissue retention and accumulation to be drawn (EU, 2001, 2003, 2004).

A number of older studies conducted during the 1970s by the Great Lakes Chemical Company with octaBDE have been recently evaluated in the EU risk assessment report (EU, 2003). Four weeks after dietary treatment with 100 or 1000 mg/kg of a commercial octaBDE mixture (8 or 88 mg/kg bw per day, respectively), a dose-related increase in total bromine content in the liver was reported in Charles River CD rats. These levels were 6–40 times higher than those found in controls. There was a slow decline of bromine levels in the tissues, indicating some capacity for bioaccumulation after repeated exposure at both doses. Since only total bromine content was determined, it is not known if the retained bromine represented parent compounds and/or metabolites.

A 2-year dietary accumulation study was done with rats that received technical decaBDE (77.4% decaBDE, 21.8% nonaBDE and 0.8% octaBDE) at doses of up to approximately 1.0 mg/kg bw per day. A variety of tissues were analysed (serum, liver, kidneys, skeletal muscle and testes); in most, bromine content was not above background (control values). In the adipose tissue, there was a dose- and time-dependent increase in bromine levels observed in rats ingesting decaBDE at 0.1 and 1.0 mg/kg bw per day. In the 0.1 mg/kg bw per day dose group, the bromine concentration was 3-fold higher than that of controls. The bromine content in the adipose tissue did not change during a recovery period of 90 days, which is in contrast to the liver, in which the bromine was eliminated within 10 days following the end of dosing (Kociba et al., 1975). In another study, the tissue retention of decaBDE after a single oral dose of 1 mg/kg bw was studied in female Sprague-Dawley rats 16 days after dosage. Based on radioactivity, measurable levels were found only in the adrenal glands (0.01% of the dose) and spleen (0.06% of the dose), but not in any other tissues (Norris et al., 1973, 1975a).

Viberg et al. (2003b) recently investigated the tissue retention of decaBDE in neonatal NMRI mice. After a single oral dose of $^{14}$C-labelled decaBDE (purity >98%; 1500 kBq/kg bw or approximately 13.8 nmol/kg bw) on postnatal days 3, 10 or 19 ($n$ = 4–7), low levels of radioactivity were detected in the brain, heart and liver 24 h and 7 days after dosing. Results from this study show that $^{14}$C label was taken up into the brain at 1% or less of the administered dose and that there were age-dependent differences in retention of $^{14}$C label in the brain (greater amounts on days 3 and 10 of dosing compared with day 19). Based on $^{14}$C radioactivity only, it cannot be concluded if this is parent decaBDE or one or more of its metabolites (Viberg et al., 2003b). In response to this paper, Vijverberg & van den Berg (2004) pointed to some inconsistencies regarding calculations in tissue retention and brain levels in these mice, which were estimated to be approximately 3 orders of magnitude higher than the highest levels of decaBDE found in humans.

Thus, with respect to the bioaccumulation potential of PBDEs, it can be concluded that there is definitely significant potential for some of the lower brominated congeners, such as BDE-47, BDE-99 and BDE-154, to bioaccumulate. However, the bioaccumulation potential of the higher brominated congeners, especially that of decaBDE, appears to be low, although measurable low concentrations in lipophilic tissues and blood of decaBDE can occur in humans (Hakk & Letcher, 2003; Sjödin et al., 2003).

In Table 3, the retentions of different PBDE congeners in the rat are summarized (Hakk & Letcher, 2003).

*(d) Metabolism*

The metabolism of only a very limited number of PBDE congeners, primarily BDE-47, BDE-99 and BDE-209, has been studied in some detail. Information regarding this metabolism has been recently summarized by Darnerud et al. (2001) and Hakk & Letcher (2003).

***Table 3. Tissue recoveries from male rats administered various PBDE congeners***

| | Male SD rat, 8.1 mg/kg po, 72 h, BDE-99 | Male SD rat, 9.2 mg/kg po, 72 h, BDE-99 | Male SD rat, 1.09 mg/kg po, 16 days, BDE-209 | Male F344 rat, 0.0277% diet, days 1–7, 9–11 cold BDE-209, at 8 days $^{14}$C BDE-209 | Male F344 rat, 4.8% diet, days 1–7, 9–11 cold BDE-209, at 8 days $^{14}$C BDE-209 | Male F344 rat, 1.07 mg/kg iv, 72 h, BDE-209 | Male SD rat, 2.0 mg/kg po, 72 h, BDE-209 |
|---|---|---|---|---|---|---|---|
| Liver | 0.9 | 0.3 | | 0.109 | 0.016 | 4.27 | 0.9 |
| Kidney | 0.1 | 0.03 | | 0.013 | <0.001 | 0.697 | 0.05 |
| Lungs | 0.1 | 0.04 | | 0.004 | 0.001 | 0.361 | <0.1 |
| Spleen | <0.1 | – | 0.06 | 0.001 | <0.001 | 0.027 | <0.1 |
| Pancreas | – | – | – | – | – | – | – |
| Adrenals | 0.1 | 0.01 | 0.01 | – | – | – | <0.1 |
| Heart | 0.03 | 0.01 | | – | – | – | <0.1 |
| Brain | – | – | | <0.001 | <0.001 | 0.047 | – |
| GI | 6.1 | 1.5 | | 0.09 | 0.60 | 5.063 | 3.5 |
| Muscle | 0.7 | – | | 0.248 | 0.008 | 12.9 | 0.7 |
| Skin | 0.4 | – | | 0.136 | 0.036 | 7.25 | 0.4 |
| Fat | 3.8 | 0.8 | | 0.048 | 0.012 | 2.99 | 0.3 |
| Blood | 0.03 | 0.007 | | 0.026 | 0.006 | 0.763 | 0.05 |
| References[a] | [1] | [1] | [2] | [3] | [3] | [3] | [4] |

From Hakk & Letcher (2003)

GI, gastrointestinal tract; iv, intravenous; po, per os (by mouth)

[a] [1] Hakk et al. (2002); [2] Norris et al. (1975a); [3] el Dareer et al. (1987); [4] Mörck & Klasson-Wehler (2001).

*(i) BDE-47*

Studies with rats and mice have shown that hydroxylated metabolites of BDE-47 are the major metabolic products (Örn & Klasson-Wehler, 1998), with noticeable differences in metabolism and excretion between both species. No debromination products were found (Darnerud et al., 2001). The metabolism of this congener in the rat is rather slow, and the parent compound was the major residue found in all tissues, including liver, adipose tissue, brain, kidney and lung. Trace amounts (<1%) of $^{14}C$ radioactivity in the form of hydroxylated metabolites were detected in liver and lung. In the faeces of the rat, six metabolites were found, including five tentatively assigned as two *ortho*-OH-tetraBDE metabolites, one *meta*-OH-tetraBDE metabolite and two *para*-OH-tetraBDE metabolites. Results from this study suggest that *ortho*- and *para*-OH-metabolites can be formed in the rat as a result of an NIH shift, with evidence for arene oxide as an intermediate. In addition, a very small amount of thiol-tetraBDE metabolite was found in the faeces, but its assignment also remains tentative due to the absence of reference compounds (Örn & Klasson-Wehler, 1998). A similar experiment with mice showed that BDE-47 is metabolized faster in this species than in the rat, with formation of five mono-OH-tetraBDEs and two mono-OH-triBDEs. In addition, evidence was obtained that BDE-47 could be metabolized to reactive intermediates, as suggested by the presence of non-extractable radioactivity in several organs, including liver, lung and kidney (Örn & Klasson-Wehler, 1998).

*(ii) BDE-99*

The metabolism of this BDE has been reported from only one study (Hakk et al., 2002). Metabolism in the rat was low, resulting in slow excretion. Only small amounts of monohydroxylated metabolites of penta- and tetraBDEs were detected in the faeces. The presence of tetraBDE metabolites indicates that at least in the rat, debromination can occur in vivo. In the bile, mono- and dihydroxy-pentaBDEs as well as two thio-substituted pentaBDEs were found. For BDE-99, evidence for the formation of reactive intermediates was also found, as a significant amount of labelled compound was apparently covalently bound in the faeces and non-extractable.

*(iii) BDE-209 (decaBDE)*

This BDE congener has been the subject of detailed metabolism studies. Using $^{14}C$-labelled decaBDE, its metabolism was studied in conventional and bile duct-cannulated rats (Klasson-Wehler et al., 2001; Mörck & Klasson-Wehler, 2001). Following a single oral dose of $^{14}C$-labelled decaBDE (3 µmol/kg bw) administered to male Sprague-Dawley rats, approximately 22–45% of the radioactivity in the faeces found from day 1 to day 3 consisted of eight phenolic metabolites. Metabolites of BDE-209 in the faeces included debrominated mono-OH- and *ortho*-MeO-OH-BDEs (Klasson-Wehler et al., 2001; Mörck & Klasson-Wehler, 2001). The methyl ester group was probably introduced by a catechol-O-methyl transferase of an *ortho* catechol substrate, but the route of formation is not known (Hakk & Letcher, 2003). It was deduced that decaBDE is metabolized via an

oxidative debromination pathway due to the presence of debrominated dihydroxy-BDEs and that dehydroxylation always occurs on the same aromatic ring. This oxidation process likely produces an epoxide as an intermediate metabolite, with further metabolism to a diol, which could explain the observed metabolites. Debromination of decaBDE to other PBDEs does not appear to be a major metabolic pathway from a quantitative point of view, as trace amounts of only three nona-BDEs were found in the faeces. The formation of reactive intermediates cannot be excluded, as a significant amount of the radioactivity in the jejunum wall and liver was non-extractable. With respect to metabolism of decaBDE in the rat, it is noteworthy that in plasma at days 3 and 7, the levels of radioactivity were approximately 4 times higher in the phenolic fraction than in the neutral fraction. This indicates significant retention of the metabolites of decaBDE compared with the parent compound. The actual cause of the plasma retention of these decaBDE metabolites could not be determined, as the nature of these metabolites in the phenolic fraction is unknown. However, it was suggested by the authors that the high plasma concentrations of hydroxy-decaBDE metabolites could be caused by reversible binding of these metabolites to transthyretin (TTR), the thyroxine (T4) hormone transporting protein in rodents (Mörck et al., 2003).

It has also been suggested that extensive metabolism of decaBDE could occur in the gastrointestinal tract after oral administration in rats (el Dareer et al., 1987). However, it should be noted that after oral or intravenous administration of decaBDE, the occurrence of the same three metabolites was noted, independent of the route of administration. This indicates a distinct role for hepatic metabolism (EU, 2004).

In general, it can be concluded that decaBDE is metabolized faster than the more biologically persistent BDE-47 and BDE-99. Several metabolic products have been described, including phenolic, neutral, non-extractable, water-soluble and lipid-bound compounds, but no glutathione metabolites have been observed so far. Based on these metabolism studies, it can also be concluded that deca-BDE is not biotransformed to the lower, more persistent BDE-47 or BDE-99. However, the structure of the hydroxylated metabolites that are retained in plasma needs to be further elucidated in order to determine if these metabolites could possibly cause biological or toxicological effects (EU, 2004).

In Figure 2, an overview is given of the proposed metabolic pathways in the rat for BDE-47, BDE-99 and BDE-209 (Hakk & Letcher, 2003).

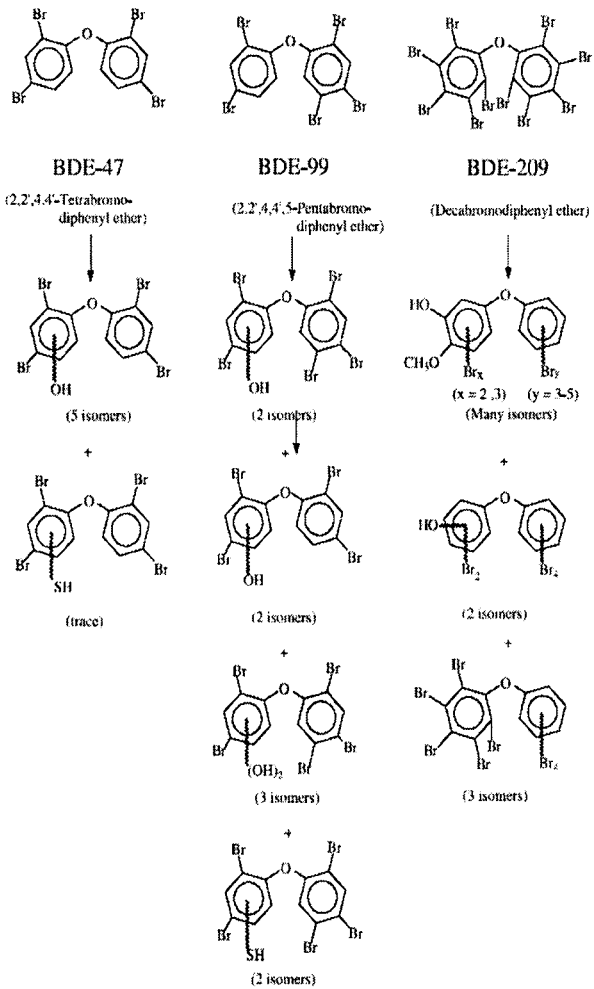
*(e) Elimination*

Information about congener-specific half-lives of PBDEs is scarce, while there are some limited data on commercial PBDE mixtures.

A toxicokinetic study using Bromkal 70, a commercial pentaBDE product, determined the elimination of tetra-, penta- and hexaBDEs in the rat. Wistar rats ($n$ = 4 per time point) were given a single oral Bromkal 70 dose of 300 mg/kg bw, and perirenal fat samples were analysed every week for 10 weeks. Half-lives depended on the degree of bromination (von Meyerinck et al., 1990) and are given

in Table 4. Congener-specific information was not provided in this study; however, based on detailed gas chromatographic–mass spectrometric (GC-MS) analysis of Bromkal 70 by Sjödin et al. (1998), the tetra congener was most likely BDE-47, the two penta congeners BDE-99 and BDE-100, and the two hexa congeners BDE-153 and BDE-154. Except for the proposed BDE-47 congener, no statistical difference was found between the sexes, and half-lives for the tetra- to hexaBDEs ranged between 25 and 91 days for females and between 19 and 119 days for males.

***Figure 2. Proposed metabolic pathways of BDE-47, BDE-99 and BDE-209 in the rat***




From Hakk & Letcher (2003)

It has been suggested (Hakk & Letcher, 2003) that the large oral dose administered in the latter study (300 mg/kg bw) was in great excess of the minimal dose required for induction of cytochrome P450 by Bromkal 70 (3–10 mg/kg bw). Therefore, it cannot be excluded that at lower environmental exposures, a different and lower elimination rate might occur. This suggestion would be in agreement with the results of a study done with male Sprague-Dawley rats orally administered a much lower dose of BDE-47 (14.5 mg/kg bw), in which only 14% and <0.5% of the dose were eliminated in faeces and urine, respectively, during the first 5 days (Örn & Klasson-Wehler, 1998). In the same experiment conducted with male C57BL mice and this PBDE congener, it was shown that this species is capable of eliminating BDE-47 more rapidly, with 33% of the dose excreted in the urine and 20% via the faeces during the first 5 days after dosage (Örn & Klasson-Wehler, 1998). A recent study by Staskal et al. (2005) determined the elimination kinetics and half-life of BDE-47 in female C57BL/6J mice. It was observed that excretion via the urine following a single oral dose of 0.1–100 mg/kg bw had a major influence on the initial whole-body half-life of 1.5 days. From a quantitative point of view, retention was stronger in lipophilic tissue such as adipose and skin. In these tissues, elimination followed a biphasic pattern, with initial half-lives between 1 and 3 days but much longer terminal half-lives (estimated by the authors to be 30–40 days in adipose), indicating the potential for bioaccumulation.

***Table 4. Half-lives of individual pentaBDE components in Wistar rats[a]***

| PentaBDE HPLC peak | Half-lives in female rats (days) | Confidence interval, $P$ = 0.05 | Half-lives in male rats (days) | Confidence interval, $P$ = 0.05 |
|---|---|---|---|---|
| $Br_4DE$ | 29.9 | 26.8–33.1 | 19.1* | 16.5–21.7 |
| $Br_5DE1$ | 47.4 | 42.5–52.4 | 36.8 | 33.7–40.0 |
| $Br_5DE2$ | 25.4 | 22.6–28.4 | 24.9 | 22.6–27.1 |
| $Br_6DE1$ | 44.6 | 37.4–51.9 | 55.1 | 48.4–61.7 |
| $Br_6DE2$ | 90.9 | 78.7–103.6 | 119.1 | 102.8–136.1 |

From von Meyerinck et al. (1990)

$Br_4DE$, tetraBDE; $Br_5DE1$, pentaBDE; $Br_5DE2$, pentaBDE; $Br_6DE1$, penta- and hexaBDE; $Br_6DE2$, hexaBDE; HPLC, high-performance liquid chromatography

* $P$ = 0.01 significant difference between sexes

[a] Single oral Bromkal 70 dose of 300 mg/kg bw dissolved in peanut oil. Groups of four rats were sacrificed consecutively until the 10th week. Concentrations of pentaBDE components in the perirenal fat were determined by HPLC, and data were corrected for the body weight of the rats.

The elimination of BDE-99 was studied in both bile-cannulated and uncannulated male Sprague-Dawley rats after an oral dose of 2.2 mg/kg bw (Hakk et al., 2002). Elimination via the faeces was the major route of excretion in both groups of rats. After 72 h, 43% of the administered dose in uncannulated and greater than

86% in cannulated rats were excreted in the faeces. This indicates a half-life in the rat of this compound of approximately 3 days or less.

Several studies have addressed the elimination of BDE-209 in the rat using different routes of administration. These studies indicated that decaBDE is metabolized faster than some lower brominated PBDEs, such as BDE-47. In several experiments, it was found that after oral dosage, 80–90% of the compound was eliminated via the faeces within 3 days (el Dareer et al., 1987; Mörck & Klasson-Wehler, 2001). The low intestinal absorption of decaBDE is thought to influence the fast elimination rates from the rat in these experiments. In male Sprague-Dawley rats ($n$ = 8) treated with a single oral dose of $^{14}$C-labelled decaBDE (3 µmol/kg bw, 555 GBq/mol), approximately 90% of the dose was eliminated via the faeces after 3 days (Mörck et al., 2003). Only a minor additional amount (1%) was eliminated after 7 days. An experiment with male Fischer rats using an intravenous BDE-209 dose of 1.07 mg/kg bw in rats showed that 74% of the dose was eliminated in the faeces within 72 h. These results indicate that the rat is capable of metabolizing this compound rather effectively (el Dareer et al., 1987). In occupationally exposed workers, the elimination of BDE-209 and BDE-183 was also estimated based on serum measurements. The estimated half-lives were 6.8 days for BDE-209 and 86 days for BDE-183 (Hagmar et al., 2000). These results indicate that the half-life for BDE-209 may be longer in humans than in rats, but the human half-life is still relatively short for such a highly halogenated aromatic compound compared with higher chlorinated biphenyls and dibenzo-*p*-dioxins.

### *2.1.2 Biochemical effects*

Darnerud et al. (2001) and de Wit (2002) recently summarized the possible hepatic enzyme induction by PBDEs.

Several studies have shown that commercial PBDE mixtures are capable of inducing phase I and phase II xenobiotic metabolizing enzymes. In Wistar rats and in rat hepatoma H4-IIE cells, Bromkal 70 was able to induce CYP1A1 and CYP1A2 as measured by increased activity of hepatic 7-ethoxyresorufin *O*-deethylase (EROD) activity (Hanberg et al., 1991; von Meyerinck et al., 1990). Hepatic enzyme induction has also been studied in female weanling Long-Evans rats with three technical PBDE mixtures, including DE-71 (tetra- and pentaBDEs), DE-79 (hepta- and octaBDEs) and DE-83R (98% decaBDE). In the rats treated with DE-71 (0.3–300 mg/kg bw per day for 4 days) and DE-79 (0.3–100 mg/kg bw per day for 4 days), a dose-dependent 10- to 20-fold induction in EROD and 30- to 40-fold induction in 7-pentoxyresorufin *O*-depentylase (PROD) were found, which indicates an induction of CYP1A1 and CYP2B by these technical PBDE mixtures (Zhou et al., 2001). Benchmark dose (BMD) estimates indicated that hepatic PROD induction was the more sensitive parameter for either DE-71 or DE-79 (0.54 and 0.40 mg/kg bw per day, respectively, for the 95% lower confidence limits). DE-83R had no effect on any measured hepatic enzyme.

In addition, other phase I enzyme activities, such as benzphetamine *N*-demethylase, *p*-nitroanisole demethylase, arylhydrocarbon hydroxylase and benzo[*a*]pyrene hydroxylase, have also been induced in vivo by technical penta- and

octaBDE mixtures in the rat (Carlson, 1980a, 1980b; von Meyerinck et al., 1990). However, decaBDE has been found to have a low enzyme-inducing potency. In Sprague-Dawley rats, the enzyme-inducing potency of BDE-47 has been compared with that of the commercial PCB mixture Aroclor 1254 (Hallgren & Darnerud, 1998). The induction of CYP1A1 (EROD) and 7-methoxyresorufin *O*-deethylase (MROD) by BDE-47 was limited and much lower than that observed in rats treated with equivalent doses of Aroclor 1254. In contrast, the inductions of CYP2B measured as PROD by BDE-47 and Aroclor 1254 were similar. Carlson (1980b) also specifically examined the hepatic enzyme induction of a commercial formulation of decaBDE. Although liver enlargement was found at a dose of 95 mg/kg bw per day (14-day dosing by gavage), no enzyme induction was observed for *O*-ethyl-*O*-*p*-nitrophenyl phenylphosphonothioate detoxification, *p*-nitroanisole demethylation, benzo[*a*]pyrene hydroxylase, uridine diphosphate glucuronosyltransferase (UDPGT), NADPH cytochrome *c* reductase and cytochrome P450. Thus, it can be concluded that at this relatively low dose of decaBDE, no hepatic enzyme induction occurs in male Sprague-Dawley rats.

Phase II enzyme induction by commercial PBDE mixtures containing various amounts of tetra-, penta-, hepta- and octabrominated congeners (14 days, 0.1 mmol/kg bw) has also been tested. With the exception of decaBDE, all of these compounds were capable of inducing prolonged UDPGT activity in rats (Carlson, 1980a). Short-term exposure (4 days) of weanling Long-Evans rats to commercial PBDEs (0.3–300 mg/kg bw per day) also produced significant induction of hepatic UDPGT activity by DE-71 and DE-79, albeit at higher doses than required for EROD and PROD induction (Zhou et al., 2001).

The issue of possible CYP1A1 induction by PBDE congeners is also highly relevant from a toxicological point of view. This type of cytochrome P450 induction is mediated via the aryl hydrocarbon (Ah) receptor, which has a high binding affinity for planar halogenated polyaromatics such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and some planar PCBs. In addition, it is also considered to be one of the most sensitive biological effects of these dioxin-like compounds (Safe, 1990). Thus, if some persistent PBDE congeners would cause induction of CYP1A1 activity, this might indicate that PBDEs could be considered in the toxic equivalency factor (TEF) concept for dioxin-like compounds (Van den Berg et al., 1998). To determine possible affinity for the Ah receptor, several in vitro studies with PBDEs have been performed using CYP1A1 (EROD) induction as an endpoint of Ah receptor-mediated biological activity. Some of the earlier studies indicated that the closely related chlorinated diphenyl ethers (PCDEs) can be weak inducers of CYP1A1 activities, depending on the number and position of the chlorine atoms (Chui et al., 1985; Howie et al., 1990; Safe, 1990; Rozman, 1991). However, in contrast with these studies, another study showed that polychlorinated dibenzofuran (PCDF) impurities lower than 1% could be responsible for the in vitro induction of EROD activity of almost all of the 29 tested PCDEs in H4IIE rat hepatoma cells (Koistinen et al., 1996). The results of the latter study are in agreement with the outcome of a quantitative structure–activity relationship (QSAR) study for binding to the Ah receptor by halogenated diphenyl ethers, which would predict that due to the non-planarity of these compounds, a low binding affinity to

the Ah receptor should exist (Gillner & Jakobsson, 1996). These results illustrate that even at low concentrations, these impurities can induce a considerable Ah receptor-mediated response, including the induction of some specific enzymes such as CYP1A1 (EROD) (Darnerud et al., 2004). In this respect, it is fair to conclude that at least in the studies using technical PBDE mixtures, the observed induction of CYP1A1 activities can very likely be attributed to the presence of known impurities in these technical formulations, such as brominated dibenzofurans. A few in vitro studies have also tested individual PBDE congeners for CYP1A1 induction or other Ah receptor-related activities. Using a recombinant rat hepatoma cell line H4IIE with a luciferase reporter gene, it was reported that several PBDE congeners might act as Ah receptor agonists, and the potencies were in the same range as those reported for some mono-*ortho* PCBs (Meerts et al., 1998). Another study with primary rat hepatocytes and individual PBDE congeners also reported congener-specific induction of both CYP1A1 messenger RNA (mRNA) and protein levels. BDE-77 and BDE-126 induced responses that were 3–5 orders of magnitude less than that of TCDD in this in vitro system. Although these PBDEs are not environmentally relevant, these results suggest that those congeners that most closely resemble TCDD or dioxin-like PCBs have the highest agonistic activity. In contrast, the environmentally common and persistent BDE-47 and BDE-99 were not active in inducing CYP1A1, which indicates no agonistic properties for the Ah receptor (Chen et al., 2001; Chen & Bunce, 2003). A recent study by Peters et al. (2004) more or less confirmed the latter results. After a rigorous cleanup of environmentally relevant PBDEs (BDE-47, BDE-99, BDE-100, BDE-153, BDE-183) for possible impurities with dioxin-like activities, no induction of CYP1A1 activity could be determined in three Ah receptor responsive cell lines — the rat hepatoma H4IIE, the human hepatoma HepG2 and breast carcinoma MCF7 cells — when tested at concentrations up to 10 µmol/l. Based on the combined results of these in vitro studies with PBDE congeners, it must be concluded that those PBDEs that are environmentally relevant and bioaccumulate do not possess dioxin-like activity. Interestingly, the latter three studies all reported antagonistic effects of PBDEs on Ah receptor-mediated activities, including CYP1A1 induction (Meerts et al., 1998; Chen & Bunce, 2003; Peters et al., 2004). This raises the question whether these antagonistic effects of PBDEs measured on this enzyme induction may also apply for toxicological end-points that are Ah receptor-mediated.

### *2.2 Toxicological studies*

The toxicity of PBDEs has been covered in several review books and articles (IPCS, 1994; Darnerud et al., 2001; de Wit, 2002; ATSDR, 2004; Gill et al., 2004). The present text on PBDE toxicity has been based on these compilations as well as on new results published thereafter.

#### *2.2.1 Acute toxicity*

Results of studies on the acute toxicity of PBDE commercial mixtures are summarized in Table 5.

*Table 5. Acute toxicity of PBDE commercial mixtures*

| Dosing regimen | Strain, species | End-point | Effects | $LD_{50}$ (oral) (mg/kg bw) | Reference |
|---|---|---|---|---|---|
| DecaBDE technical grade, single oral dose | SD rats, female | Mortality, gross pathological changes | No deaths | >2000 | Norris et al. (1975b) |
| DecaBDE technical grade, single oral dose | Spartan rats, male | Mortality, weight gain | No deaths | >5000 | Great Lakes (1974) |
| DE-79 (OctaBDE), single oral dose | Charles River rats, male | Mortality, weight gain | No deaths | >5000 | Great Lakes (1987, 1990) |
| Saytex 111 (OctaBDE), single oral dose | Rats, sex not specified | Mortality, weight gain, gross pathological changes | No deaths | >10 000 | Ethyl Corporation (1985) |
| PentaBDE, technical grade, single oral dose | Charles River rats, male | Mortality, weight gain | 5000 mg/kg bw: 4/5 dead; 0, 50, 500 mg/kg bw: no deaths | 500–5000 | Great Lakes (1975) |
| PentaBDE, technical grade, single oral dose | Rats, male and female | Mortality, weight gain, gross pathological changes | Decreased growth and activity, diarrhoea, postmortem effects, liver and stomach | male: 7400<br>female: 5800 | Great Lakes (1975) |
| Saytex 115 (PentaBDE), single oral dose | Rats, sex not specified | Mortality | Lack of information | 5000 | BIBRA (1977) |
| DE-71 (PentaBDE), single oral dose | Rats, sex not specified | Mortality | Lack of information | 6200 | PAI (1984) |
| Bromkal 70 (PentaBDE), single oral dose | Wistar rats, male | Liver weight and microsomal enzyme content/ activity | Induction of EROD at threshold dose 3 mg/kg bw | – | von Meyerinck et al. (1990) |

*(a) DecaBDE*

*(i) Rat*

In female Sprague-Dawley rats ($n$ = 5), gastric intubation of a single DecaBDE (77.4% decaBDE congener, 21.8% nonaBDE congeners, 0.8% octaBDE congeners; in 10% corn oil suspension) dose of 0, 126, 252, 500, 1000 or 2000 mg/kg bw did not result in any indication of toxicity or gross pathological changes during a 14-day observation period (Norris et al., 1975b).

In male Spartan rats ($n$ = 5) receiving DecaBDE at up to 5000 mg/kg bw by a single gavage dose in corn oil suspension, no deaths occurred, and the weight gain was normal during a 14-day observation period (Great Lakes, 1974).

*(b) OctaBDE*

*(i) Rat*

Male Charles River CD rats ($n$ = 5) were intubated with a single dose of OctaBDE (DE-79; in corn oil suspension) at 0, 50, 500 or 5000 mg/kg bw, followed by an observation period of 14 days. The rats showed normal weight gain, and no mortality was observed (Great Lakes, 1987, 1990).

Rats were intubated with a single dose of Saytex 111, a PBDE mixture containing several congeners from penta- to decaBDE, of which the hepta- and octaBDEs are most abundant (45% and 34% of all congeners, respectively), at 0, 500, 2500, 7500 or 10 000 mg/kg bw in corn oil and studied for effects during a 72-h period (Ethyl Corporation, 1985). None of the animals died during this study, and no signs of toxicity were observed immediately after the dosing period. No effect on weight gain and no gross pathological changes were observed. The $LD_{50}$ was greater than 10 000 mg/kg bw.

Acute oral $LD_{50}$ doses for OctaBDE in rats were reported to be >28 g/kg bw (Kalk, 1982).

*(c) PentaBDE*

*(i) Rat*

Groups of male albino Charles River CD rats ($n$ = 5) were given PentaBDE at 0, 50, 500 or 5000 mg/kg bw by gavage in corn oil and observed for 14 days. The rats receiving 50 and 500 mg/kg bw survived and had normal body weight gain, whereas four of five rats dosed with 5000 mg/kg bw died within 5 days. The remaining rats survived and had a normal weight gain (Great Lakes, 1975).

Groups of male and female Wistar rats ($n$ = 5) were given PentaBDE in single doses of 0, 2400, 4800, 7621 or 9600 mg/kg bw (in corn oil) and subsequently observed for 44 days. From this study, the estimated $LD_{50}$ was 7400 mg/kg bw for male rats and 5800 mg/kg bw for female rats. Observed symptoms included decreased growth, diarrhoea, piloerection, reduced activity, tremors of the forelimbs, red staining around eyes and nose and a continual chewing movement of

the jaws. Examination postmortem showed enlarged, mottled and necrotic livers and multiple small ulcers of the gastric mucosa (Great Lakes, 1975).

Single-dose oral $LD_{50}$ values for PentaBDE, in studies with rats during 14 days of observation, were reported to be 5000 mg/kg bw (BIBRA, 1977) and 6200 mg/kg bw (PAI, 1984) for Saytex 115 and DE-71, respectively.

Male Wistar rats ($n$ = 3) were administered a single oral Bromkal 70 dose of 0, 3, 10, 30 or 100 mg/kg bw and killed 3 days after dosing (von Meyerinck et al., 1990). The Bromkal 70 treatment increased the relative liver weight, the content of cytochrome P450 and the activity of microsomal liver enzymes in a dose-dependent manner. The EROD activity was induced at the lowest dose tested, 3 mg/kg bw, which the authors concluded was the threshold dose for induction of this enzyme.

*(d) BDE congeners*

No information is available on the acute toxicity of any specific BDE congeners.

### 2.2.2 Short-term studies of toxicity

Studies on the short-term toxicity of PBDEs are summarized in Table 6.

*(a) DecaBDE*

*(i) Mouse*

In an oral 14-day study, groups of B6C3F1 mice ($n$ = 5, both sexes) were exposed to BDE-209 in the diet at concentrations of 0, 5, 10, 20, 50 or 100 g/kg diet. No effects were observed on health, survival or body weights, and no compound-related clinical signs or gross pathological effects were reported (NTP, 1986).

A 13-week study was performed in which B6C3F1 mice of both sexes ($n$ = 10) were given DecaBDE (two different lots: >97% and 99% purity, respectively) in the diet at concentrations of 0, 3.1, 6.2, 12.5, 25 or 50 g/kg diet. No evidence was found for compound-related effects on the studied parameters, including body weight gain, survival, physical appearance and gross and microscopic pathology (NTP, 1986).

*(ii) Rat*

In a 14-day study, DecaBDE was administered in the diet to Fischer 344/N rats of both sexes ($n$ = 5) at doses of 0, 5, 10, 20, 50 or 100 g/kg diet. No compound-related clinical signs or gross pathological effects were observed (NTP, 1986).

In 28-day feeding studies with Charles River CD rats ($n$ = 10, both sexes, three separate studies), DecaBDE was given in the diet at doses of 0, 100 or 1000

mg/kg. In these studies, adverse effects or lesions associated with DecaBDE administration were not found (observation of appearance, mortality, food consumption, body weight gain, organ weights, gross pathological and microscopic examination) (Great Lakes, 1974).

***Table 6. Short-term toxicity data for PBDEs***

| Dosing regimen | Species, strain, sex | End-point | NOEL[a] | LOEL | Reference |
|---|---|---|---|---|---|
| DecaBDE, technical grade, in diet, 14 days | Mice, B6C3F1, both sexes | Survival, body weight, clinical and gross pathology | 100 g/kg diet<br>males: 13.3 g/kg bw<br>females: 15.6 g/kg bw | >100 g/kg diet | NTP (1986) |
| DecaBDE, technical grade, in diet, 13 weeks | Mice, B6C3F1, both sexes | Survival, body weight gain, gross/ microscopic pathology | 50 g/kg diet<br>males: 6.65 g/kg bw<br>females: 7.78 g/kg bw | >50 g/kg diet | NTP (1986) |
| DecaBDE, technical grade, in diet, 14 days | Rats, Fischer 344/N, both sexes | Clinical signs, gross pathology | 100 g/kg diet<br>males: 4.5 g/kg bw<br>females: 5.1 g/kg bw | >100 g/kg diet | NTP (1986) |
| DecaBDE, technical grade, in diet, 28 days | Rats, Sprague-Dawley, male | Liver enlargement, thyroid hyperplasia | 8 mg/kg bw per day | 80 mg/kg bw per day | Norris et al. (1973, 1975b) |
| DecaBDE, technical grade, in diet, 90 days | Rats, Fischer 344/N, both sexes | Liver enlargement, male rats | 12.5 g/kg diet<br>males: 560 mg/kg bw<br>females: 600 mg/kg bw | 25 g/kg diet<br>males: 1120 mg/kg bw<br>females: 1200 mg/kg bw | NTP (1986) |
| OctaBDE, technical grade, in diet, 28 days | Rats, Charles River, both sexes | Liver enlargement and histo-pathology | – | 100 mg/kg diet | Great Lakes (1987) |
| OctaBDE, technical grade, in diet, 28 days | Rats | Liver histo-pathology lesions | – | 100 mg/kg diet | Great Lakes (1975) |

*Table 6.* (contd)

| Dosing regimen | Species, strain, sex | End-point | NOEL[a] | LOEL | Reference |
|---|---|---|---|---|---|
| OctaBDE, technical grade, in diet, 30 days | Rats, Sprague-Dawley, male | Liver enlargement, thyroid hyperplasia, histology liver and kidney lesions | – | 8 mg/kg bw per day | Norris et al. (1975b) |
| OctaBDE, technical grade, in diet, 13 weeks | Rats, Sprague-Dawley, both sexes | Increased liver weight, microscopic hepatic changes | – | 8 mg/kg bw per day | Great Lakes (1987) |
| DE-71 (PentaBDE), single or repeated gavage | Mice, C57BL, female | Relative liver and thymus weight (thyroid effects reported separately) | 36 mg/kg bw per day (14 days) | 72 mg/kg bw per day (14 days) | Fowles et al. (1994) |
| PentaBDE, technical grade, in diet, 28 days | Rats, Charles River CD, both sexes | Increased liver weight, liver lesions | – | 10 mg/kg bw per day | Great Lakes (1975) |
| DE-71 (PentaBDE), repeated gavage, 28 days | Rats, Sprague-Dawley, both sexes | Increased liver weight, increased seum glucose and cholesterol levels, decreased LDH levels (thyroid effects reported separately) | 5 mg/kg bw per day | 25 mg/kg bw per day | Rowsell et al. (2004) |
| DE-71 (PentaBDE), in diet, up to 90 days | Rats, Sprague-Dawley, both sexes | Decreased food consumption and body weight, increased cholesterol levels | 10 mg/kg bw per day | 100 mg/kg bw per day | Great Lakes (1975) |
| | | Relative liver weight increase | 2 mg/kg bw per day | 10 mg/kg bw per day | |

*Table 6.* (contd)

| Dosing regimen | Species, strain, sex | End-point | NOEL[a] | LOEL | Reference |
|---|---|---|---|---|---|
| (contd) | | Slight liver cell degeneration and necrosis (females) | – | 2 mg/kg bw per day | |
| Bromkal 70-5-DE (PentaBDE), repeated gavage, 14 days | Rats, Sprague-Dawley, female | Decreased hepatic vitamin A levels | – | 18 mg/kg bw per day | Hallgren et al. (2001) |
| Bromkal 70-5-DE, gavage, 28 days | Rats, Sprague-Dawley, both sexes | Decreased hepatic vitamin A levels, increased hepatic EROD activity | 2.5 mg/kg bw per day | 25 mg/kg bw per day | Fattore et al. (2001) |

EROD, 7-ethoxyresorufin *O*-deethylase; LDH, lactate dehydrogenase; LOEL, lowest-observed-effect level; NOEL, no-observed-effect level

[a] For the NTP (1986) studies, per kg bw daily intake estimations are based on body weight and feed intake data as indicated in the reference.

Male Sprague-Dawley rats ($n$ = 5) were given diets consisting of 0, 0.01, 0.1 or 1% DecaBDE for 30 days (roughly equivalent to 0, 8, 80 or 800 mg/kg bw per day). The DecaBDE product contained 77% deca, 22% nona and some extent of octa congeners. Food intake and body weight gain were not different between the groups. No difference was noted in heart, testes, brain and kidney weights or in haematology and urinalysis parameters. The livers of rats receiving DecaBDE at 80 and 800 mg/kg bw per day were enlarged, and liver lesions consisted of centrilobular cytoplasmic vacuolization (at 800 mg/kg bw per day). In addition, degenerative changes in the kidney (at 800 mg/kg bw per day) and thyroid hyperplasia (at 80 and 800 mg/kg bw per day) were found (Norris et al., 1973, 1975a, 1975b).

No toxic effects were observed in a 90-day study with Fischer 344/N rats of both sexes ($n$ = 10) when DecaBDE (containing >97% BDE-209) was given in the diet (0, 3.1, 6.2, 12.5, 25 or 50 g/kg diet), but increased liver weight was suggested in male rats consuming the two highest doses (NTP, 1986).

*(b) OctaBDE*

*(i) Rat*

Charles River CD rats (both sexes, $n$ = 10) were given OctaBDE in the diet at various concentrations for 28 days. In sub-study I, the dietary doses were 0, 100

or 1000 mg/kg diet. Most studied parameters did not change between the groups. However, liver weights (both absolute and relative) were significantly increased in female rats at 100 mg/kg and in rats of both sexes at 1000 mg/kg. Moreover, compound-related histopathological liver lesions, consisting of enlarged centrilobular and midzonal liver parenchymal cells containing eosinophilic "round bodies," were seen at both dose levels. The incidence and severity of the liver lesions were dose-related and more severe in the male animals. In addition, rats at the 1000 mg/kg dose exhibited hyperplasia of the thyroid, but it was unclear whether this effect was compound-related (Great Lakes, 1987).

In sub-study II with OctaBDE in rats, the doses were 0, 100, 1000 or 10 000 mg/kg diet. The control group consisted of 35 animals from a 90-day feeding study (see below). At the end of the 28-day study, five animals per group were sacrificed, whereas the other five were maintained on control diet for an additional 4 weeks. No changes in behaviour, appearance or mortality were seen. The food intake and weight gain were slightly higher in the control group than in the OctaBDE exposure groups. Serum urea nitrogen levels were slightly higher in some of the rats on the 10 000 mg/kg diet. Increases in absolute and relative liver weights were observed in rats given the 1000 and 10 000 mg/kg diets. The histopathology of liver from all three dose levels showed enlargement of the centrilobular and midzonal hepatocytes, with the presence of "round bodies" in cytoplasm. In the highest dose group, vacuolization of hepatocytes and necrosis of individual hepatocytes were seen. Generally, the liver lesions were less severe after the 4-week recovery period. In addition, an increase in bromine levels in the liver was seen in rats in all treated groups, but the levels decreased in the recovery period (Great Lakes, 1975).

In a 30-day study with male Sprague-Dawley rats given diets containing 0, 0.01, 0.1 or 1.0% OctaBDE (corresponding to 0, 8, 80 and 800 mg/kg bw per day), the authors reported liver enlargement, thyroid hyperplasia and histological lesions in liver and kidney (hyaline degenerative cytoplasmic changes) at all dose levels and decreased packed cell volume, decreased total red blood cell count and increased kidney weight at the highest dose level (Norris et al., 1973, 1975b).

The same strain of rat was given commercial OctaBDE in the feed at dietary levels of 0, 100, 1000 or 10 000 mg/kg for 13 weeks ($n$ = 35, male and female animals in separate dose groups) (Great Lakes, 1987). Behaviour, appearance, body weight and other important parameters were studied after 1 and 2 months and after 13 weeks, i.e. the end of the feeding period (five animals per sex per group). The remaining animals were studied 13 and 21 weeks and 6 months after withdrawal of the OctaBDE exposure. A few animals died during the study, but without any apparent dose relationship. In the 100 mg/kg diet group (corresponding to about 8 mg/kg bw per day), the only effect seen was an increase in absolute and relative liver weights, coupled to microscopic hepatic changes (granular cytoplasm) in some of the rats. At the 1000 mg/kg diet level (about 80 mg/kg bw per day), there was a decrease in body weight, in spite of normal blood chemistry, urine and haematology parameters. There was also an increase in absolute and relative liver and thyroid weights. Microscopic hepatic lesions (including vacuolization and hyaline inclusions) were observed in centrilobular and midzonal hepato-

cytes. After administration of the 10 000 mg/kg diet (about 800 mg/kg bw per day), the animals had a decrease in body weight gain, which persisted during the withdrawal period. Decreases in haemoglobin, haematocrit and erythrocyte counts were also observed, along with significant increases in the absolute and relative weights of the liver, kidney and thyroid. In the liver, autopsy revealed accentuated lobulation and yellowish mottling of the liver and brownish discoloration of the liver and kidney. After the recovery phase (1 year), no such changes were observed. Microscopic examination of the liver revealed granular cytoplasmic changes, cytoplasmic vacuolization, necrosis of parenchymal and centrilobular cells, centrilobular fibrosis and pigmented Kupffer cells. In the kidney, there was an occurrence of small to moderate numbers of cortical regenerative tubules, with one rat having severe tubular necrosis. In the thyroid, the observed cellular changes — a tall columnar epithelium instead of the normal cuboidal type (seen in 4/35 males and in 1/35 females at the highest dose) — were described by the authors as being compound-related. The observed histological changes decreased in severity and frequency during the recovery period. A hyperplastic nodule was found, after 6 months' withdrawal, in one rat from each of the 1000 and 10 000 mg/kg dose groups (Great Lakes, 1987).

*(c) PentaBDE*

*(i) Mouse*

In a study by Fowles and co-workers (Fowles et al., 1994) on immunological and endocrine effects of the PentaBDE mixture DE-71 in mice, organ and body weights were also measured. Female C57BL/6J mice ($n$ = 6) were dosed either once by gavage with DE-71 at 0, 0.8, 4, 20, 100 or 500 mg/kg bw or by repeated gavage at daily oral doses of 0, 18, 36 or 72 mg/kg bw during 14 days. After an undefined survival time, the animals were killed, and spleen, thymus, liver and body weights were measured. The relative liver weight was dose-dependently increased compared with controls following subchronic exposure. After acute exposure, the highest dose (500 mg/kg bw) gave a similar increase in relative liver weight. The relative thymus weight was increased only at the highest subchronic exposure (72 mg/kg bw per day for 14 days). Neither the relative spleen weights nor the absolute body weights were significantly changed following DE-71 treatment.

*(ii) Rat*

In a 28-day study, Charles River CD rats ($n$ = 10 per sex) were given PentaBDE in the diet at 0, 100 or 1000 mg/kg (roughly equivalent to 0, 10 and 100 mg/kg bw per day). Liver weights were significantly increased in female rats at 100 mg/kg diet and in both female and male rats at 1000 mg/kg diet. No gross pathological lesions were seen. Liver lesions were observed, were more prevalent in males and increased with dose. At the highest dose, a significant decrease in the relative weights of the pituitary and adrenal glands was observed. Microscopic studies revealed enlargement of parenchymal liver cells (centrilobular and midzonal) and the presence of granular structures and eosinophilic "round bodies" in

the cytoplasm at both dose levels. Hyperplasia of the thyroid was seen in both dose groups and in control animals. Therefore, whether these changes were considered compound-related is not clear (Great Lakes, 1975).

In a recent study (Rowsell et al., 2004), a 28-day gavage study was performed with a technical PentaBDE mixture (DE-71) mainly containing tetra- (46%) and penta- (49%) BDE congeners. Male and female Sprague-Dawley rats ($n$ = 10 per sex) were given daily doses by gavage of 0, 0.05, 0.5, 5 or 25 mg/kg bw in corn oil, and the animals were sacrificed on the 29th day. The liver and selected other organs were weighed, and a liver sample was taken for analysis of microsomal enzyme activities. Blood was collected, and serum chemistry analysis was performed for a number of parameters. In addition, serum was also analysed for total and free thyroid hormone levels — total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3) and free thyroxine (FT4). No clinical sign of toxicity was seen, and the growth rates between control and treated groups did not differ. Liver weights were increased in both males and females in the 25 mg/kg bw per day group. Hepatic microsomal enzyme induction (benzyloxyresorufin *O*-deethylase [BROD], EROD, PROD) was seen in animals from the two highest dose groups. TT4 and FT4 levels were significantly lower in the 25 mg/kg bw per day male and female groups. TT3, but not FT3, levels were significantly reduced in the 25 mg/kg bw per day males only. Regarding clinical chemistry, female animals in the highest dose group had significantly higher levels of serum cholesterol and increased levels of glucose. Both males and females in the highest dose group had decreased lactate dehydrogenase (LDH) levels ($P < 0.05$).

PentaBDE (DE-71) was given in the diet to Sprague-Dawley rats ($n$ = 30 per dose per sex) at dose levels of 0, 2, 10 or 100 mg/kg bw per day for a maximum of 90 days. The animals were killed after 4 weeks (10 per sex), 90 days (10), 90 + 6 weeks of recovery (5) and 90 + 24 weeks of recovery (5). Decreases in food consumption (highest dose, females) and body weight (highest dose, both males and females) were observed. No increased mortality or clinical effects were obvious. Increased cholesterol values were seen in the 100 mg/kg bw per day dose group animals, whereas T4 levels were decreased in animals exposed to 10 and 100 mg/kg bw per day. Relative liver weights were increased in the 10 and 100 mg/kg bw per day groups, but the remaining increase at 6 weeks of recovery had disappeared after 24 weeks of control diet. Urine and liver porphyrin levels were increased in the highest dose group after 90 days, the urine values being about 10 times higher and the liver levels almost 400 times higher than the control levels. Under microscopic examination, hepatocytomegaly and thyroid hyperplasia were seen, of which the thyroid effects were reversible after 24 weeks of recovery, but the liver effects partially persisted (slight hepatocytomegaly in the 10 and 100 mg/kg bw per day groups). After the 24-week recovery period, the lowest dose (2 mg/kg bw per day) resulted in slight liver cell degeneration and necrosis in female but not in male rats (Great Lakes, 1975).

Effects on vitamin A were followed in female Sprague-Dawley rats (approximately 175 g at start) after daily gavage of PentaBDE (Bromkal 70-5-DE; 0, 18 or 36 mg/kg bw per day) for 14 days (Hallgren et al., 2001). Twenty-four hours after the last gavage, the animals ($n$ = 8–12 per dose) were anaesthetized and killed by

exsanguination. Liver samples were collected and stored at −70 °C before vitamin A analysis. Results showed that Bromkal 70 exposure significantly decreased vitamin A levels at both doses (approximately 75% of control) and that the effects were seen irrespective of presenting results as concentrations or as amounts in whole liver. No dose relation in vitamin A effects could be observed. In female C57BL mice studied under the same experimental conditions, no obvious PBDE effects on hepatic vitamin A levels were observed.

*(d) BDE congeners*

No information is available on short-term toxicity of individual BDE congeners.

### *2.2.3 Long-term studies of toxicity and carcinogenicity*

The long-term toxicity/carcinogenicity studies on PBDEs are summarized in Table 7.

*(a) DecaBDE*

Rodent carcinogenicity bioassays have been carried out only for DecaBDE. A mouse study and a rat study have been reported by the United States National Toxicology Program (NTP, 1986), and a rat study has been conducted by the Dow Chemical Company (Kociba et al., 1975).

*(i) Mouse*

In the NTP mouse study (NTP, 1986), DecaBDE (purity 94–99%; no brominated dioxins or furans were found) mixed in diet was given to groups of 50 male and 50 female B6C3F1 mice for 103 weeks, and all the survivors were killed at 112–113 weeks of age. The concentration of DecaBDE in the diet was 0, 25 and 50 g/kg diet, with average daily exposure to DecaBDE estimated to be 3200 and 6650 mg/kg bw in low- and high-dose males and 3760 and 7780 mg/kg bw in low- and high-dose females, respectively. Body weight development and survival of DecaBDE-treated mice were comparable to controls. Stomach ulcers were reported at an increased incidence in high-dose female mice. Liver granulomas were observed in low-dose males, and liver hypertrophy was seen in low- and high-dose males. A significantly increased combined incidence of hepatocellular adenomas and carcinomas was observed in male mice (8/50 in controls, 22/50 in low-dose and 18/50 in high-dose males; trend not significant), whereas the combined incidences of thyroid follicular cell adenomas and carcinomas in males (0/50 in controls, 4/50 in low-dose and 3/50 in high-dose males) and females (1/50 in controls, 3/50 in low-dose and 3/50 in high-dose females) were only non-significantly increased. Furthermore, thyroid follicular cell hyperplasia was increased at both dose levels in males and females, and the response was stronger in male animals (high-dose males 19/50; high-dose females 7/49).

*Table 7. Chronic toxicity/carcinogenicity and reproductive/developmental toxicity*

| Dosing regimen | Species, strain, sex | End-point | Effect level | Reference |
|---|---|---|---|---|
| DecaBDE, technical grade, in diet, 103 weeks | Mice, B6C3F1, both sexes | Hepatocellullar adenoma/ carcinoma | Male: 8/50, 22/50, 18/50 | NTP (1986) |
| Dose: 0, 3200 mg/kg bw per day (LD), 6650 mg/kg bw per day (HD) | | Thyroid follicular cell adenoma/ carcinoma | Male: 0/50, 4/50, 3/50; female: 1/50, 3/50, 3/50 | |
| | | Thyroid follicular cell hyperplasia | Male HD: 19/50; female HD: 7/49 | |
| DecaBDE, technical grade (77% decaBDE congener), in diet, 100–105 weeks | Rats, Sprague-Dawley, both sexes | Tumour development, survival, body weight, clinical chemistry parameters | No observed toxic effects | Kociba et al. (1975) |
| Dose: 0, 0.01, 0.1, 1 mg/kg bw per day | | | | |
| DecaBDE, technical grade, in diet, 103 weeks | Rats, Fischer 344/N, both sexes | Liver adenoma | Male: 1/50, 7/50, 15/49 ($P < 0.001$ for trend); female: 1/50, 3/49, 9/50 ($P = 0.002$ for trend) | NTP (1986) |
| Dose: 0, 1120, 2240 mg/kg bw per day | | Pancreas adenoma | Male: 0/49, 0/50, 4/49 ($P = 0.017$ for trend) | |
| | | Hepatocellular carcinoma | No dose-related effect | |
| DecaBDE, technical grade, in diet, 60 days prior to mating to end of lactation | Rats, Sprague-Dawley, both sexes | Reproductive performance, pup maturation | No observed effects | Norris et al. (1975b) |
| DecaBDE, technical grade, oral gavage, GD 6–15 | Rats, Sprague-Dawley, pregnant | Increased frequency of resorptions | 10 mg/kg bw | Norris et al. (1975b) |
| | | Increased number of subcutaneous oedema and delayed ossification | 1000 mg/kg bw | |
| DecaBDE, technical grade, oral gavage, GD 0–19 | Rats, Sprague-Dawley, pregnant | Maternal toxicity, fertility, gestation or fetal development | No observed effects | Hardy et al. (2002) |

***Table 7.*** (contd)

| Dosing regimen | Species, strain, sex | End-point | Effect level | Reference |
|---|---|---|---|---|
| DE-79 (OctaBDE), oral gavage, GD 6–15 | Rats, Charles River COBS CD, pregnant | Fetus: reduced weight, oedema, reduced ossification, bent rib bones | 50 mg/kg bw (NOEL 15 mg/kg bw) | Great Lakes (1986) |
| | | Mother: Reduced weight gain | 50 mg/kg bw (NOEL 25 mg/kg bw) | |
| Saytex 111 (OctaBDE), oral gavage, GD 6–15 | Rats, Charles River SD, pregnant | Fetus: Body weight | 10 mg/kg bw (dose dependent) | US EPA (1986) |
| | | Delayed ossification, fetal malformations | 25 mg/kg bw | |
| | | Mother: Reduced weight gain | 25 mg/kg bw | |
| Saytex 111 (OctaBDE), GD 7–19 | Rabbits, New Zealand White, pregnant | Fetus: Delayed ossification | 2 mg/kg bw | Breslin et al. (1989) |
| | | Fetus: Retrocaval ureter and fused sternebrae | 5 mg/kg bw | |
| | | Mother: Reduced weight gain, enlarged liver | 15 mg/kg bw | |
| PentaBDE, technical grade, GD 6–15 | Rats, pregnant | Maternal weight gain | 100 mg/kg bw | BFRIP (1990) |
| DE-71 (PentaBDE), 31 days: PND 22–41 (females), PND 23–53 (males) | Rats, Wistar, post-weaning | Delay in vaginal opening | 30 mg/kg bw | Stoker et al. (2004a) |
| | | Delay in preputial separation | 60 mg/kg bw | |
| | | Ventral prostate and seminal vesicle weight decrease | 60 mg/kg bw | |
| BDE-99, single oral dose, GD 6 | Rats, Wistar, female offspring (killed PND 90) | Lesion in ovarian tissues (electron microscopic study) | 60 µg/kg bw | Talsness et al. (2003) |
| BDE-99, single oral dose, GD 6 | Rats, Wistar, male offspring (assessed PND 140–160) | Spermatid, sperm number and sperm production decrease; decrease in ejaculation frequency | 60 µg/kg bw | Kuriyama et al. (2004a) |

GD, gestation day; HD, high dose; LD, low dose; NOEL, no-observed-effect level; PND, postnatal day

*(ii) Rat*

In a study by the Dow Chemical Company (Kociba et al., 1975), groups of 25 male and 25 female Sprague-Dawley rats were given "decaBDE" (containing decaBDE 77.4%, nonaBDE 21.8% and octaBDE 0.8%) in the diet for 100–105 weeks. The dose levels were 0, 0.01, 0.1 or 1 mg/kg bw per day. The treatment did not have any influence on survival rates, appearance, body weights, feed consumption, haematology, urinalysis or organ weights. There were no other discernible toxic effects and no significant differences in the number of rats developing tumours between the groups. The International Agency for Research on Cancer (IARC) Working Group noted that the dose levels were very low (IARC, 1990).

In the NTP rat study (NTP, 1986), groups of 50 male and 50 female Fischer 344/N rats received DecaBDE (purity 94–99%; no brominated dioxins or furans were found) mixed in diet for 103 weeks, with all survivors killed at 111–112 weeks of age. The concentration of DecaBDE in the diet was 0, 25 and 50 g/kg diet, and the estimated average daily dose of DecaBDE was 1120 and 2240 mg/kg bw per day in low- and high-dose males and 1200 and 2550 mg/kg bw per day in low- and high-dose females, respectively. Body weights of the DecaBDE-treated rats were not significantly different from those of controls throughout the study. After week 102, low-dose male rat survival was significantly lower than controls, but the author suggested that this decreased survival may not have been compound-related. In high-dose males, thrombosis and degeneration of the liver, fibrosis of the spleen, lymphoid hyperplasia and acanthosis of the forestomach were observed. The incidences of neoplastic nodules of the liver (adenomas) were significantly increased in both males (1/50 in controls, 7/50 in low-dose and 15/49 in high-dose males; $P < 0.001$, incidental tumour test for trend) and females (1/50 in controls, 3/49 in low-dose and 9/50 in high-dose females; $P = 0.002$, incidental tumour test for trend). However, no differences in the incidence of hepatocellular carcinomas were detected between the groups. A significantly increased incidence of acinar cell adenomas of the pancreas was observed in males (0/49 in controls, 0/50 in low-dose and 4/49 in high-dose rats; $P = 0.017$, incidental tumour test for trend). Additionally, a high incidence of mononuclear cell leukaemia was observed in both treated and control rats of both sexes.

In summary, it can be concluded from these studies that there is limited evidence for the carcinogenicity of DecaBDE in experimental animals. In the IARC assessment of DecaBDE, this compound was considered not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1990). The lack of genotoxicity (see next section) suggests that the mechanism of the possible carcinogenic potency of decaBDE would be epigenetic.

### *2.2.4 Genotoxicity*

The in vivo genotoxic potency of DecaBDE has been studied by cytogenetic examination of bone marrow cells from maternal Sprague-Dawley rats and their offspring, following exposure 60 days prior to mating as well as during mating, gestation and lactation (0, 3, 30 or 100 mg/kg bw per day; DecaBDE mixture

containing 77% decaBDE congener and 22% nonaBDE congener) (Norris et al., 1975b). No increase in chromosomal aberrations in maternal or neonatal rats was seen at any of the doses. Mutagenicity tests with DecaBDE were negative in four strains of *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) (NTP, 1986) and in a yeast (*Saccharomyces cerevisiae*) model (Great Lakes, 1974) when tested both with and without metabolic activation at doses up to 10 000 µg/plate. Similarly, studies on DecaBDE in a eukaryotic cell model utilizing the TK locus of the mouse lymphoma cell line L5178Y, as well as chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells (both with and without metabolic activation), were all negative (NTP, 1986).

A commercial OctaBDE preparation, at dose levels of 60–300 µg/ml, was found to be negative in the unscheduled DNA synthesis assay in the human fibroblast cell line WI-38 with and without metabolic activation. It also did not induce mutations in *S. typhimurium* or *S. cerevisiae* or cause sister chromatid exchanges in Chinese hamster ovary cells (exposed to 7.5–750 µg/ml of OctaBDE for 2 h) with or without metabolic activation (Great Lakes, 1987). Also, in an assay of cytogenicity with human lymphocytes, cells were exposed to OctaBDE at 125–500 µg/ml or 32–125 µg/ml in the absence and presence of metabolic activation, respectively. No significant increases in structural and numerical chromosome aberrations were observed with or without metabolic activation relative to the solvent control group (Great Lakes, 1999).

Ames tests were performed on the PBDE mixtures Muster 13, 82 and 84, defined by the United States Environmental Protection Agency (US EPA) as OctaBDEs (US EPA, 1990a, 1990b, 1990c). Neither Muster 13 nor Muster 84 induced an increase in the number of revertant colonies in *S. typhimurium* strains TA98, TA100 or TA1535, with or without an exogenous S9 metabolic activation system at concentrations up to 5000 µg/plate. However, Muster 82 exhibited evidence of weak mutagenicity without metabolic activation in strain TA100. Muster 82 was tested at concentrations ranging from 2500 to 10 000 µg/plate and in a repeated test on TA100 without activation at concentrations from 2500 to 10 000 µg/plate.

Mutagenicity studies with a commercial PentaBDE preparation (doses unknown) in four strains of *S. typhimurium* (TA98, TA100, TA1535 and TA1537) and in *S. cerevisiae,* with and without metabolic activation, were all negative (Great Lakes, 1975). Mutagenicity tests with PentaBDE (1.6–1000 µg/plate) in the above-mentioned *Salmonella* strains, with or without metabolic activation, were also negative (Dead Sea Bromide Works, 1984). Moreover, negative results with PentaBDEs (100–10 000 µg/plate) in the same *Salmonella* strains were shown by Zeiger and co-workers (Zeiger et al., 1987) and Chemische Fabrik Kalk GmbH (Kalk, 1978). However, in one study of PentaBDE using *S. typhimurium* strains TA100, TA1535, TA1536 and TA1537, induction of point mutations (3-fold increase in number of revertant colonies) was seen at the highest dose (10 000 µg/plate) in strains TA1535 and TA1538, in the absence of metabolic activation (ISCCL, 1977). This was considered a chance finding in the EU risk assessment on PentaBDE (EU, 2001).

Negative results were shown in a cytogenetic assay measuring structural chromosomal aberrations with human lymphocytes exposed to PentaBDE at concentrations up to 3759 µg/ml, both with and without metabolic activation (CMA, 1996). The tetraBDE congener BDE-47 (present in technical PentaBDE mixture) and lower brominated PBDE congeners (2-monoBDE and 3,4-diBDE) were tested (dose range 0–40 µg/ml) in two assays for intragenic recombination at an endogenous mammalian cell locus (SPD8 and Sp5). In the SPD8 assay, all three BDE congeners significantly increased the recombination frequency, whereas in the Sp5 assay, only the lower brominated congeners (2-monoBDE and 3,4-diBDE) caused significant increases in recombination frequency (Helleday et al., 1999). The possible role of this type of increased intragenic recombination in human diseases remains to be clarified.

By using Chinese hamster ovary cell lines with different defects in DNA repair, a screening method for the detection of genotoxic substances has been proposed (Johansson et al., 2004). According to the authors, depending on the cell line (in this case, EM9, UV4 and UV5), different kinds of DNA lesions could be suggested and screened for. Among the studied substances, BDE-47 was tested; in this model, it was found to be inactive and therefore suggested by the authors not to be genotoxic.

BDE-99 was assessed for mutagenicity and clastogenicity in vitro by use of bacterial reverse mutation assays in *S. typhimuriun* strains TA98 and TA100 and in *Escherichia coli* WP2 uvrA and with the *Allium cepa* chromosome aberration test (Evandri et al., 2003). In the bacterial assays, the concentrations were 12.5–200 µmol/l (greater doses were not soluble, according to the authors); in the *Allium* test, doses from 1 to 100 µmol/l were used. Results showed that BDE-99 was negative in the bacterial mutagenicity assay, with or without S9 mix. Also, the frequency of chromosomal aberration was not significantly higher than that of the control, and no signs of cytotoxiciy were observed in BDE-99-treated *A. cepa*.

### 2.2.5 *Reproductive/developmental toxicity*

The reproductive toxicity of PBDEs has been studied using technical Deca-, Octa- and PentaBDE preparations, including Saytex 111. All except the first study under this heading are teratogenicity studies in rats, and only Saytex 111 has been studied in both rats and rabbits. The reproductive/developmental toxicity studies are summarized in Table 7.

#### *(a) Rat*

Effects of DecaBDE on reproductive performance were studied in male and female Sprague-Dawley (Spartan) rats given commercial DecaBDE in the diet at dose levels of 0, 3, 30 or 100 mg/kg bw per day (Norris et al., 1975a, 1975b). The group sizes were 20 males and 40 females (control group), 10 males and 20 females (the low and middle dose groups) and 15 males and 30 females (the highest dose group). The treatment was commenced 60 days prior to mating and

continued throughout gestation and lactation. No treatment-related changes were reported in reproductive performance or maturation of pups.

In a teratogenicity study with Sprague-Dawley (Spartan) rats, commercial DecaBDE (77.4% decaBDE, 21.8% nonaBDE, 0.8% octaBDE) was given at dose levels of 0, 10, 100 or 1000 mg/kg bw per day by oral gavage on gestation days (GD) 6–15, and fetuses were collected by caesarean section on GD 21 (Norris et al., 1975b). No maternal toxic effects, in terms of clinical signs, body weight gain, food consumption or liver weights, were observed. Similarly, the number of corpora lutea, position and number of fetuses in utero, individual fetal weight, crown–rump length and sex ratio were not affected by the treatment. However, significantly increased incidences in resorptions were observed at the lower dose levels, but not at 1000 mg/kg bw per day. In the absence of numerical as well as historical control data, the possibility of embryolethality cannot, therefore, be ruled out. No external abnormalities were observed in fetuses, but soft tissue and skeletal examinations revealed increased numbers of litters with subcutaneous oedema and delayed ossification of normally developed bones of the skull at the dose level of 1000 mg/kg bw per day. Analysis of maternal and fetal livers for bromine concentration (reflecting liver concentration of DecaBDE) showed significantly increased concentrations only in maternal livers at the highest dose. Although this study is inadequately reported, it suggests that DecaBDE is not teratogenic, but it is clearly fetotoxic at dose levels that are not maternally toxic.

Female Sprague-Dawley rats ($n$ = 25 per dose) were treated by gavage with DecaBDE (composite of three commercial lots; purity 97.3%) at doses of 0, 100, 300 or 1000 mg/kg bw from GD 0 to GD 19. Fetuses were collected on GD 20 and assessed for external, visceral and skeletal anomalies/defects. No effects were observed with respect to maternal toxicity, fertility, gestation or fetal development (Hardy et al., 2002).

The teratogenicity of a commercial OctaBDE preparation (DE-79) was studied in Charles River COBS CD rats ($n$ = 10) receiving the test compound by gavage at 0, 2.5, 10, 15, 25 or 50 mg/kg bw per day on GD 6–15 (Great Lakes, 1986). Reduced maternal body weight gain and slightly increased cholesterol levels, but no histopathological changes in livers or kidneys, were observed at 50 mg/kg bw per day. These maternal effects were associated with marked fetal toxicity, as indicated by increased numbers of late resorptions, significantly reduced mean fetal weights, severe generalized oedema (anasarca), reduced ossification of the skull and various unossified bones. In addition, developmental variations, such as bent limb bones and bent ribs, were reported at 50 mg/kg bw per day. No treatment-related effects were observed at 15 mg/kg bw per day or lower, but the results at 25 mg/kg bw per day were not reported. Based on these findings, suggested no-observed-effect levels (NOELs) are 25 mg/kg bw per day for maternal toxicity and 15 mg/kg bw per day for fetal effects.

The teratogenicity of the commercial OctaBDE mixture Saytex 111 was studied in four groups of 25 Charles River (SD) rats (US EPA, 1986). They were administered corn oil suspensions of the test substance by gavage at 0, 2.5, 10 or 25 mg/kg bw per day on GD 6–15. Fetuses were examined on day 20 for gross

visceral and skeletal abnormalities. The test substance was found to be more toxic to the fetuses than to the dams, as shown by a dose-dependent reduction of fetal body weight at the two highest dose levels. At 25 mg/kg bw per day, Saytex 111 also increased the number of early and late resorptions, delayed skeletal ossification and induced fetal malformations, such as enlarged heart and rear limb malformations (type of malformation not specified). The only maternal effect noted was a reduced body weight gain in the high-dose animals.

A teratogenicity study with a commercial PentaBDE preparation was carried out in rats (strain and number of animals not specified) (BFRIP, 1990). The test compound suspended in corn oil was given by gavage at 0, 10, 100 or 200 mg/kg bw per day on GD 6–15. Maternal body weight gain was decreased at 100 and 200 mg/kg bw per day, and a slight (non-significant) reduction of fetal body weight was observed at 200 mg/kg bw per day.

*(b) Rabbit*

The teratogenicity of Saytex 111 was also studied in groups of 26 New Zealand White rabbits by the Dow Chemical Company (Breslin et al., 1989). The rabbits were administered the test substance by gavage at 0, 2, 5 or 15 mg/kg bw per day on GD 7–19, and the fetuses were collected on GD 28. Approximately half of the fetuses in each litter were randomly assigned for soft tissue examination, in addition to all the fetuses being examined for skeletal alterations. Maternal body weight showed a dose-dependent decrease compared with the control group, which was statistically significant only at 15 mg/kg bw per day (93% of control weight). Also, the absolute and body weight-related maternal liver weights were increased at this dose level. One rabbit at 5 mg/kg bw per day and two rabbits at 15 mg/kg bw per day delivered their litters prior to GD 28. In addition, one rabbit at 15 mg/kg bw per day was killed after exhibiting signs of abortion. This animal had multiple resorption sites in the uterus. Excluding these animals, the number of resorptions was not affected by the treatment. Signs of fetal toxicity included slight (non-significant) decreases in fetal body weights at 5 and 15 mg/kg bw per day and increased incidences of delayed ossification of the hyoid, dental process at 5 mg/kg bw per day only and sternebrae at 2, 5 and 15 mg/kg bw per day (statistically significant only at 15 mg/kg bw per day). Treatment-related fetal anomalies included increased incidences of retrocaval ureter and fused sternebrae at all dose levels of Saytex 111, with the maximum incidence at 5 mg/kg bw per day (statistically significant). These variants were absent from the concurrent controls, but they were reported to have occurred at relatively high incidence in some historical controls. This outcome and the lower incidence at 15 mg/kg bw per day compared with 5 mg/kg bw per day led the authors (Breslin et al., 1989) to consider them as spontaneous. To conclude, Saytex 111 caused fetal toxicity and may also induce fetal anomalies at maternally non-toxic dose levels.

The reproductive/developmental toxicity studies illustrate that, in general, fetuses are more sensitive than mothers and that the increased incidence of developmental variants/anomalies is a frequent fetal effect observed with commercial Octa- and PentaBDE formulations. Although it is known that maternal toxicity

can influence fetal ossification (Khera, 1984), the fetal effects seem to appear at lower doses than those indicative of maternal toxicity.

*(c) Multigeneration reproductive toxicity*

No information is available on multigeneration reproductive toxicity studies involving PBDEs.

### *2.2.6 Special studies*

*(a) Thyroid hormone system*

*(i) Mixtures*

*Mouse*

Depending on the dose, effects of PBDEs on the thyroid hormone system may occur, as the structure of thyroid hormones is very similar to that of halogenated diphenyl ethers, but with iodine instead of bromine substituents. Acute (0, 0.8, 4, 20, 100 or 500 mg/kg bw; $n$ = 6 per group) or subchronic (0, 18, 36 or 72 mg/kg bw per day for 14 days, relating to total doses of 0, 250, 500 and 1000 mg/kg bw; $n$ = 6–8 per group) oral exposure by gavage to the technical mixture DE-71 was tested in adult female C57BL/6J mice. Acute exposure resulted in decreased serum TT4 concentration at all doses tested, with the exception of 100 mg/kg bw. The maximum reduction measured was approximately 50% at the 20 mg/kg bw dose. Dose-dependent reductions in circulating TT4 and FT4 were caused by subchronic treatment at 18 mg/kg bw per day or higher doses, resulting in maximum reduction of about 40% and 60% for TT4 and FT4 at the highest dose, respectively (Fowles et al., 1994).

Juvenile C57BL/6N mice ($n$ = 8 per group, controls $n$ = 12) and Sprague-Dawley rats ($n$ = 6 per group, controls $n$ = 10) were exposed to the technical mixture Bromkal 70-5-DE (18 or 36 mg/kg bw per day by gavage for 14 days, resulting in total doses of 250 or 500 mg/kg bw, respectively). Animals were examined for altered thyroid hormone concentrations in plasma. In both species, a dose-dependent depression of TT4 and FT4 was observed, with decreases to about 50% and 20% of control values for TT4 and FT4, respectively, in rats at the highest dose of Bromkal 70 and of about 60% for both TT4 and FT4 in mice. Plasma thyroid stimulating hormone (TSH) levels were not changed in any species. Induction of the phase II metabolizing enzyme UDPGT was found at the highest dose in rats, while increases in activity of this enzyme were not significant in mice (Hallgren et al., 2001). The activities of phase I enzymes EROD and MROD were significantly induced at both doses of Bromkal 70 in rats and mice, whereas induction of PROD was seen only in rats exposed to 18 or 36 mg/kg bw per day.

In a recent study by Skarman et al. (2005), NMRI dams ($n$ = 13 per treated group and $n$ = 22 controls) were exposed by gavage to Bromkal 70-5-DE (0 or 80 µmol/kg bw on every third day from GD 4 to postnatal day [PND] 17, resulting in 10 applications). The main constituents of this mixture are BDE-47 (35%) and

BDE-99 (37%). All dams delivered in the Bromkal 70 group, and 20 of 22 in controls. Four dams per group were sacrificed on GD 17, and the remaining dams on PND 20. Differences in FT4 and TT4 were not significant in dams at either time point. TT4 and FT4 plasma levels were decreased in exposed offspring ($n$ = 6–16; sex not given) to approximately 70% of control levels on PND 11, but not on PND 18. Hepatic UDPGT activity did not show exposure-related effects on PND 11, while there was a borderline significance on PND 18 (Skarman et al., 2005). However, treatment with the same molar dose of BDE-99 did not result in any significant changes in dams and offspring.

*Rat*

In a study in weanling female Long-Evans rats, effects of short-term exposure to three different technical mixtures (DE-71, DE-79 and DE-83R, representing penta-, octa- and decaBDE, respectively) were examined for TT4 and TT3 concentrations in serum, TSH and activity of hepatic enzymes (UDPGT, EROD, PROD) 24 h after the last treatment. Following gavage dosing with 0, 0.3, 1, 3, 10, 30, 60 or 100 mg/kg bw per day (for DE-71, substitute 60 mg/kg bw per day with 300 mg/kg bw per day; $n$ = 8 per group, except for low dose of DE-71, where $n$ = 4), there were dose-dependent decreases in serum TT4 by DE-71 and DE-79 at daily doses greater than 3 mg/kg bw, together with a 2.5- to 5-fold increase in hepatic UDPGT activity. Serum TT3 concentrations were significantly reduced at doses ≥60 mg/kg bw per day by both the penta- and octaBDE mixtures. Maximum reductions were 80% and about 30% for serum TT4 and TT3, respectively. BMD calculations revealed influences on thyroid hormones and hepatic enzyme activity at comparable levels (see Tables 85 and 86 in section 10 below for the BMD and lower confidence limit on the BMD [BMDL] of thyroid hormones). Circulating TSH concentrations were not affected. Relative liver weights were significantly increased at DE-71 and DE-79 at doses above 10 mg/kg bw per day. Also, DE-83R (0–100 mg/kg bw per day) did not alter any of the end-points studied, thus indicating that decaBDE is much less effective than lower brominated congeners (Zhou et al., 2001).

In a follow-up of this study, developmental treatment of Long-Evans rats with DE-71 (0, 1, 10 or 30 mg/kg bw per day by gavage; $n$ = 47–55 per group) was used from GD 6 to PND 21. The PBDE mixture decreased serum T4 by about 50% at the highest dose in dams on GD 20 and on PND 22 ($n$ ≥ 8 per group). Reductions in serum T4 (down to 70% of control values at the highest dose) were also found in pups on PND 4 and 14, at doses of 10 and 30 mg/kg bw per day ($n$ ≥ 8 litters per group). T4 values in the offspring recovered by PND 36. UDPGT activity was induced by DE-71 in dams and pups at the highest dose level. Elevations in hepatic EROD and PROD activities were observed at doses above 1 mg/kg bw per day in both dams and offspring. Serum triiodothyronine (T3), maternal and offspring body weights and time of eye opening were not affected (Zhou et al., 2002). The BMD and BMDL for T4 and hepatic enzymes are shown in Tables 85 and 86 in section 10 below.

Using pubertal protocols, oral exposure by gavage of Wistar rats to DE-71 (0, 3, 30 or 60 mg/kg bw per day) from PND 23 to PND 53 in male rat pups and from

PND 22 to PND 41 in female rat pups or for 5 days only (males: PND 23–27, females: PND 22–26) resulted in decreases in circulating serum TT4 at the two highest dose levels and both exposure durations in females (levels decreased to about 30% of control values). Similar effects were observed in the males, except all three doses of DE-71 significantly reduced total serum T4 following exposure for 31 days, with the maximum reduction at the highest dose to about 20–25% of the control level. Values of T3 were reduced by 35% only in males exposed for 31 days at both higher dose levels. In these groups, there was also an elevation of TSH by up to a factor of 2 at the highest dose. Relative liver weights were also significantly increased in the 30 and 60 mg/kg bw per day dose groups (both sexes) for both exposure periods. Morphological changes in the thyroid gland were found in both sexes exposed to the highest dose of DE-71 for 21 or 31 days. These results indicate that the 31-day protocol is more sensitive at detecting thyrotoxicity (Stoker et al., 2004a). The BMD and BMDL for serum T4 are shown in Tables 85 and 86 in section 10 below.

In a similar study, developmental exposure of Long-Evans rats to DE-71 from GD 6 to PND 21 (gavage with 0, 5, 30 or 100 mg/kg bw per day) caused a dose-dependent decline of serum TT4 in the early postnatal period. Maximal decreases to less than 20% of control levels at the highest dose on PND 14 were observed, with recovery to control values by PND 36 (Gilbert et al., 2004). However, this recovery of hormone levels does not necessarily imply that secondary effects of thyroid hormones (e.g. on the developing nervous system) are reversible, since a lack of hormone supply during a critical developmental period may result in long-lasting changes that persist after normalization of circulating hormone concentrations.

Thyroid hyperplasia is a common sign of subchronic and chronic PBDE exposure. Feeding decaBDE (BDE-209) to male Sprague-Dawley rats for 30 days (0, 100, 1000 or 10 000 mg/kg diet, relating to an average intake of 0, 8, 80 or 800 mg/kg bw per day, respectively) caused thyroid hyperplasia at concentrations of 1000 mg/kg diet (equivalent to about 80 mg/kg bw per day; total dose 2400 mg/kg bw) or higher. The corresponding NOEL was 100 mg/kg diet, or 8 mg/kg bw (total dose 240 mg/kg bw). However, the decaBDE formulation had a purity of approximately 77% and included about 22% nonaBDE and 1% octaBDE (Norris et al., 1975b). DE-79, a technical PBDE mixture containing mainly octaBDE, also caused slight to moderate thyroid hyperplasia in another study in Charles River CD rats, which used dietary exposure (0, 100 or 1000 mg/kg diet for 28 days or 0, 100, 1000 or 10 000 mg/kg diet for 90 days; IRDC, 1976, 1977; reviewed in Gill et al., 2004). The NOEL in these studies was 100 mg/kg diet for both exposure durations. Increased thyroid weights were reported in male Sprague-Dawley rats after dietary exposure to the pentaBDE mixture DE-71 (average daily intake of 2, 10 or 100 mg/kg bw for 90 days, relating to total doses of 180, 900 or 9000 mg/kg bw, respectively). The NOEL for thyroid weight change was 10 mg/kg bw per day, with the increased weight persisting after an exposure-free interval of 168 days (WIL Research Laboratories, 1984; reviewed in Gill et al., 2004).

*(ii) Single congeners and metabolites*

*Mouse*

Thyroid hyperplasia has been detected in mice after exposure to decaBDE with a purity of 95%. Diets containing decaBDE at 0, 25 or 50 g/kg diet were fed to B6C3F1 mice ($n$ = 50) for 2 years, leading to an average daily intake of 3.2 or 6.65 g/kg bw in males and 3.76 or 7.78 g/kg bw in females. Mice from both dose groups developed follicular cell hyperplasia. In both sexes, a marginal occurrence (not statistically significant) of follicular cell adenoma was seen (NTP, 1986; reviewed in Gill et al., 2004).

In the study by Hallgren et al. (2001), daily oral exposure (gavage) of female C57BL/6N mice to BDE-47 at 18 mg/kg bw per day for 14 days (total 250 mg/kg bw; $n$ = 8) resulted in reductions of TT4 and FT4 in plasma, measuring about 70% and 60% of control values, respectively. There were no significant effects on TSH levels and hepatic UDPGT activity.

A group of NMRI dams exposed to BDE-99 at 80 µmol/kg bw (45.2 mg/kg bw) on every 3rd day from GD 4 to PND 17 ($n$ = 13, controls $n$ = 22) was also included in the experiment by Skarman et al. (2005). Ten and 20 dams delivered in the BDE-99 and control group, respectively. Neither TT4 nor FT4 plasma levels differed significantly from control values in dams or offspring, suggesting that other constituents of the Bromkal 70-5-DE mixture might have caused the reported serum T4 differences in offspring on PND 11. Also, UDPGT activity was not enhanced by BDE-99.

*Rat*

In a subsequent study by Hallgren & Darnerud (2002), the same experimental design was used in 7-week-old female Sprague-Dawley rats (gavage with BDE-47 at 0, 1, 6 or 18 mg/kg bw per day for 14 days, equivalent to total doses of 0, 14, 84 or 250 mg/kg bw; $n$ = 6 per group). Groups of rats were also exposed to daily doses of technical PCB mixture Aroclor 1254 (4 mg/kg bw per day) and a mixture of the chlorinated paraffin Witaclor 171P (6.8 mg/kg bw per day) by gavage for 14 days. In addition, rats were exposed to all the possible two- or three-substance mixtures of BDE-47, Aroclor 1254 and Witaclor 171P. Ex vivo binding of [$^{125}$I]T4 to the serum transport protein TTR and morphology of the thyroid were examined, in addition to hormone levels and hepatic enzyme activities, 1 day following the last dose. FT4, but not TT4, was decreased by about 35% after exposure to the highest dose of BDE-47. UDPGT activity showed a dose-dependent increase (by 25% at the highest dose), and TTR-bound radioactivity exhibited a dose-dependent decrease (to 70% of control values at the highest dose). TSH and thyroid weights were not affected by BDE-47, and morphology of the thyroid did not reveal signs of glandular activation. However, thyroid glandular activation was found in the group with combined exposure to BDE-47 and the technical PCB mixture Aroclor 1254 alone or in combination with a mixture of chlorinated paraffins (Witaclor 171P). The combination of BDE-47 and PCBs generally led to additive effects; however, synergistic effects were indicated by effects of combined

exposure to BDE-47 and chlorinated paraffins on FT4 (Hallgren & Darnerud, 2002). The authors concluded that the effects of exposure to these halogenated compounds on circulating thyroid hormones are mainly due to the disturbed serum transport of thyroid hormones, caused by binding of metabolites or parent compounds of PBDEs or PCBs to TTR. Additional reductions may occur by the induction of metabolizing enzymes, leading to increased metabolism of thyroid hormones (Hallgren & Darnerud, 2002). The conclusion that competition for binding sites on the transport proteins of thyroid hormones is the main cause for decreases in circulating levels in rats is supported by a comparative study in two additional rat strains, Wistar and Gunn, which demonstrated similar reductions of serum FT4 and TT4 in both strains by PCBs, despite the absence of hepatic UDPGT enzymes due to a genetic mutation in Gunn rats (Kato et al., 2004). However, these authors concluded that the cause of the reduction in circulating T4 concentration remains unclear, since both mechanisms, competition for TTR and induction of UDPGT, do not apply for all species and other mechanisms, such as effects on the hypothalamus–pituitary–thyroid axis, sulfation of iodothyronines and changes in activity of deiodinases, have not been sufficiently examined.

Binding of PBDEs, in particular hydroxylated PBDEs, to TTR (Meerts et al., 2000) and thyroid hormone receptors (Marsh et al., 1998) has been demonstrated in vitro. In rats, hydroxylated metabolites of BDE-47, BDE-99 and BDE-209 have been identified, while in human plasma, a potential hydroxylated derivative of BDE-47 has been found (reviewed in Hakk & Letcher, 2003). In humans, the major transport protein is not TTR, but thyroxine binding globulin (TBG), which is reported to have low affinities to hydroxylated PBDEs (Cheek et al., 1999).

When female juvenile Long-Evans rats were dosed with BDE-47 ($n$ = 8–14) for 4 consecutive days (0, 0.3, 1, 3, 10, 30 or 100 mg/kg bw per day by gavage), dose-related decreases in TT3 and TT4 (by 25% and 75% at the highest dose, respectively) were observed in serum, in the absence of altered TSH concentrations (Hedge et al., 2004).

In a recent study, Wistar rats ($n$ = 10) were treated by gavage with low doses of BDE-99 (0, 60 or 300 µg/kg bw) on GD 6. Total serum T4 was reduced in dams of both dose groups (approximately 65% of control value) on PND 1, while offspring of both sexes from the high dose group exhibited significant reductions in circulating T4 (free and total) on PND 22, but not PND 1 (Kuriyama et al., 2004a). TSH levels were also reduced in the low-dose-group offspring on PND 1. Treatment of Wistar rat dams with BDE-47 on GD 6 (0, 140 or 700 µg/kg bw; $n$ = 7, 10 and 9, respectively) caused a reduction in serum TT3 to approximately 50% of control values in male offspring on PND 1. On PND 14, decreases were found in both exposed groups, but the effect was slightly stronger at the low dose level (to about 60% of control values) than at the highest dose (about 70%). TSH was also decreased at this age, but the reduction was significant only at the lower dose (by about 10%). On PND 22, TT4 was dose-dependently elevated (by about 10% in the high dose group) and TSH significantly depressed to about 65% of control values at the lower dose. The reduction was smaller at the high dose, measuring about 80% of control values. Body weights of the high-dose male offspring were significantly decreased (approximately 12%) at PND 22. In addition, there was a

decrease of follicle stimulating hormone (FSH) to approximately 65% of control levels in the high dose group (Andrade et al., 2004). In dams, significant decreases in TT4 (to about 80% of control values) and TSH (to nearly 30% of control values) were found only at the high dose level on PND 1. All effects had normalized by PND 22 (Kuriyama et al., 2004b).

Dose-related decreases in thyroid weights, down to 60–65% of control values, were observed in adult male and female Long-Evans rats ($n$ = 8 per group) after maternal exposure to BDE-99 (1 or 10 mg/kg bw per day) from GD 10 to GD 18 (Lilienthal et al., 2004).

*(iii) Summary of thyroid effects from rodent studies*

From the available data in rodent studies, it appears that TT4 is one of the more sensitive parameters associated with PBDE exposure. FT4 may be as sensitive, but it was usually determined in fewer studies. In contrast, TT3 seems to be less sensitive by factors of 3–6 (Zhou et al., 2001; Stoker et al. 2004a). In one report (Stoker et al., 2004a), limited decreases in serum TT3 were seen only in males following 31 days of exposure to DE-71. Also, elevation of serum TSH was found only in males in this experiment, whereas effects on TT4 do not show a clear sex difference in pubertal protocols (Stoker et al., 2004a). From short-term exposures in post-weanling female rats, it seems that the higher brominated octaBDE mixture DE-79 is more potent than the lower brominated DE-71 (Zhou et al., 2001), which may be due to greater accumulation of higher brominated congeners. Of single congeners, only BDE-47 and BDE-99 (and technical-grade decaBDE) have been studied so far; thus, the data are not sufficient for conclusions about differential potencies. However, it appears that decaBDE is much less potent than lower brominated congeners in altering thyroid hormones. In one study, effects on TT4 were reported in offspring after a single gestational treatment with a very low dose of BDE-99 (Kuriyama et al., 2004a). Reductions in circulating thyroid hormone concentrations were observed in dams and developing animals, but the data indicate that thyroid hormone levels recovered by PND 39. In another study, recovery to normal hormone levels was observed 2 weeks after termination of perinatal treatment (Gilbert et al., 2004). Since induction of EROD has been found at similar doses, which caused decreases in thyroid hormone concentrations in many studies using PBDE mixtures or congeners, a contribution of dioxin-like contaminants is likely, as purified PBDEs were reported not to induce EROD in vitro. Several mechanisms may be responsible for decreased thyroid hormones in serum. Competition of hydroxylated PBDEs for TTR binding and induction of UDPGT cannot explain effects in all species, and there is a lack of knowledge about PBDE effects on the hypothalamus–pituitary–thyroid axis, sulfation of iodothyronines and altered activities of deiodinases. Thus, the cause for reduction of thyroid hormones remains unclear (Kato et al., 2004). In contrast to reduced hormone levels, thyroid hyperplasia was found at much higher exposure levels (Norris et al., 1975a, 1975b; Gill et al., 2004). However, long-lasting decreases in thyroid weights have been detected after maternal exposure to BDE-99 (Lilienthal et al., 2004).

*(b) Steroid hormones*

*(i) Mixtures*

*Mouse*

In the study by Fowles et al. (1994), subchronic exposure to the technical mixture DE-71 elevated serum concentrations of corticosterone. Female C57BL/6 mice ($n$ = 6) were treated by gavage with DE-71 (0, 18, 36 or 72 mg/kg bw per day) for 14 consecutive days and then assessed for changes in serum corticosterone. The results suggested that an interaction between the acute stress of necropsy procedures (repeated cage disruptions) and DE-71 exposure resulted in increased corticosterone levels in all dosed groups compared with controls.

*Rat*

Oral exposure of Wistar rats to DE-71 (0, 3, 30 or 60 mg/kg bw per day by gavage) from PND 22 to PND 41 in females and from PND 23 to PND 53 in males resulted in decreased weights of seminal vesicles (about 20% reduction) and ventral prostate (about 15% reduction) in males at the highest dose tested, whereas testes and epididymis weights were unaltered ($n$ = 15 per group). Preputial separation was slightly delayed (1.7–2.1 days) at 30 and 60 mg/kg bw per day, while in females, a delay of vaginal opening (1.8 days) was detected at 60 mg/kg bw per day (Stoker et al., 2004a). No significant differences were noted in body weight increase over the dosing period. Serum testosterone, serum and pituitary luteinizing hormone (LH) and pituitary prolactin were not altered by exposure in males, in contrast to serum prolactin, which was increased 2-fold at the highest dose. No reproductive hormones were measured in female animals. Effects in males may be caused by interference of PBDEs with androgenic stimulation, while vaginal opening is estrogen-dependent. However, secondary effects due to reduced thyroid hormones could not be entirely excluded.

*(ii) Single congeners and metabolites*

*In vitro*

Estrogenicity of hydroxylated PBDE and parent compounds was studied in different cell lines using an estrogen receptor-based reporter gene assay (ER-CALUX). In human T47D breast cancer cells, several PBDEs exerted estrogenic responses, but with relative potencies ($EC_{50}$) 6 orders of magnitude lower (2.5–7.3 µmol/l) than that of estradiol. Several PBDE congeners exhibited more than 50% maximum luciferase induction, with the highest value found for BDE-30 (114%). Potencies of hydroxylated PBDE were generally higher. The metabolite 2-bromo-4-(2,4,6-tribromophenoxy)phenol caused an induction response exceeding that of estradiol, but at concentrations 50 000 times higher. In an estrogen receptor (ERα) specific transfected human embryonic kidney cell line, the hydroxylated congener 4-(2,4,6-tribromophenoxy)phenol showed an induction similar to that of estradiol, with an $EC_{50}$ of <0.1 µmol/l. In the analogous ERβ-specific cell line, the same compound showed 50% of the estrogenic potency of estradiol, with an $EC_{50}$ value

of ≤5 µmol/l (Meerts et al., 2001). These results demonstrate that parent PBDEs and, in particular, hydroxylated derivatives have the ability to induce estrogenic responses, albeit at relative potencies orders of magnitude lower than that of estradiol. Metabolism of PBDEs to hydroxylated derivatives in vivo is suggested to result in increased potencies (Meerts et al., 2001).

BDE-47, BDE-99, BDE-100 and BDE-154 were examined in a rat ventral prostate assay for their ability to compete with R1881 (synthetic androgen) androgen receptor (AR) binding. The results indicated that BDE-47 and BDE-100, in particular, are more potent at inhibiting the binding of labelled R1881 to the AR, showing 60% and 98% inhibition, respectively, at a concentration of 33 µmol/l (explicit $IC_{50}$ values were not given). These two congeners also inhibited dihydrotestosterone (DHT) induced human androgen receptor (hAR) transcriptional activation in the MDA-kb2/luciferase cell line, with $IC_{50}$ values of about 5 µmol/l (Stoker et al., 2004b). According to the results of inhibition constant $K_i$ determinations, BDE-100 appears to be a competitive inhibitor of $^3$H-labelled R1881 binding to hAR. In addition, rat ventral prostate cytosol was incubated overnight at 4 °C with increasing concentrations of labelled R1881 in the presence of BDE-100 at 0, 6, 9 or 18 µmol/l. Suppression of R1881 binding was observed, with an $IC_{50}$ of approximately 5 µmol/l.

*In vivo: rat*

In a developmental toxicity study, daily exposure of Sprague-Dawley rats during gestation (GD 0–19) to BDE-209 (0, 100, 300 or 1000 mg/kg bw per day by gavage; $n$ = 25 dams per group) did not influence the fetal sex distribution (Hardy et al., 2002).

Pregnant Wistar rats ($n$ = 9–12) were dosed by gavage from GD 10 to GD 16 with BDE-47 (20 mg/kg bw per day) or 6-OH BDE-47 (5 mg/kg bw per day) and offspring assessed for various developmental landmarks. No effects were seen in terms of sex ratio, anogenital distance, age at vaginal opening or age at preputial separation (Buitenhuis et al., 2004).

Following maternal exposure of Long-Evans rats ($n$ = 7–9 litters per group) to BDE-99 from GD 10 to GD 18 (1 or 10 mg/kg bw per day subcutaneously), dose-dependent delays of vaginal opening and a 20% increase in ovary weights were detected at the highest dose. In male offspring, acceleration of preputial separation was observed, together with reduced weights of the epididymis at both dose levels (by about 12% at the higher dose), increased weight of the ventral prostate at the lower dose (by about 25%) and a dose-dependent increase in dorsal prostate weight, measuring 20% at the higher dose (Ceccatelli, 2004). The decreased epididymis weight seen in this study is likely due to gestational exposure, since it was not observed in the study by Stoker et al. (2004a) using postnatal exposure to a technical PBDE mixture (DE-71), which contains mainly pentabrominated congeners. Gene expressions of AR, ERα and ERβ and of insulin-like growth factor I (IGF-I) were studied in several reproductive organs. In the ventral prostate, marked decreases in AR mRNA were detected at both doses (less than 20% of control values), as well as dose-dependent reductions in ERα

mRNA (to zero level at the higher dose), ERβ mRNA (to 5% of control values at the higher dose) and IGF-I mRNA (down to about 50%). In the dorsal prostate, IGF-I mRNA was unchanged, AR mRNA showed marked dose-dependent increases (3-fold at the higher dose), ERα mRNA was increased at the higher dose (about 2-fold) and ERβ mRNA was reduced at both doses (by about 50%). These results demonstrate that different lobes of the prostate respond differentially to PBDE exposure. In the uterus, mRNA levels of the progesterone receptor (PR) were down-regulated in a dose-related manner (by about 50% at the higher dose). ERα was not altered, but ERβ mRNA was up-regulated at the low dose (2-fold) and reduced at the high dose (down to 40% of control level). After injection of estradiol in gonadectomized rats, induction of IGF-I mRNA was reduced in the ventral prostate of low-dose rats (by about 60%) and dose-dependently elevated in the uterus (3- to 4-fold at the higher dose), thus demonstrating exposure-related influences on regulation of this gene (Ceccatelli, 2004). In the uterus, the IGF-I receptor is assumed to mediate actions of estradiol (Richards et al., 1996). Estradiol did not change ERα mRNA in uteri of exposed females, but ERβ mRNA was strongly induced at the higher dose, while it was nearly zero in controls and in the lower PBDE dose group (Ceccatelli, 2004). In addition, AR mRNA was decreased in uteri of low-dose females (down to about 15% of control levels). There were also PBDE-related effects on gene expression in the brain (see section 2.2.2).

Using the same perinatal exposure protocol with BDE-99, marked decreases in circulating estradiol and testosterone were observed in weanling male offspring, which became more pronounced in adulthood (estradiol down to 20% of control values, testosterone approximately 40% of controls; $n$ = 8 per group). Anogenital distance was marginally decreased in male offspring at the higher exposure level. Vaginal opening was delayed at 10 mg/kg bw per day in female rats, while the lower dose resulted in a slight acceleration of preputial separation in males ($n$ = 22–25 litters per group). These findings were seen together with elevated sweet preference (by about 35% at the higher dose), which is a sexually dimorphic behaviour, thus indicating behavioural feminization in male rats ($n$ = 9–12 per group). In addition, dose-dependent reductions in serum concentrations of the steroid hormone 1,25-dihydroxyvitamin $D_3$ (by about 50% at the higher dose) were detected in female offspring at weaning ($n$ = 8 per group). Male offspring exhibited PBDE-induced alterations in conditioned taste aversion (40% change at higher dose; $n$ = 10–11 per group) using 1,25-dihydroxyvitamin $D_3$ as the aversive stimulus (Lilienthal et al., 2004).

*(iii) Summary of steroid effects*

With the exception of one study on corticosterone (Fowles et al., 1994), all in vivo data so far have been obtained in rats. From the data available, early developmental exposure seems to be more effective than exposure in pubertal animals (see Tables 88 and 89 in section 10 below). Influences on pubertal onset and weights of reproductive organs have been observed at lower exposure levels following maternal treatment (Ceccatelli, 2004). However, these effects were found using a single congener (BDE-99), whereas the other study used the

technical mixture DE-71 (Stoker et al., 2004a). Since DE-71 contains mainly pentaBDE, influences by exposure period seem to be more likely. These differences may also explain the accelerated pubertal onset (preputial separation) in male offspring detected by Ceccatelli (2004) and Lilienthal et al. (2004), in contrast to delayed pubertal onset described by Stoker et al. (2004a). Marked reduction in circulating estradiol was found after gestational exposure to BDE-99 (Lilienthal et al., 2004), and this treatment also resulted in marked decreases in AR mRNA in the ventral prostate of exposed offspring (Ceccatelli, 2004). Anti-androgenic effects on DHT-induced AR activation and inhibition of AR agonist binding in vitro have been described for BDE-47 and BDE-100, in particular (Stoker et al., 2004b). Estrogenic activities have been reported for hydroxylated PBDE metabolites in vitro (Meerts et al., 2001).

*(c) Immunotoxicity*

Following exposure to high dietary doses of DecaBDE for 103 weeks, an increased frequency of splenic lesions was observed (NTP, 1986). The lesions were splenic fibrosis (males, 2240 mg/kg bw per day) and splenic haematopoiesis (females, 1200 and 2550 mg/kg bw per day). Lymphoid hyperplasia was also increased in high-dose male rats (2240 mg/kg bw per day).

The effects of a PentaBDE mixture (DE-71) on sheep erythrocyte plaque-forming cell (PFC) response and natural killer (NK) cell activity were studied in female C57BL/6J mice ($n$ = 6) upon gavage dosing (Fowles et al., 1994). Single doses of PentaBDE (0, 0.8, 4, 20 or 500 mg/kg bw) did not affect the PFC response in mice. However, repeated daily dosing by gavage (14 days) significantly reduced the PFC response at doses of 18, 36 and 72 mg/kg bw per day and also decreased thymus weight at 72 mg/kg bw per day. NK cell activity, studied only after repeated dosing, was not altered by exposure to up to the highest tested dose of the PentaBDE mixture.

The PentaBDE mixture Bromkal 70-5-DE was administered to C57BL mice ($n$ = 8; control $n$ = 12) and Sprague-Dawley rats ($n$ = 6; control $n$ = 10) (in both species, female animals of Charles River strains) (0, 18 or 36 mg/kg bw per day), and the PBDE congener BDE-47 was administered only to mice (18 mg/kg bw per day) by daily gavage doses for 14 days (Thuvander & Darnerud, 1999). Twenty-four hours after the last dose, animals were killed, organs excised and lymphocytes obtained from thymus and spleen. Subsequently, analysis was conducted for spleen and thymus weights, splenic and thymic lymphocyte subset numbers and in vitro immunoglobulin G (IgG) production in pokeweed mitogen-stimulated splenocytes. Certain effects of the PBDE exposure were seen in exposed mice but not in rats. Mouse splenocyte numbers (total numbers, as well as CD4+, CD8+ and CD45R+ thymic lymphocyte subsets) were markedly decreased after exposure to BDE-47. Also, a reduced in vitro production of IgG antibodies from pokeweed-stimulated splenocyte cultures was observed in mice after exposure to Bromkal 70-5-DE at 36 mg/kg bw per day.

*(d) Neurotoxicity*

*(i) In vitro*

*Mixtures*

The administration of the PBDE mixture DE-71 (3–50 µg/ml medium) to primary cultures of Long-Evans rat cerebellar granule cells resulted in a stimulation of the release of [$^3$H]arachidonic acid (ARA) by a phospolipase $A_2$ ($PLA_2$) dependent mechanism (Kodavanti & Derr-Yellin, 2002). The release was time-dependent and could be blocked by the $PLA_2$ inhibitor methyl arachidonylfluorophosphonate. Removal of external calcium caused a significant, but modest, reduction of the PBDE-stimulated ARA release. In contrast to the pentaBDE mixture DE-71, the octaBDE mixture DE-79 was not effective in this model. The potency of DE-71 to stimulate ARA release was similar to the potency of the PCB mixtures Aroclor 1016 and Aroclor 1254 when expressed in molar terms (>10 µmol/l). Since ARA and $PLA_2$ have been implicated in synaptic plasticity, the authors suggested that these findings indicate that alteration of neuronal ARA may be involved with the PBDE-induced effects on learning and memory in animals (Kodavanti & Derr-Yellin, 2002).

The pentaBDE mixture DE-71 inhibited the uptake of dopamine into synaptic vesicle preparations from adult rat brains, with an $IC_{50}$ value of 8 µmol/l. Only minor effects of pentaBDE were detected for uptake of dopamine and glutamate into synaptosomes (Mariussen & Fonnum, 2003). The observed effect was described by the authors as possibly related to changes in membrane potential. OctaBDE (DE-79) and decaBDE (DE-83R) were not effective in this system, in contrast to other brominated flame retardants, such as hexabromocyclododecane and tetrabromobisphenol-A.

*Single congeners and metabolites*

The cellular accumulation of BDE-47 was examined in primary cultures of neocortical cells, neurons and glia cells prepared from newborn Long-Evans rats. Incubation of cultures with BDE-47 at 0.01–3.0 µmol/l in serum-free medium for 60 min led to a concentration-dependent uptake in cells. There was a 100-fold accumulation in cells compared with medium; thus, 1 µmol/l in the medium resulted in a cellular concentration of about 100 µmol/l. The proportion of BDE-47 accumulated in cells was on average 15%, with 55% remaining in the medium and 30% associated with the plastic dish. Saturation was observed after 120 min. Cellular accumulation of BDE-47 decreased markedly when serum proteins were added to the incubation medium. These results show that the use of media concentrations underestimates cellular concentrations by about 2 orders of magnitude (Mundy et al., 2004).

BDE-99 caused an increase in apoptotic cell death in an astroglia cell line (human 132-1N1 astrocytoma cells) at concentrations of 50 µmol/l or higher (24-h exposure) and an inhibition of the mitochondrial reduction capacity (MTT assay), with an $IC_{50}$ of 26.5 µmol/l. Cytotoxicity, as assessed by trypan blue dye exclusion

and cellular LDH release, was not affected by BDE-99 concentrations up to 100 µmol/l. Translocation of three protein kinase C (PKC) isozymes was not diminished by preincubation with a PKC inhibitor (GF109203X) or down-regulation of PKC by the phorbol ester, phorbol myristate acetate. The results indicate that PKC activation is not critically involved in cytotoxic effects of BDE-99 in these cells. In addition, no effects on cytotoxicity were observed after application of the calcium chelator BAPTA-AM, the tyrosine kinase inhibitor genistein and a mitogen-activated protein kinase (MEK) inhibitor (PD98059). However, cytotoxicity was enhanced by a phosphatidylinositol 3 kinase inhibitor (LY290042) that is involved in cellular apoptotic processes (Madina et al., 2004).

*(ii) In vivo*

*Mixtures: Rat*

Following perinatal exposure of rat dams (strain not given) to the pentaBDE mixture DE-71 (0, 5, 30 or 100 mg/kg bw by gavage) from GD 6 to PND 21, impairments of cue-conditioned fear (up to a 5-fold change in the first minute) were observed in adult offspring (age not given). There were no observed effects on spatial learning, as assessed by the Morris water maze and context-conditioned fear (Taylor et al., 2003). The highest dose caused elevated baseline population spikes (nearly 50%; $n$ = 11 per group) in the dentate gyrus of the hippocampus after high-frequency stimulation of the perforant path. Measurements of long-term potentiation (LTP), an electrophysiological model of synaptic plasticity, revealed impaired LTP at this dose level. These effects were thought to be related to the reduced serum T4 observed in offspring at PND 6 and PND 14 (Crofton et al., 2003; Gilbert et al., 2004).

*Single congeners and metabolites: Mouse*

Male NMRI mice were exposed by gavage to equimolar doses of BDE-47 (0, 0.7 or 10.5 mg/kg bw) or BDE-99 (0, 0.8 or 12 mg/kg bw) on PND 10. Animals were then tested for locomotor activity over a 60-min period at the ages of 2 and 4 months ($n$ = 8 per group). Indices of spontaneous behaviour, as determined by locomotion, rearing and total activity, were significantly decreased by both PBDEs in a dose-related manner (down to 40% and 60% of control values at the higher doses of BDE-47 and BDE-99, respectively) during the first 20 min of the measuring period. During the last 20-min testing period, activity was usually increased compared with controls, mainly in the high-dose BDE-47 group and both dose groups of BDE-99. The ability of the mice in the same dose groups to habituate to a novel environment (habituation capability) appeared to become worse with age, as the indicated effects were more pronounced in mice at 4 months of age in comparison with 2 months. In addition, mice exposed to the higher dose level of BDE-99 exhibited signs of impaired reversal learning (learning and memory function) ($n$ = 16–18 per group) in a water maze when tested at 5 months of age (Eriksson et al., 2001).

In a subsequent study of similar design, three different time points (PND 3, 10 and 19) were used for the administration of a single gavage dose of BDE-99

(8 mg/kg bw or 14 µmol/kg bw; $n$ = 10 per group). The same pattern of impairment of motor behaviour as in the first study was seen in 4-month-old male NMRI mice treated on PND 3 or PND 10 (50% decrease in activity in the early testing phase and 8- to 10-fold increase in locomotion in the late phase of testing), while exposure on PND 19 was without effect. The application of $^{14}$C-labelled BDE-99 revealed no differences between the three ages in terms of the amount of radioactivity in the brain (3.7–5.1% of administered dose) 24 h after treatment. Lower (1.3–2.8% of dose), but comparable, amounts of labelled BDE-99 were found in brains from mice of all groups 7 days after the administration, thus showing that the neurobehavioural effects are due not to differences in internal exposure in the brain, but to the time of exposure. This indicates a critical period for PBDE exposure to induce alterations in motor activity (Eriksson et al., 2002).

In a follow-up of this experiment, it was shown that the behavioural alterations induced by BDE-99 (0 or 8 mg/kg bw orally on PND 10; $n$ = 12 per group) may be mediated by the cholinergic system. In control mice, nicotine (80 µg/kg bw subcutaneously) increases motor activity about 3-fold in the early phase of the testing period, while in the mice exposed to BDE-99, the opposite effect (hypoactivity) was observed following nicotine dosing (Viberg et al., 2002). Subsequent investigations with BDE-99 (12 mg/kg bw by gavage on PND 10) demonstrated decreases by about 30% in densities of nicotinic cholinergic receptors in the hippocampus ($n$ = 10 per group). One week prior to neurochemical measurements, these mice had been tested for locomotor behaviour. The known changes in spontaneous behaviour were detected at a BDE-99 dose of 12 mg/kg bw, whereas lower doses of 0.2 or 0.4 mg/kg bw were not effective (Viberg et al., 2004a). In addition, in a replicate experiment, but with a different strain of mice, it was shown that behavioural effects of BDE-99 can be detected in both sexes and two strains of mice (C57BL and NMRI). Exposure of C57BL mice ($n$ = 8 per group per sex) to a single gavage dose of BDE-99 on PND 10 (0, 0.4, 0.8, 4.0, 8.0 or 16.0 mg/kg bw) resulted in the same pattern of dose-dependent influences on spontaneous behaviour when tested at 2, 5 and 8 months of age (Viberg et al., 2004b). At doses of ≥0.4 mg/kg bw, significant alterations in behaviour were noted in both sexes, which became more pronounced with age.

Dose-related effects on activity ($n$ = 10 per group), learning and memory ($n$ = 19–24 per group) and nicotinic cholinergic receptors ($n$ = 10 per group), similar to those described for BDE-99, were also found in male NMRI mice after exposure to BDE-153 at doses of 0, 0.45, 0.9 or 9.0 mg/kg bw by gavage on PND 10 (Viberg et al., 2003a). Significant alterations in spontaneous behaviour and decreased performance in the Morris water maze (spatial learning) were observed in mice from the middle and high dose groups.

Using the same experimental design, this group also examined effects of decaBDE (BDE-209) in neonatal NMRI mice. Three age points for dosing (PND 3, 10 and 19) were selected and compared, and three dose levels were used (PND 3 and 19: 0, 2.22 or 20.1 mg/kg bw; PND 10: 0, 1.34, 13.4 or 20.1 mg/kg bw by gavage; $n$ = 10 per group). Tests of activity revealed the familiar pattern of effects as seen with BDE-99 and BDE-153 in NMRI mice treated with the highest dose on PND 3, with decreases by 40% in locomotion in the early phase and very marked

elevations in spontaneous behaviour during the late phase of testing. The alterations became more pronounced with aging from 2 to 4 and 6 months. Administration of BDE-209 on PND 10 and PND 19 was not effective at causing any behavioural alterations. The application of [U-$^{14}$C]decaBDE revealed that labelled decaBDE can be found throughout the body, including the brain, and that radioactivity increases in the brain from 24 h to 7 days after treatment when applied on PND 3 or 10. In contrast, only very low levels could be detected after administration on PND 19 (Viberg et al., 2003b).

These findings were extended in a subsequent study in which males of the same strain of mice were exposed by gavage to equimolar doses of BDE-183, BDE-203 or BDE-206 (21 µmol/kg bw or 15.2, 16.8 or 18.5 mg/kg bw on PND 3 and PND 10, respectively). At 2 months of age, effects on locomotion were detected in mice exposed to BDE-203 at PND 3 or PND 10 and after exposure to BDE-206 on PND 10. In contrast, BDE-183 caused only minor effects. Alterations of spatial learning and memory (Morris water maze) were observed in mice at 3 months of age after exposure to both BDE-203 and BDE-206 on PND 10. Taken together, the octabrominated BDE-203 was described as being the most effective congener (Eriksson et al., 2004).

Maternal exposure of CD-1 Swiss mice to BDE-99 (0, 0.6, 6 or 30 mg/kg bw per day by gavage) from GD 6 to PND 21 caused a delay (approximately 2 days) in maturation of the screen climbing response as a measure of sensorimotor development in pups of the highest dose group around PND 14 ($n$ = 12–16). Testing locomotor activity at different ages ($n$ = 6–8 per group) revealed higher activity levels in mice from the low and middle dose groups at PND 34 and PND 60 (3- to 4-fold), while at PND 120, these animals showed reduced activity in comparison with controls (by 50–60%). The high dose did not differ from controls. Ultrasonic vocalizations and the homing test did not show exposure-related differences (Branchi et al., 2002).

When BDE-99 was administered by a non-stressful feeding method (dissolved in oil and given in drinking tubes) to CD-1 Swiss mice from PND 1 to PND 21 (0, 18 or 36 mg/kg bw per day), slight reductions in the activity of choline acetyltransferase were observed in the hippocampus, but not in striatum and cortex, in offspring on PND 26 (sex and response magnitude not given; Wiegand et al., 2003).

*Single congeners and metabolites: Rat*

Wistar rat dams were injected subcutaneously with BDE-99 at 0 or 30 mg/kg bw per day from GD 2 to GD 9 or from GD 11 to GD 19 and their offspring tested for locomotor activity around PND 70. Female, but not male, offspring exposed from GD 11 to GD 19 exhibited higher values in locomotion and rearing during the late phase of the measurement period (2- to 3-fold). No effects were found after exposure from GD 2 to GD 9 (Wiegand et al., 2003).

Following behavioural testing, the brains were examined for contents of proteins associated with the glutamate–nitric oxide–cGMP pathway, a major signal transduction system. Concentrations of calmodulin and guanylate cyclase were

raised by about 100% and 30%, respectively, in the cerebellum from rats exposed from GD 11 to GD 19. In the hippocampus, calmodulin was also increased by about 100%, while guanylate cyclase was unchanged. No alterations of these proteins were found in the cortex, and content of neural nitric oxide synthase (nNOS) was not changed in all three regions. Exposure from GD 2 to GD 9 led to significant changes in nNOS in the cerebellum (10% decrease) and in the hippocampus (about 15% increase), while no change was detected in the cortex. Calmodulin was reduced by about 20% in the hippocampus and the cortex, and guanylate cyclase was elevated by about 15% and 20% in the cerebellum and hippocampus, respectively. No influence of either exposure period was found on the contents of MAP kinase 2 (MAP-2). This protein was reduced by about 30% in the hippocampus, but not in the cerebellum and cortex, irrespective of early or late gestational exposure. Microdialysis studies showed that stimulation with the glutamate agonist *N*-methyl-D-aspartate (NMDA) resulted in an enhanced increase of extracellular cGMP, which was more pronounced after BDE-99 exposure from GD 2 to GD 9 (about 2-fold and 3-fold increase in peak levels after early and late exposure, respectively). These findings are supported by corresponding measurements in vitro and ex vivo (Wiegand et al., 2003).

Recently, findings of altered activity in mice were extended to male Sprague-Dawley rats exposed to a single BDE-99 dose of 0, 0.8, 8 or 16 mg/kg bw on PND 10. Adult rats exhibited dose-related effects on spontaneous behaviour similar to those seen in mice when tested at 2 months of age, with the effects being significant at doses of 8 and 16 mg/kg bw (Viberg, 2004; Viberg et al., 2004c).

Maternal exposure of Wistar rats to BDE-99 by gavage on GD 6 (0, 60 or 300 µg/kg bw; $n$ = 10 per group) caused elevated basal locomotor activity in offspring in the higher dose group at weaning (about 25% increase) and in both dose groups at puberty (about 10% at both exposure levels). Similar changes were observed at PND 36 in rats after developmental treatment with propylthiouracil (0.05% in drinking-water from GD 7 to GD 21), which was used as a positive control for thyroid-mediated effects. However, by puberty, activity levels had normalized in this group compared with controls (Kuriyama et al., 2004a).

The same exposure protocol, but with a single dose of BDE-47 on GD 6 (0, 140 or 700 µg/kg bw by gavage; $n$ = 17–22 dams per group), resulted in similar effects on different parameters of basal locomotor activity as in BDE-99-exposed rat offspring on PND 35 and PND 70. Effects on PND 70 were significant only in females, while on PND 35, males of the higher dose group were also affected. Increases of approximately 10–25% were found in this behaviour. In addition, activity in the open field and behaviour in the elevated plus maze were examined on PND 80 and PND 150, respectively. Both sexes of the high dose group exhibited raised activity in the open field (20% and 50% increase in females and males, respectively). Also, males of the high dose group spent more time than controls in open and closed arms of the elevated plus maze, suggesting activity-related differences. The number of entries in open arms of the maze was increased (by approximately 50%) in males at the high dose, but decreased (by about 25%) in females at the low dose (Kuriyama et al., 2004c).

A different protocol, using exposure of Long-Evans rats to BDE-99 (0, 1 or 10 mg/kg bw per day, subcutaneous injection from GD 10 to GD 18), resulted in elevated sweet preference in adult male offspring, indicating behavioural feminization (see above). This effect was found together with decreased circulating concentrations of sex steroids. In addition, male offspring exhibited dose-dependent elevations in conditioned taste aversion induced by 1,25-dihydroxyvitamin $D_3$ at 6–7 months of age. Decreased serum concentrations of this steroid hormone had been detected in female offspring at weaning (see above). The onset of catalepsy induced by haloperidol was more rapid in PBDE-exposed adult offspring at both dose levels (about 50% increase in latencies; $n$ = 10–11). No effects were seen in context- versus cue-conditioned fear ($n$ = 10 per group per condition) when rats were tested on the test day after conditioning; however, exposed males exhibited significantly less activity after aversive stimulation on the conditioning day (about 50–60% decrease in comparison with controls), indicating enhanced reactivity (Lilienthal et al., 2004). Brain slices from littermates of these rats were examined for LTP ex vivo ($n$ = 6–8 per group). Recordings from cortical slices of immature rats demonstrated reduced LTP and paired pulse facilitation at the higher dose level (depression by 10–20%). In hippocampal slices, only effects on LTP were detected (decreased by about 20%). These effects persisted in aged rats (>1 year), despite the decline of internal exposure levels in adipose tissue to control values (Wiegand et al., 2003, 2004).

After exposure to the same dosing protocol, the sexual dimorphism in PR mRNA expression in the ventromedial hypothalamic nucleus (VMH) was abolished in female offspring by BDE-99 at both doses due to a decrease in PR mRNA. No changes were observed in the medial preoptic area (MPO), but there were exposure-related elevations of ERα mRNA in both brain regions. Also, mRNA of preproenkephalin, the precursor of the neuropeptide enkephalin, was found to be increased in the VMH in both sexes and decreased in the medial preoptic area in male offspring, but only at the lower dose (Lichtensteiger et al., 2003, 2004). Adult male offspring from the high dose group that were gonadectomized and treated with estradiol ($n$ = 6–9 per group) exhibited a 30% increase in PR mRNA in the VMH compared with ectomized and estradiol-treated controls and a decrease by approximately 25% at the low dose. In contrast, in females, a dose-related decrease to about 70% of control values was found at the high dose. In the MPO, there were decreases in both sexes and at both dose levels. In intact female offspring, there was a marked reduction (down to about 10% of control values) in mating behaviour in the high dose group.

#### *(iii) Summary of neurotoxic effects*

The majority of investigations examining neurotoxicity in vivo used exposure to single congeners in mice and rats. In mice, single exposure of neonates on 1 postnatal day was chosen in almost all experiments. Decreased locomotor activity in the early phase of measurement and impaired habituation of activity in the late phase were observed in these studies (see Table 90 in section 10). Progressively, more pronounced effects were detected with ageing of mice, with the early postnatal period of exposure being more sensitive (Eriksson et al., 2002; Viberg et

al., 2003b). BDE-99 and BDE-153 appear to be more potent than BDE-47 in altering these measures (Eriksson et al., 2001; Viberg et al., 2004a, 2004b). BDE-209 was also reported to induce neurobehavioural changes, but at higher doses compared with the lower brominated congeners (Viberg et al., 2003b). For BDE-99, a BMD has also been calculated based on results from Viberg et al. (2004b) (Sand et al., 2004; see Table 85 in section 10). Effects on locomotor activity were also seen in the other experiments with mice using perinatal exposure to BDE-99 (Branchi et al., 2002); exposed young mice tended to be hyperactive compared with controls between PND 34 and 60 but hypoactive by PND 120. In rats, exposure on 1 day postnatally resulted in the same effects on activity and habituation found in mice (Viberg et al., 2004c). Studies from one group reported altered activity levels after exposure to a very low dose of BDE-47 and BDE-99 on GD 6 (Kuriyama et al., 2004a, 2004c; see Table 91 in section 10). Perinatal exposure to the technical mixture DE-71 did not influence spatial learning and context-conditioned fear (Gilbert et al., 2004), but impaired cue-conditioned fear (Taylor et al., 2003). On the same behavioural task, altered reactivity to aversive stimulation was also found after gestational treatment with BDE-99 (Lilienthal et al., 2004). In this study, effects on haloperidol-induced catalepsy were also found, together with alterations in steroid-dependent behaviour. In addition, BDE-99 abolished the sexual dimorphism in PR mRNA expression in the VMH of female offspring and markedly reduced mating behaviour (Lichtensteiger et al., 2003, 2004). Perinatal exposure to DE-71 impaired LTP in the hippocampus (Gilbert et al., 2004), whereas BDE-99 caused decreases of LTP in the cortex after gestational treatment. This difference was also found in aged offspring when adipose tissue concentrations of BDE had declined to control values (Wiegand et al., 2003, 2004). LTP is the electrophysiological correlate of synaptic plasticity.

*(e) Effects on development of reproductive organs*

Post-weanling Wistar rats ($n$ = 15) were treated by gavage to DE-71 (0, 3, 30 or 60 mg/kg bw per day) for either 20 (PND 22–41, females) or 31 consecutive days (PND 23–53, males) and then assessed for pubertal development and reproductive end-points. The commercial lot of DE-71 was reported to be composed of 58.1% pentaBDE and 24.6% tetraBDE. There was a significant delay (1.8 days) in vaginal opening in the high-dose females, while preputial separation was significantly delayed (1.7–2.1 days) in males from the two highest dose groups. Ventral prostate and seminal vesicle weights were also significantly decreased (15–19%) in males from the high dose group compared with controls (Stoker et al., 2004a). No significant differences were noted with respect to body weight gain in any treatment group.

Effects of the PBDE congener BDE-99 were presented in a short study in Wistar rats (Talsness et al., 2003). Pregnant rats (number not given) were given BDE-99 at 0, 60 or 300 µg/kg bw by gavage as a single dose on GD 6. The female offspring were killed in estrus at about PND 90, and the ovaries were excised and studied using electron microscopy. At the 60 µg/kg bw dose, destruction of luminal surfaces of the serosal epithelial cell was apparent, and organelles seemed to be in a process of dissolution. At 300 µg/kg bw, the degenerative changes were more

pronounced, and the authors suggested a dissolution of the endoplasmic reticulum and tubular mitochondria. In sections from control animals, the cell structures seemed intact and of normal appearance. The number of animals in each group subjected to microscopy was not reported.

Pregnant Wistar rats were treated with a single oral dose of BDE-99 (0, 60 or 300 µg/kg bw; $n$ = 16–20) on GD 6, with male offspring ($n$ = 12–20) undergoing reproductive assessment between PND 140 and PND 160. There was a dose-related decrease in relative testis weight (approximately 10% at the highest dose group) and a minor decrease for both dose groups in relative epididymis weight. Spermatid, sperm number and daily sperm production were decreased by both PBDE doses, with maximum declines reaching approximately 34% of control values (Kuriyama et al., 2004a). No effects were observed with respect to serum LH or testosterone levels. While no effects were observed with respect to male sexual performance, only 39% and 21% of the 60 and 300 µg/kg bw dose groups, respectively, were able to achieve a second ejaculation during a 20-min mating period, compared with 53% of controls (statistically significant at the high dose).

Exposure of pregnant Wistar rats to daily oral doses (gavage) of either BDE-47 (20 mg/kg bw per day) or 6-OH BDE-47 (5 mg/kg bw per day) between GD 10 and GD 16 had no effect on offspring sex ratio, growth, timing of various developmental landmarks (vaginal opening, preputial separation) or estrous cycle length between PND 210 and PND 230 (Buitenhuis et al., 2004).

## 2.3 Observations in humans

### 2.3.1 Biomarkers of effect

In vitro immunotoxic response was studied in human lymphocytes after exposure to PBDE congeners at doses from $10^{-5}$ to $10^{-9}$ mol/l (Fernlof et al., 1997). No effects on pokeweed mitogen-stimulated DNA proliferation or IgG synthesis were found after exposure to BDE-47 or BDE-85.

### 2.3.2 Clinical observations

DecaBDE is the only PBDE for which limited human data are available. Skin sensitization potential of "decaBDE" (Dow Chemical, USA; containing 77.4% decaBDE, 21.8% nonaBDE and 0.8% octaBDE) was studied in 50 volunteers (Norris et al., 1975b). A 5% suspension of decaBDE in petroleum was applied to the skin 3 times per week for 3 weeks, followed by a challenge treatment 2 weeks after the last induction application. No skin sensitization responses were observed during the study. Another skin sensitization study was carried out in 80 male and 120 female volunteers, who were exposed to two batches of decaBDE (purity not stated) (described in IPCS, 1994). The volunteers were treated with nine induction patches at 2-day intervals, and the test substance was kept in contact with skin for 24 h. The induction regimen was followed by a period of 12 days without treatment, after which a new skin site was used for a 24-h challenge patch. Skin reactions were observed at 24 and 48 h after removal of the challenge patch. The study revealed no evidence of skin sensitization.

### *2.3.3 Epidemiological studies*

Workers exposed to polybrominated biphenyls (PBBs) and PBDEs, including decaBDE, during manufacture were reported to have a higher than normal prevalence of primary hypothyroidism and a significant reduction of sensory and motor neuron conductance velocities, but no other neurological or dermatological changes (Bahn et al., 1980). It was not possible to conclude whether these changes were attributed to PBB or PBDE exposure; however, no decaBDE could be detected in serum of the exposed workers.

Four epidemiological studies have been conducted on workers of facilities where flame retardant polymers have been extruded (not retrievable, but reviewed in IPCS, 1994). The workers were potentially exposed to brominated flame retardants, including PBDEs, and in some cases also to polybrominated dibenzo-*p*-dioxins (PBDDs) and dibenzofurans (PBDFs). According to the International Programme on Chemical Safety (IPCS) review (IPCS, 1994), these studies did not find any adverse effects attributable to the exposure to these chemicals.

In an epidemiological study from Sweden, an association was reported between the risk of non-Hodgkin lymphoma (NHL) and adipose tissue levels of BDE-47 (Hardell et al., 1998). In the study, BDE-47 levels from 19 patients with NHL, 23 with malignant melanoma and 8 other cancer patients were compared with concentrations in 27 selected controls with no cancer diagnosis. The authors stated that a "nonsignificant elevated risk" was found when cases and controls were compared with the two highest concentration groups with the lowest group (<2.05 ng/g lipid), with an odds ratio of 1.9 (confidence interval [CI] 0.3–1.4) or 3.8 (CI 0.7–26), respectively.

In a follow-up study, Hardell and co-workers (2001) found higher BDE-47 levels in adipose/blood samples collected from Swedish patients diagnosed with NHL compared with matched controls. In samples from 80 patients, the mean BDE-47 level was 8.2 ng/g (0.1–134 ng/g), and in control samples (83 individuals), 2.4 ng/g (0.05–28 ng/g). The results from the patients were further grouped according to Epstein-Barr early antigen (EA) titres; patients with high BDE-47 levels and high EA titres had a higher odds ratio than samples showing lower EA titres. The odds ratios for these two groups were 21 (CI = 1.9–24) and 13, respectively.

In a study on Swedish and Latvian fish consumers, the levels of BDE-47 and several hormones were determined in plasma of 110 men with various consumption (0–32 meals per month) of Baltic Sea fish (Hagmar et al., 2001). The study showed a weak negative correlation between BDE-47 and TSH, after adjustment for age. However, BDE-47 could explain only approximately 10% of the variance in TSH ($P < 0.001$), and the authors concluded that such a significant correlation could result from pure chance.

## 3. ANALYTICAL METHODS

### 3.1 Commercial PBDE production

PBDE products are typically produced in three different degrees of bromination, mostly identified with an average bromine content of pentaBDE, octaBDE and decaBDE. These products contain diphenyl ethers with mainly 4–6, 6–10 and 10 bromine atoms, respectively. The number of PBDE congeners present in each of the commercial products is surprisingly small, i.e. 2 major and 10 minor components are present at levels exceeding 1% in the technical PentaBDE preparation Bromkal 70-5-DE (Sjödin, 2000). In commercial PCB mixtures, the number of PCB congeners is considerably larger. This smaller number of congeners is reflected in biological samples as well. The first report of the presence of PBDE congeners containing 4–6 bromines in fish from a Swedish river was given by Andersson & Blomkvist (1981).

### 3.2 Description of analytical methods

#### 3.2.1 Introduction

The analytical procedure from collection of samples to the final identification and quantification of the analytes consists of a number of well defined steps. Each of these steps is equally important to the final results. Depending on the type of sample, the kind of sampling or sampling procedure that will be seen as the best way to receive relevant and representative data for the samples must be considered. Storage of samples collected is also an important aspect for saving samples over longer periods of time. The procedure used for preparation of the samples must be designed in a way that the analytes remain intact while the remaining sample matrix is removed and/or degraded. For instrumental analysis, the technique applied must be sensitive and specific enough to identify and quantify the analytes of interest. In the following, techniques and methods used in various laboratories are reviewed.

#### 3.2.2 Congeners analysed

The total number of PBDE congeners is 209. For reasons of occurrence in samples and analytical capability, only a limited number of congeners have been measured in the last few years. This number ranges between three and nine congeners (given in **bold** in Table 8). Due to increasing analytical power and availability of standards, the number of congeners measured in experienced laboratories is in the mid-30s.

#### 3.2.3 Screening tests

The knowledge on screening tests for PBDEs is quite limited. Behnisch et al. (2003) did development work in this area. They measured for up to 13 individual PBDE congener DR-CALUX-REP and Micro-EROD-REP values. The most sensitive component was found to be BDE-126.

*Table 8. Thirty-two PBDE congeners measured in biological samples*[a]

| Bromines per molecule | BDE congener number |
|---|---|
| MonoBDEs | 1, 2, 3 |
| DiBDEs | 7, 10, 13, 15 |
| TriBDEs | **47**, 49, **66**, 75, 77 |
| PentaBDEs | 85, **99**, **100**, 116, 126 |
| HexaBDEs | 138, **153**, **154**, 155, 166 |
| HeptaBDEs | 181, **183** |
| OctaBDEs | 197, 203 |
| NonaBDEs | 207 |
| DecaBDE | **209** |

[a] The numbers given in bold should be "standard" in laboratories involved.

### *3.2.4 Quantitative methods*

Due to the analytical method applied for the detection of PBDEs, there are important restrictions in the procedure. The application of the isotope dilution method by using $^{13}C$-labelled standards is strongly recommended. The electron capture detection (ECD) and electron capture negative ionization–low-resolution mass spectrometry (ECNI-LRMS) techniques measure only halogens or bromine-containing substances. In Table 9, the advantages and disadvantages of different detection techniques for PBDEs are given. However, the distinction between advantages and disadvantages of a method is dependent on the particular application and on personal preferences.

An important part of the analytical procedure is the determination of the adequate detection limit. Table 10 gives an overview of typical sample amounts and resulting detection limits. The detection limits are estimations and relevant for measurements performed by use of modern high-resolution mass spectrometric (HRMS) instrumentation.

*(a) Extraction, cleanup methods*

Several methods for extraction of biological samples have been proposed in the literature. For extraction of solid material, the Soxhlet procedure is used in many laboratories. This method is, however, a time-consuming technique that, in addition, requires large quantities of organic solvent. Other techniques include supercritical fluid extraction (SFE), microwave-assisted extraction (MAE) and solid-phase extraction (SPE). A schematic representation of analytical methods used for extraction and cleanup of solid and lipid biological samples is given in Figure 3.

*Table 9. Advantages and disadvantages of different detection techniques for PBDEs*

| Detection | Advantages | Disadvantages |
|---|---|---|
| ECD | Low-cost analysis, maintenance cost low, relatively easy to use | Fair sensitivity for PBDEs, instability of linear range, poor selectivity, no isotope dilution method possible |
| EI-LRMS | Facilitates the use of $^{13}C$-labelled standards, good selectivity | Relatively low sensitivity |
| ECNI-LRMS | Good sensitivity, good selectivity for brominated compounds | Interference with other brominated components possible, frequent source maintenance required, no isotope dilution method possible |
| EI-HRMS | Good sensitivity, very good selectivity, use of $^{13}C$-labelled standards, "gold standard" in PBDE analysis | Purchase cost, maintenance cost, needs highly trained personnel |

ECD, electron capture detection; ECNI, electron capture negative ionization; EI, electron impact; HRMS, high-resolution mass spectrometry; LRMS, low-resolution mass spectrometry

*Table 10. Required sample amounts and typical detection limits*

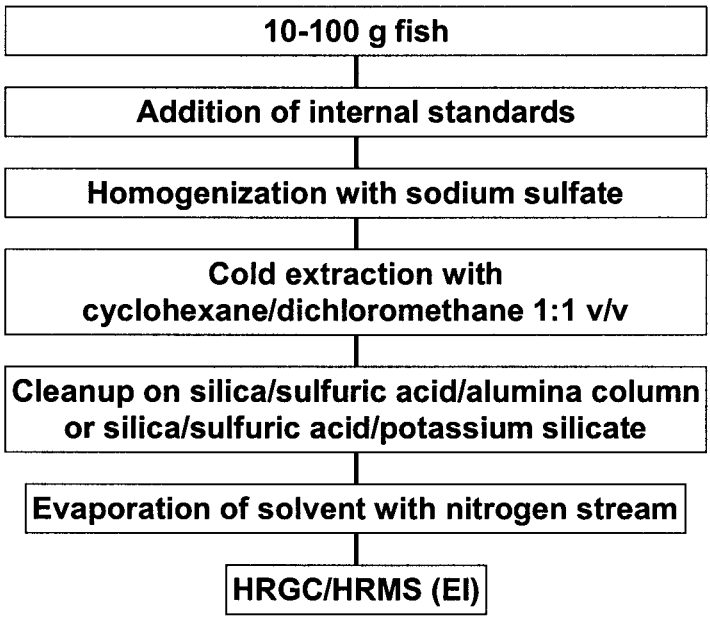
| Sample type | Typical sample amount | Limit of detection (LOD)[a] lipid based (ng/g) |
|---|---|---|
| Human milk, 3% lipid | 10–25 ml | 0.005 |
| Cows' milk, 3% lipid | 10–100 ml | 0.005 |
| Human blood, 0.3% lipid | 10–25 ml | 0.05 |
| Human serum, 0.5% lipid | 5–15 ml | 0.05 |
| Fish, 1–10% lipid | 10–200 g | 0.01 |
| Meat, 2–20% lipid | 5–100 g | 0.01 |

[a] LOD for tetra- and pentaBDE congeners.

An overview of various typical treatments of biological samples is presented in Table 11 for food and in Table 12 for human samples. The tables present information on pretreatment of samples, extraction type, cleanup procedure, type of detection and typical recovery rates.

As can be seen from both tables, there is a general difference in pretreatment of liquid and solid samples. Solid samples are normally mixed with sodium sulfate and then eluted by an adequate solvent, whereas liquid samples are extracted by a liquid–liquid extraction procedure.

*Figure 3. Example of analytical treatment of fish samples for the analysis of PBDEs*




Adapted from Päpke et al. (2004)

*(b) Instrumental analysis*

Brominated substances are often analysed under chemical ionization conditions, monitoring the negative ions formed by electron capture reactions (ECNI). The predominant ions formed from organobromine substances under such conditions are the bromine isotopes m/z 79 and 81. This technique is more sensitive and less costly than other alternatives, such as HRMS. However, the latter technique has a higher selectivity than MS (ECNI) detection of bromine ions, since the accurate mass of the molecular ion or fragment ion is recorded. The higher specificity of HRMS to reduce the risk of misinterpretation of interfering substances resulted in the selection of this method as the "gold standard" in determination of PBDEs.

The response of PBDE congeners studied — especially under ECNI — decreases with increasing numbers of bromine atoms in the molecule. Hence, the implementation of a congener-specific analysis using authentic reference standards is of importance. In the case of applying HRMS, this issue is easily resolved by using the $^{13}C$-labelled internal standards. The use of this type of internal standard offers the exact observation of the whole analytical procedure inclusively and the knowledge of the recoveries of the surrogates used.

*Table 11. PBDE analysis (extraction/cleanup/detection) for biota samples (mussels, fish, marine mammals, birds, eggs, meat)*

| Sample | Pre-treatment | Extraction | Cleanup | Detection | Recovery (%) | References |
|---|---|---|---|---|---|---|
| Fish | Mixing with $Na_2SO_4$ | Soxhlet (16 h), DCM/Hex = 1:1 | (1) Florisil, elution with Hex/DE = 94:6<br>(2) Treatment with conc. $H_2SO_4$ | AED | >80 | Johnson & Olson (2001) |
| Fish, marine mammals | Mixing with $Na_2SO_4$ | Soxhlet (6 h), Hex/Acet = 3:1 | (1) GPC for lipid removal<br>(2) Silica, elution with Hex<br>(3) Treatment with concentrated $H_2SO_4$ | ECNI-MS | not reported | de Boer et al. (2001) |
| Fish | Mixing with $Na_2SO_4$ | Soxhlet (24 h), Hex/Acet = 1:1 | (1) GPC for lipid removal<br>(2) Silica, elution with DCM | EI or ECNI-MS | 70–120 | Dodder et al. (2002) |
| Fish | Mixing with $Na_2SO_4$ | Column extraction with 300 ml DCM | (1) GPC on Bio-beads SX3, eluent DCM/Hex<br>(2) Silica, elution with DCM | EI-HRMS | 65–120 | Alaee et al. (2001) |
| Salmon | Mixing with $Na_2SO_4$ | SLE with Hex/Acet and Hex/DE | (1) GPC for lipid removal<br>(2) KOH/EtOH partitioning neutral compounds<br>(3) Silica, elution with Hex<br>(4) Treatment with concentrated $H_2SO_4$ | ECNI-MS | 80–90 | Asplund et al. (1999) |
| Fish, fish feed | Mixing with $Na_2SO_4$ | Soxhlet (2 h), Hex/Acet = 3:1 | Acidified silica, elution with Hex | EI-MS, ECNI-MS | >80 | Jacobs et al. (2002) |
| Fish oil | Dilution in Hex | – | Acidified silica, elution with Hex | ECNI-MS | >80 | Jacobs et al. (2002) |
| Seal, herring | Mixing with $Na_2SO_4$ | Column extraction with 300 ml Hex/Acet = 7:3 and 300 ml Hex/DE = 9:1 | (1) GPC on PL-gel, eluent Hex/DCM = 1:1<br>(2) Florisil, elution with Hex/DCM = 1:1 | EI-MS | 50–115 | Haglund et al. (1997) |
| Fish, bird eggs | Homogenization with Ultra-Turrax | SLE, Hex/Acet (1:2.5) and and Hex/DE (9:1) | (1) Treatment with conc. $H_2SO_4$<br>(2) GPC, eluent DCM/Hex = 1:1<br>(3) Silica, elution with Hex and Hex/DE = 4:1 | ECNI-MS | 39–65 | Jansson et al. (1991) |

*Table 11.* (contd)

| Sample | Pre-treatment | Extraction | Cleanup | Detection | Recovery (%) | References |
|---|---|---|---|---|---|---|
| Bird eggs | Mixing with $Na_2SO_4$ | ASE (3 × 15 min, with Hex/Acet = 1:1) | (1) GPC<br>(2) Silica, elution with Hex/Tol = 6:4 | EI-LRMS | not reported | Herzke et al. (2001) |
| Bird eggs | Mixing with $Na_2SO_4$ | Soxhlet with D/H = 1:1 | (1) GPC<br>(2) Florisil, elution with Hex | EI-HRMS | not reported | Norstrom et al. (2002) |
| Fish, meat, vegetables | Freezing-drying | (1) Saponification with KOH/EtOH (2 h)<br>(2) LLE with Hex | (1) Multicolumn with $AgNO_3$/silica – acid silica – silica – basic silica, elution with DCM/Hex = 5:95<br>(2) Active carbon, elution with DCM/Hex = 1:3 | EI-HRMS | >80 | Ohta et al. (2002) |
| Fish | Mixing with $Na_2SO_4$ | Cold extraction with DCM and CHex | Multicolumn with acid silica – silica – basic silica, alumina | EI-HRMS | >60 | Päpke et al. (2004) |
| Milk | Adding of K-oxalate and EtOH | Extraction with DE and ether | Multicolumn with acid silica – silica – basic silica, alumina | EI-HRMS | >60 | Päpke et al. (2004) |
| Fish | Mixing with $Na_2SO_4$ | Soxhlet with D/H = 1:1 | (1) GPC<br>(2) Florisil, silica, alumina | EI-HRMS | not reported | Hites et al. (2004) |

Solvents: Acet, acetonitrile; CHex, cyclohexane; DCM, dichloromethane; DE, diethyl ether; EtOH, ethanol; Hex, hexane; Tol, toluene

Methods: AED, atomic emission detection; ASE, accelerated solvent extraction; D/H, deuterium/hydrogen ratio; ECNI, electron capture negative ionization; EI, electron impact; GPC, gel permeation chromatography; HRMS, high-resolution mass spectrometry; LLE, liquid–liquid extraction; LRMS, low-resolution mass spectrometry; MS, mass spectrometry; SLE, supported liquid extraction

*Table 12. PBDE analysis (extraction/cleanup/detection) of human tissues and fluids (adipose tissue, serum, milk)*

| Sample | Sample pretreatment | Extraction | Cleanup | Detection | Recovery (%) | References |
|---|---|---|---|---|---|---|
| Adipose tissue | Drying with $Na_2SO_4$ | Soxhlet (2 h), Hex/DCM/Acet = 3:1:1 | (1) Acid silica<br>(2) Acid silica/alumina, elution Hex | EI-MS | 81–102 | Covaci et al. (2002a, 2002b) |
| Adipose tissue | Drying with $Na_2SO_4$, mixing with alumina | SFE with $CO_2$, 40 °C, 30.4 MPa, trapping on PX21/$C_{18}$, elution with Hex/DCM | – | EI-MS, TOF-MS | not reported | van Bavel et al. (1999) |
| Adipose tissue/liver | Homogenization | Ultra Turrax extraction with i-PrOH/Hex = 2:3 and Hex | (1) Lipide x 5000 partitioning (after mixing with i-PrOH, formic acid)<br>(2) Column elution with MeOH in $H_2O$ and Acet<br>(3) Alumina and silica columns, elution with Hex<br>(4) GPC on Bio-beads SX-3 | EI-HRMS | 57–84 | Meironyté Guvenius et al. (2001) |
| Adipose tissue | Homogenization | Soxhlet (24 h), Tol | (1) Silica gel<br>(2) Activated carbon (Carbopack C)<br>(3) Activated alumina | EI-HRMS | 42–104 | Strandman et al. (1999) |
| Human breast adipose tissue | Homogenization | Hex/DCM | (1) GPC<br>(2) Florisil, elution with Hex | ECNI-MS | not reported | She et al. (2000); Petreas et al. (2002) |
| Serum | HCl and i-PrOH addition | Hex/MTBE = 1:1 | (1) Washing with KCl solution<br>(2) KOH/EtOH partitioning<br>(3) Treatment with concentrated $H_2SO_4$<br>(4) Acid silica, elution with Hex | ECNI-MS | 69–95 | Sjödin et al. (1999) |

*Table 12.* (contd)

| Sample | Sample pretreatment | Extraction | Cleanup | Detection | Recovery (%) | References |
|---|---|---|---|---|---|---|
| Serum | (1) Formic acid/ i-PrOH (4:1)<br>(2) Ultrasonication<br>(3) Dilution with $H_2O$ | SPE on Isolute ENV+ (200 mg, 6 ml) | (1) Lipid decomposition with conc. $H_2SO_4$<br>(2) Wash with $H_2O$, acetate buffer and $H_2O$/MeOH<br>(3) Elution with DCM/MeOH = 1:1 | ECNI-MS | 56–111 | Thomsen et al. (2001) |
| Milk | Homogenization, mixing with formic acid and Lipide x 5000 | (1) Wash with MeOH/$H_2O$<br>(2) Elute with Acet | Alumina and silica columns, elution with Hex<br>GPC on Bio-beads SX-3, elution with Hex/DCM | EI-HRMS | 57–84 | Meironyté Guvenius et al. (2001) |
| Milk | (1) Formic acid/ i-PrOH (4:1)<br>(2) Ultrasonication<br>(3) Dilution with $H_2O$ | SPE on Osais HLB (500 mg, 6 ml) | (1) Lipid decomposition with conc. $H_2SO_4$<br>(2) Wash with $H_2O$, acetate buffer and $H_2O$/MeOH<br>(3) Elution with DCM/MeOH = 1:1 | ECNI-MS | 49–83 | Thomsen et al. (2003) |
| Milk | Saponification with ethanolic KOH | LLE with Hex | (1) Multilayer column acid silica – silica – base silica, elution with Hex | EI-HRMS | >80 | Ohta et al. (2002) |
| Milk | – | LLE with Hex/Acet | (1) Conc. $H_2SO_4$<br>(2) GPC<br>(3) Florisil, elution with H | EI-HRMS | 85–10 | Ryan & Patry (2000) |
| Milk | Adding of K-oxalate and EtOH | Extraction with DE and ether | Multicolumn with acid silica – silica – basic silica, alumina | EI-HRMS | >60 | Päpke et al. (2001) |
| Milk | Adding of K-oxalate and EtOH | Extraction with DE and ether | GPC, multicolumn with acid silica – silica | EI-HRMS | not reported | Fürst (2001) |

***Table 12.*** (contd)

| Sample | Sample pretreatment | Extraction | Cleanup | Detection | Recovery (%) | References |
|---|---|---|---|---|---|---|
| Whole blood | Adding of EtOH and water | LLE with Hex/ISOP | Multicolumn with acid silica – silica – basic silica, alumina | EI-HRMS | >60 | Päpke et al. (2004) |

Solvents: Acet, acetonitrile; DCM, dichloromethane; DE, diethyl ether; EtOH, ethanol; Hex, hexane; i-PrOH, 2-propanol; ISOP, isopropanol; MeOH, methanol; MTBE = methyl *tertiary*-butyl ether; Tol, toluene

Methods: ECNI, electron capture negative ionization; EI, electron impact; GPC, gel permeation chromatography; HLB, hydrophilic–lipophilic balance; HRMS, high-resolution mass spectrometry; LLE, liquid–liquid extraction; MS, mass spectrometry; SFE, supercritical fluid extraction; SPE, solid-phase extraction; TOF, time of flight

Following EPA method 1614 (US EPA, 2003), recoveries of $^{13}C$ standards of PBDEs should be expected within the ranges shown in Table 13.

***Table 13. Recoveries of internal standards***

| PBDE group | BDE congener number | Recovery (%) |
|---|---|---|
| TriBDEs | 28 | 50–150 |
| TetraBDEs | 47 | 50–150 |
| PentaBDEs | 99, 100 | 50–150 |
| HexaBDEs | 153, 154 | 50–150 |
| HeptaBDEs | 183 | 50–150 |
| DecaBDE | 209 | 25–200 |

*(c) Selection of GC columns*

The physical and chemical properties of BDE-209 put great demands on the analytical method, including sampling, extraction and cleanup, as well as final chromatographic separation. The problems encountered during the analysis of high-molecular-mass BDE congeners are associated with thermal instability, rather than their high boiling points. The degradation of, particularly, BDE-209 is increased with temperatures, time spent at elevated temperatures and presence of catalytic sites. For best yield of the decabrominated congener, these parameters should be kept as low as possible. The GC separation of PBDEs is often performed on two separate columns, a 30- to 60-m-long column for analysis of the low-molecular-mass BDE congeners and a shorter column for the analysis of the high-molecular-mass BDE-209.

Björklund et al. (2003) demonstrated that columns with supposedly similar stationary phases may result in a large difference in the yield of PBDEs. Furthermore, losses of high-molecular-mass BDE congeners do occur in the GC column and are correlated with the column length and the stationary film thickness. The time, temperature and catalytic sites all contribute to reduce the yield of the high-molecular-mass congeners. To obtain a high yield of these components, especially for BDE-209, short inert columns with a thin stationary phase are preferred. In Table 14, possible columns for PBDE analysis are given.

Table 15 shows the increasing relative response for BDE-209, depending on column type and length.

*(d) GC injection techniques*

The injection of PBDEs into the GC system is a critical and important part of the chromatographic analysis. Thus, careful selection and optimization of the injection techniques have to be performed in order to reduce the discrimination of these compounds. Splitless is the most commonly used injection technique for GC

separation of PBDEs. However, both the septum-equipped temperature programmable injector, the programmable temperature vaporizing injector as well as on-column injectors have been successfully used. Large-volume injections using either programmable temperature vaporizing in solvent elimination mode or the loop-type interface have also been used (Tollbäck et al., 2003).

***Table 14. Columns for possible use in PBDE analysis***

| Column | Length (m) | Inner diameter (mm) | Phase thickness (μm) | Comments |
|---|---|---|---|---|
| J & W DB-5 | 15 | 0.25 | 0.10 | |
| J & W DB-5 | 15 | 0.25 | 0.25 | |
| J & W DB-1 MS | 5, 15, 30 | 0.25 | 0.10 | |
| Agilent HP-1 | 15 | 0.25 | 0.10 | |
| Agilent XLB | 15, 30 | 0.25 | 0.10 | Extremely low bleed |
| Varian factorFOUR™ | 5, 15, 30 | 0.25 | 0.10 | Ultra low bleed |

From Björklund et al. (2003)

***Table 15. Relative response for BDE-209 vs BDE-99 and estimated LOD for BDE-209 on different columns***

| Column | Estimated LOD (30 m) (picograms injected) | Relative response, BDE-209 vs BDE-99 | | |
|---|---|---|---|---|
| | | 30 m | 15 m | 5 m |
| FactorFour | 1.3 | 0.06 | 0.36 | 0.46 |
| XLB | 250 | 0 | 0.008 | –[a] |
| DB-5MS | 0.9 | 0.05 | 0.33 | 0.50 |

From Björklund et al. (2003)

LOD, limit of detection

[a] Not investigated.

In Table 16, the yield for the high-boiling decaBDE using different injection techniques is presented.

***Table 16. Yield of BDE-209 obtained using different injection techniques***

| Injection type | Peak area BDE-209 (instrument response) |
|---|---|
| Mean splitless | 20 000 |
| Optimized splitless | 50 000 |
| On-column | 165 000 |
| Direct injection | 165 000 |

From Tollbäck et al. (2003)

*(e) Phytolytic decomposition of PBDEs*

Various studies have shown that PBDEs (especially decaBDE) and other brominated organic compounds in solvents undergo rapid photolytic debromination in the presence of ultraviolet light under laboratory conditions (Sellström et al., 1998; Herrmann et al., 2003). Due to this fact, it is strongly recommended that all analytical treatments be undertaken in brown glass or in glassware covered with aluminium foil.

*(f) Analysis of method blanks*

The analysis of blank samples has a special importance for the determination of PBDEs in various biological tissues. Due to marginal contamination of solvents and adsorbents used during PBDE analysis, all material has to be tested in advance. In parallel to method development, the reduction of a potential blank contamination needs special attention.

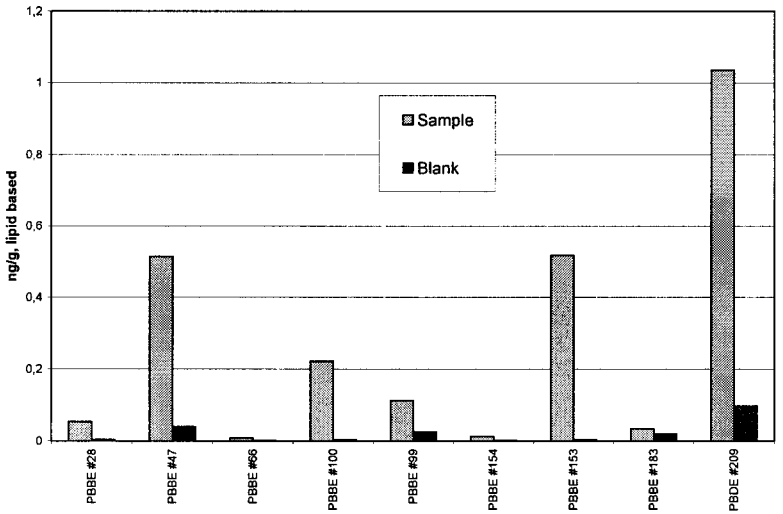
Along with each batch of samples, blank samples should be analysed as well. Values for samples should be reported only if the sample level is at least twice the blank level.

In Figure 4, a fish sample contaminated with low levels of PBDEs is compared with a blank sample. The figure indicates the relatively low influence of the blank on the sample values. It should be mentioned that blanks — depending on sample type, sample amount, applied cleanup procedure and finally laboratory equipment — may be quite different. Therefore, it is strongly recommended that a separate block of blanks be available at least for each type of sample.

In the case of an unsatisfying influence of blanks on samples, a significant reduction of the blank values could be achieved by the following procedures:

- Rotary evaporators should not be used in order to reduce the risk of contamination. Volume reduction can be reached by moderate heating or by a gentle stream of cleaned nitrogen/air.
- All glassware should be rinsed by analytical-grade solvents prior to use.
- Solvents and reagents should be tested before the laboratory procedures.
- Silica gel and sodium sulfate should be pre-washed.
- No plastic equipment should be used.
- Due to potential contamination of solvents and chemicals via air, containers/bottles should be closed as soon as possible after usage.
- The methodology should be miniaturized by reducing solvent volumes, if possible.

***Figure 4. Comparison of PBDE levels in a blank and a fish sample***

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*(g) Example of a GC/HRMS run*

In Figure 5, a typical GC/HRMS run of a medium-contaminated fish sample is presented. In this figure, only one trace of each isomeric pattern is shown.

*(h) Quality control and quality assurance*

Quality control (QC) and quality assurance (QA) represent an important tool of the total analytical concept. In total, more than 30% of the whole analytical effort is covered by QC/QA measures.

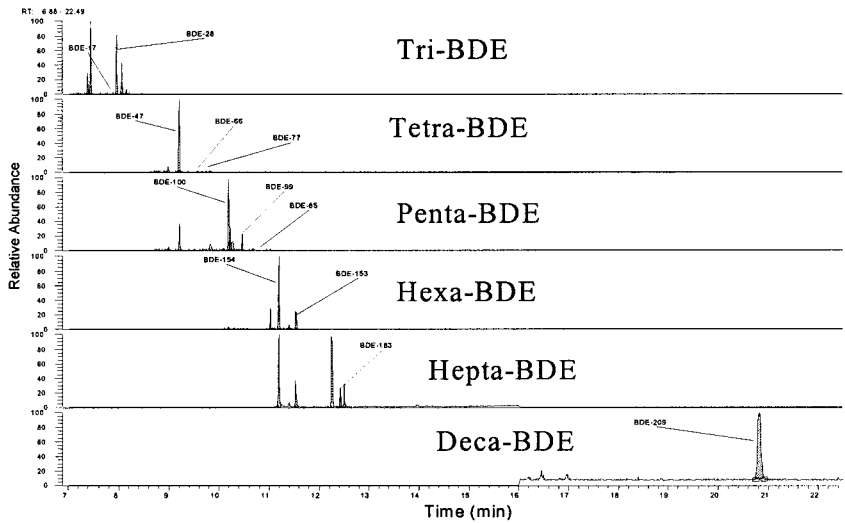
*(i) Internal measures*

Internal measures performed on a routine basis include:

- regular chemical and glassware checks (blanks), once a block of 4, 6 or 10
- regular checks of so-called instrument blanks (GC/MS)
- regular checks of QC samples (e.g. blood pools) (GC/MS)
- daily calibration verification tests
- regular GC performance tests (separation, retention time windows)

- identification based on definite abundance ratio and retention time criteria, with the use of internal and external standards
- quantification based on the isotope dilution method with the use of internal and external standards
- establishing a five- to seven-point calibration curve and regular repetition of single concentration points
- regular method performance checks by analysing control samples of known PBDE concentrations
- daily MS performance checks to control the resolution and sensitivity

***Figure 5. Mass fragmentograms of PBDEs in a fish sample***




Reprinted from *Talanta*, Vol. 63, Päpke, O., Fürst, P. & Herrmann, T., Determination of polybrominated diphenyl ethers (PBDEs) in biological tissues with special emphasis on QC/QA measures, pp. 1203–1211, 2004, with permission from Elsevier.

*(ii) External measures*

External measures should include:

- regular participation in interlaboratory QC studies and proficiency tests covering those matrices that are regularly analysed
- exchange of samples and control measurements of standards and samples with other qualified laboratories

More detailed information with respect to QA/QC measures is given by Päpke et al. (2004).

## 4. SAMPLING PROTOCOLS

There are no specific guidelines for sampling protocols for food samples to be analysed for their PBDE content. Therefore, basic rules for sampling for organic contaminants or pesticides should be followed. The primary requirement is a representative, homogeneous laboratory sample with no secondary contamination.

### 4.1 Personnel

A qualified, authorized person should perform sampling.

### 4.2 Representative sample

Samples must be representative of the lots or sublots from which they are taken. Compliance with maximum levels or action levels should be established on the basis of the concentrations determined in the laboratory sample.

- Lots are identifiable quantities of food delivered at one time and determined by the official to have common characteristics, such as origin, variety, type of packaging, packer, consigner or markings. In the case of fish, they should be of comparable size.
- Sublots are designated parts of a large lot to which the sampling method is applied. Each sublot must be physically separate and identifiable.
- An incremental sample is a quantity of material taken from a single place in a lot or sublot. As far as possible, incremental samples should be taken at various places distributed throughout the lot or sublot.
- An aggregate sample is the combined total of all the incremental samples taken from the lot or sublot. It should be at least 1 kg, unless impractical.
- A laboratory sample for the purposes of enforcement, trade and refereeing should be taken from the homogenized aggregate sample, unless this conflicts with Member States' regulations on sampling. The sample used to ensure enforcement should be large enough to allow at least duplicate analysis.

### 4.3 Packaging, transport and storage of aggregate and laboratory samples

Each aggregate and laboratory sample should be placed in a clean, inert container offering adequate protection from contamination, loss of analytes by adsorption to the internal wall of the container or damage in transit. Glassware offers good protection from contamination and can be cleaned easily. Polyethylene and polypropylene containers also provide protection against damage during transit. Containers made from halogenated substances (such as polyvinyl chloride) are not considered suitable for this purpose. Although PBDEs are

chemically stable, samples must be stored and transported in such a way that the food sample does not deteriorate. In particular, the fat content should not be changed (e.g. by microbiological or enzymatic processes), as the content of the compounds in food of animal origin is generally calculated on a fat basis.

### *4.4 Human milk samples*

No guidelines are set for storage and transport of human milk samples. However, the guidelines recommended by WHO in the case of dioxins can be used. Specifically, WHO recommended the addition of potassium dichromate tablets to human milk samples during collection of portions and for transport in the third round of studies of exposure, if freezing of the portions cannot be guaranteed. This helps to avoid microbiological deterioration of the samples. If the portions can be frozen immediately after collection and the collected portions can be shipped in a frozen state, addition of potassium dichromate tablets is unnecessary.

### *4.5 Sealing and labelling*

Each sample taken for official use should be sealed at the place of sampling and identified following Member States' regulations. A record must be kept of each sampling, permitting each lot to be identified unambiguously and giving the date and place of sampling, together with any additional information likely to be of assistance to the analyst.

### *4.6 Edible parts*

For determination of PBDEs in food, only the edible parts are analysed. Vegetables should be washed with water to separate them from adhering soil.

## *5. EFFECTS OF PROCESSING*

No data were available on the effects of processing on PBDE levels in foods. However, as PBDEs are chemically stable, lipophilic substances, little changes in PBDE content with processing would be expected.

Results of studies on the effect of processing on the dioxin content of foods are assumed to apply in the absence of studies on PBDEs. Smoking of meat or fish samples has been shown to increase the dioxin and furan content, depending on the smoking conditions (Körner & Hagenmaier, 1990; Mayer, 1998; Mayer & Jahr, 1998). Broiling of hamburger samples resulted in an approximately 50% decrease in the total toxic equivalents (wet weight) per hamburger, but the decrease appeared to be due solely to the decrease in wet weight associated with loss of water and loss of PCDDs/PCDFs with the fat (Schecter et al., 1996). In further studies, it was shown that the total toxic equivalents (PCDDs/PCDFs and PCBs) in hamburger, bacon and catfish decreased by an average of 50% as a result of broiling. However, the concentration remained the same in hamburger,

increased by 84% in bacon and decreased by 34% in catfish (Schecter et al., 1997). On average, the total measured concentration (pg/kg whole weight) increased by 14% in hamburger and by 29% in bacon and decreased by 33% in catfish (Schecter et al., 1998). In a study of the effect of pan-frying beef patties, the PCDD/PCDF concentration was reduced by 40–50% by cooking. Most of the reduction was accounted for by the amount in fat liberated from the patties during cooking (Petroske et al., 1997, 1998). No de novo synthesis of dioxins was observed after deep frying of scallops of pork covered with egg and crumbs either with or without salt and pepper. The frying temperature was high (180 °C).

Based on these results and the assumption that processing will have the same effect on PBDE levels as it does on dioxin levels, it is unlikely that PBDEs are formed or lost during usual cooking processes. Changes in PBDE content can be expected to be seen on a fresh weight basis owing to changes in fat and water content. As a whole, the PBDE content on a mass balance basis is expected to be constant in meat, fat and juices. However, since PBDEs concentrate in the fat portions of the food, such as the fatty tissue of the fish, removing the skin and visible fat and using cooking methods that allow fat to drip off can reduce levels in foods as consumed and the associated exposures.

## 6. LEVELS AND PATTERNS OF CONTAMINATION OF FOOD COMMODITIES

### 6.1 Surveillance data

Data were submitted by two countries, Canada and Germany, and published studies summarizing PBDE concentrations for various types of food samples were submitted by the Netherlands, the United Kingdom and the United States. Published data were also available for Finland, Japan, Spain and Sweden.

#### 6.1.1 Canada

The PBDE data available for Canada were from two total diet studies (TDS) conducted in Whitehorse in 1998 (Health Canada, 2004a) and Vancouver in 2002 (Health Canada, 2004b), as well as a specific survey on fish and seafood conducted in 2002 in Vancouver, Toronto and Halifax (Health Canada, 2004c).

Each TDS consists of the purchase of foods at retail outlets, preparation and cooking of individual foods where applicable, combining some food samples into composites and laboratory analyses. The foods are typically purchased from three or four supermarkets and processed as for consumption in the average household kitchen (i.e. raw meats are cooked; fresh vegetables are cooked or properly peeled, trimmed or otherwise cleaned for serving, if not cooked). The processed foods are then mixed according to each category to make composites for analysis. For PBDEs, about 50 food composites consisting of foods known to contain these compounds, such as those of animal origin and relatively high fat content, along with a few other individual food samples, have been analysed. The data available from these two TDS are provided in Table 17.

*Table 17. PBDE concentrations in food samples collected in Canada (TDS)*

| Code | Food | Concentration (ppt), wet based | | Code | Food | Concentration (ppt), wet based | |
|---|---|---|---|---|---|---|---|
| | | Whitehorse | Vancouver | | | Whitehorse | Vancouver |
| A01 | Whole milk | 0 | 3.39 | C03 | Liver paté | n/a | 244.8 |
| A02 | 2% milk | 0 | 0.11 | D01 | Marine fish | 101.23 | 1164.9 |
| A03 | 1% milk | 0 | 0.15 | D02 | Freshwater fish | 374.88 | 1461.9 |
| A04 | Skim milk | 0 | 0.01 | D03 | Canned fish | n/a | 36.3 |
| A05 | Evaporated milk, canned | 24.44 | 0.02 | D04 | Shellfish | 101.64 | 58 |
| A06 | Cream | 24.19 | 20.81 | E01 | Meat soups | 21.6 | 5.5 |
| A07 | Ice cream | 60.35 | 18.35 | E03 | Soup broth | n/a | 0.2 |
| A08 | Yoghurt | 5.66 | 8.47 | E04 | Soups, dehydrated | 1.51 | 1.3 |
| A09 | Cheddar cheese | 67.21 | 94.9 | I01 | Cooking fat | 121.44 | 121.4 |
| A10 | Cottage cheese | 1.61 | 0.5 | I02 | Margarine | 6.59 | 4.4 |
| A11 | Processed cheese | 62.35 | 81.4 | I04 | Mayonnaise | n/a | 96.7 |
| A12 | Butter | 55.5 | 264.5 | J01 | Chocolate | n/a | 189.7 |
| B01 | Beef steak | 150.97 | 46.2 | L03 | Baby dinner | n/a | 45.2 |
| B02 | Beef roast | 48.07 | 25.3 | L04 | Baby dinner | 43.36 | 16 |
| B03 | Ground beef | 227.55 | 120.8 | L05 | Formula, milk | 14.48 | 0.3 |
| B04 | Fresh pork | 143.53 | 40.8 | L06 | Formula, soya | n/a | 1.1 |
| B05 | Pork cured | 72.76 | 169.2 | L08 | Baby dinner, meat | 152.68 | 57.6 |

***Table 17.*** (contd)

| Code | Food | Concentration (ppt), wet based | | Code | Food | Concentration (ppt), wet based | |
|---|---|---|---|---|---|---|---|
| | | Whitehorse | Vancouver | | | Whitehorse | Vancouver |
| B06 | Veal | n/a | 205.7 | M02 | Frozen entrée | n/a | 47.1 |
| B07 | Lamb | 50.84 | 39.6 | M04 | Frozen entrée | 210.05 | n/a |
| B08 | Cold cuts | 195.13 | 217.4 | M06 | Frozen dinner | 13.35 | n/a |
| B09 | Luncheon meat, canned | 99.13 | 248.4 | N01 | Pizza | 71.05 | 274.9 |
| B10 | Organ meats | 31.38 | 19.2 | N02 | French fries | 104.22 | 35.6 |
| B11 | Wieners | 1188.74 | 163.2 | N03 | Hamburger | 21.76 | 58.5 |
| C01 | Eggs | 333.43 | 79.6 | N04 | Fish burger | 14.03 | n/a |
| C02 | Poultry | 79.41 | 37.7 | | | | |

From Health Canada (2004a, 2004b)

n/a, not applicable; ppt, part per trillion (equivalent to pg/g or ng/kg)

The survey on fish and seafood sampled farmed and wild-caught fish and seafood products sold at the retail level. Samples of farmed and wild-caught char, oysters, salmon, shrimp and tilapia were analysed for PBDEs. At the time of sampling, there was only limited availability of wild-caught oysters, salmon, shrimp and tilapia in retail outlets, and edible portions only (skin and bone removed) were analysed for the various targeted contaminants. The data are shown in Table 18.

### *6.1.2 Finland*

Kiviranta et al. (2004) measured concentrations of PBDEs in 10 market basket surveys consisting of almost 4000 individual food samples representing 228 different food items collected between April 1997 and June 1999 from supermarkets, farmers' markets and food producers and wholesalers in Finland. Five PBDE congeners were analysed (BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154). The concentrations of the sum of PBDEs ranged from 0.82 to 850 pg/g fresh weight, and the fish basket had the highest concentrations of PBDEs. Table 19 summarizes the detected concentrations.

### *6.1.3 Germany*

Values for various food samples were submitted from Germany. Time of collection was between May 2001 and September 2003. All reported values are summarized in Tables 20 to 22. The concentrations are given for total PBDEs (sum of BDE-28, BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154) in ng/g lipid. Due to the relatively high limit of quantification (LOQ) of 1 ng/g lipid, only values for positive samples are reported in the summary tables.

Additional data on contamination levels in foods in Germany were available from several publications. Concentrations in 13 fish samples from the German market analysed by Päpke et al. (2004) are reported in Table 23.

### *6.1.4 Japan*

Ashizuka et al. (2004) analysed foods collected by a market basket food study. The authors measured the levels of PBDEs in various fish samples and the TDS food groups. The PBDE values found in the fish samples are relatively high, between 79 and 747 pg/g wet weight (see Figure 6). Of the 13 food group samples in the TDS, PBDEs were found in Groups IV (Oil), X (Fish), XI (Meat and eggs) and XII (Milk and milk products) at concentrations of 122, 1259, 65 and 8.6 pg/g, respectively. In the other groups, PBDEs were below the detection limit.

Ohta et al. (2002) measured the concentrations of PBDEs in fish, shellfish, meat and vegetables sold in two food markets in the city of Hirakata, Osaka prefecture. Table 24 summarizes the measured concentrations.

***Table 18. Contaminants in retail fish and seafood products: Summary statistics for total PBDE levels***

| Species | Source | *n* | PBDE concentration (ppb) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Mean | Standard error of the mean | Standard deviation | Minimum | Maximum |
| Char | Farmed | 5 | 1 | 0.4 | 1 | 0.4 | 2.7 |
| | Wild | 5 | 0.6 | 0.1 | 0.3 | 0.3 | 1.1 |
| Oysters | Farmed | 11 | 0.7 | 0.1 | 0.5 | 0.006 | 1.4 |
| | Wild | 4 | 0.4 | 0.08 | 0.2 | 0.3 | 0.6 |
| Salmon | Farmed | 19 | 2.2 | 0.3 | 1.4 | 0.4 | 5.5 |
| | Wild | 3 | 0.6 | 0.2 | 0.3 | 0.1 | 1.3 |
| Shrimp | Farmed | 13 | 0.2 | 0.06 | 0.2 | <0.001 | 0.7 |
| | Wild | 4 | 0.1 | 0.05 | 0.09 | 0.009 | 0.2 |
| Tilapia | Farmed | 12 | 0.6 | 0.4 | 1.4 | 0.04 | 5 |
| | Wild | 3 | 0.1 | 0.09 | 0.2 | 0.01 | 0.3 |

From Health Canada (2004c)

ppb, part per billion (equivalent to µg/kg or ng/g)

***Table 19. Concentrations of PBDEs and fat percentages of 10 market baskets and total diet basket***

| Food basket | Fat content (%) | Sum of PBDEs (pg/g fresh weight) | |
|---|---|---|---|
| | | NQ = 0 | NQ = LOQ |
| (1) Liquid milk products | 2 | 0.82 | 2 |
| (2) Solid milk products | 21 | 34 | 40 |
| (3) Fish | 6.4 | 850 | 850 |
| (4) Meat and eggs | 11 | 13 | 15 |
| (5) Fats | 79 | 180 | 220 |
| (6) Cereal products | 2.1 | 15 | 15 |
| (7) Potato products | 0.34 | 1.3 | 1.4 |
| (8) Vegetables | 0.9 | 17 | 17 |
| (9) Fruits and berries | 1.3 | 3.8 | 4.2 |
| (10) Beverages, spices, sweets | | 5.4 | 5.5 |
| Total diet basket | 3.5 | 43 | 43 |

From Kiviranta et al. (2004)

LOQ, limit of quantification; NQ, not quantified

***Table 20. PBDEs in milk, milk products and eggs and poultry[a]***

| Sample type | Total number of | | | % positive samples | Positive samples (values in ng/g lipid) | |
|---|---|---|---|---|---|---|
| | Samples | ND samples | Positive samples | | Mean | Range |
| Farm collection milk/raw milk | 96 | 91 | 5 | 5 | 2 | 1–4 |
| Cheese | 32 | 31 | 1 | 3 | 2 | |
| Goat cheese | 4 | 4 | 0 | 0 | | |
| Butter | 38 | 34 | 4 | 11 | 1.3 | 1–2 |
| Eggs | 106 | 76 | 30 | 28 | 1.7 | 1–5 |
| Chicken | 38 | 24 | 14 | 37 | 3.6 | 1–12 |
| Duck, goose | 22 | 11 | 11 | 50 | 2 | |
| Turkey | 10 | 3 | 7 | 70 | 3.7 | 2–7 |

ND, not detected

[a] LOQ = 1 ng/g.

***Table 21. PBDEs in fish samples from the German market[a]***

| Sample type | Total number of | | | % positive samples | Positive samples (values in ng/g lipid) | | Lipid content (%) |
|---|---|---|---|---|---|---|---|
| | Samples | ND[b] samples | Positive samples | | Mean | Range | |
| Butterfish | 6 | 6 | 0 | 0 | ND | – | 19.7 |
| Herring shark | 4 | 0 | 4 | 100 | 43 | 5–131 | 0.4 |
| Plaice | 29 | 0 | 29 | 100 | 28.3 | 5–84 | 1.4 |
| Trout | 16 | 0 | 16 | 100 | 33.4 | 8–100 | 3.1 |
| Renke | 6 | 0 | 6 | 100 | 34.8 | 9–55 | 5.8 |
| Pike | 3 | 0 | 3 | 100 | 150 | 122–172 | 0.2 |
| Roach | 5 | 0 | 5 | 100 | 38.4 | 16–68 | 0.9 |
| Bream | 2 | 0 | 2 | 100 | 20.5 | 14–27 | 2.9 |
| Tench | 2 | 0 | 2 | 100 | 26.5 | 26–27 | 3.2 |
| Carp | 2 | 0 | 2 | 100 | 17.5 | 17–18 | 6.7 |
| Eel | 5 | 0 | 5 | 100 | 145 | 8–383 | 19.5 |
| Perch | 12 | 0 | 12 | 100 | 205 | 56–422 | 0.3 |
| Cod | 11 | 1 | 11 | 92 | 43 | ND–109 | 0.3 |
| Ocean perch | 44 | 1 | 44 | 98 | 16.7 | ND–56 | 2.7 |
| Nile perch | 2 | 1 | 1 | 50 | 1[a] | ND–1 | 1.4 |
| Victoria Lake perch | 1 | 1 | 0 | 0 | – | – | 0.1 |

ND, not detected

[a] LOQ = 1 ng/g.
[b] Only from positives.

*Table 22. PBDEs in meat samples from the German market*[a]

| Sample type | Total number of | | | % positive samples | Positive samples (values in ng/g lipid) | | Lipid content (%) |
|---|---|---|---|---|---|---|---|
| | Samples | ND samples | Positive samples | | Mean | Range | |
| Rabbit | 14 | 6 | 8 | 57 | 11 | 1–59 | 3.2 |
| Lamb | 1 | 1 | 0 | 0 | – | | 2.7 |
| Sheep | 2 | 2 | 0 | 0 | – | | – |
| Fallow deer (Damwild) | 1 | 0 | 1 | 100 | 1 | | – |
| Calf | 2 | 2 | 0 | 0 | – | | – |
| Cow (Kuh/Rind) | 36 | 34 | 2 | 6 | 3 | 1–4 | 6.5[b] |
| Bull | 2 | 2 | 0 | 0 | – | | – |
| Horse | 1 | 0 | 1 | 100 | 2 | | – |
| Pig | 48 | 38 | 10 | 21 | 4.6 | 1–16 | – |
| Game | 2 | 0 | 2 | 100 | 2 | 2 | 1.1 |
| Wild boar | 2 | 0 | 2 | 100 | 1 | 1 | 2.3 |

ND, not detected.

[a] LOQ = 1 ng/g.

[b] Only from $n = 4$.

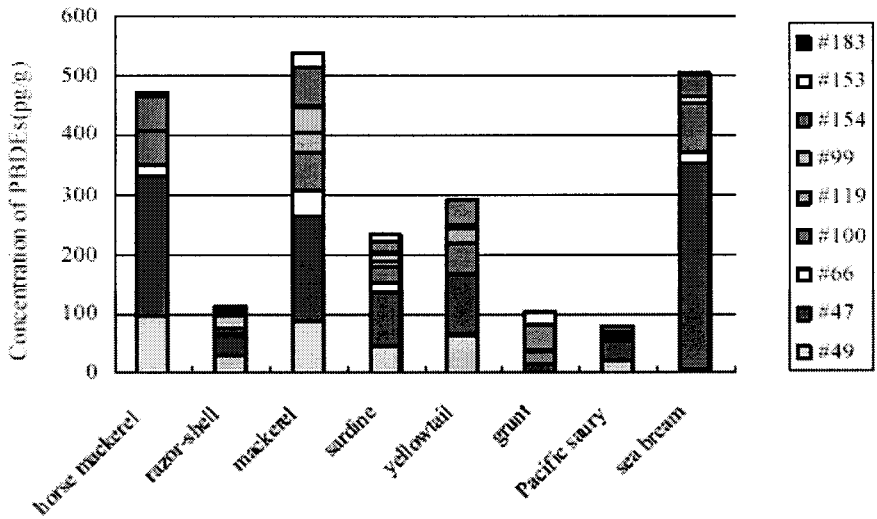
***Table 23. Concentrations of PBDE congeners in fish samples from the German market***

| Sample | Lipid content (%) | Concentrations (ng/g lipid) of BDE congener number: | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 17 | 28 | 47 | 66 | 77 | 99 | 100 | 153 | 154 | 183 | 209 | Total |
| Herring | 20.7 | 0.13 | 0.45 | 7.43 | 0.56 | 0.03 | 2.61 | 2.15 | 0.12 | 0.40 | ND | ND | 13.9 |
| Salmon | 12.7 | 0.01 | ND | 1.01 | 0.06 | ND | 0.37 | 0.20 | 0.02 | 0.09 | ND | ND | 1.76 |
| Plaice | 2.3 | 0.15 | 0.28 | 3.57 | 0.32 | ND | 1.23 | 0.57 | 0.19 | 0.35 | 0.04 | ND | 6.65 |
| Trout | 9.6 | 0.05 | 0.27 | 5.61 | 0.33 | ND | 1.98 | 0.93 | 0.14 | 0.42 | ND | ND | 9.74 |
| Ocean perch | 3.6 | 0.02 | 1.57 | 34.7 | 0.40 | 0.01 | 1.09 | 4.77 | 0.95 | 3.76 | 0.04 | 0.36 | 47.6 |
| Ocean perch | 3.2 | ND | 0.39 | 11.2 | 0.18 | ND | 0.28 | 1.9 | 0.29 | 2.1 | ND | 0.04 | 16.4 |
| Halibut | 13.6 | ND | ND | 0.34 | 0.02 | ND | 0.05 | ND | ND | 0.02 | ND | ND | 0.42 |
| Halibut | 11.1 | ND | 0.19 | 3.0 | 0.13 | ND | 0.28 | 0.34 | 0.07 | 0.34 | ND | ND | 4.35 |
| Halibut | 11.2 | 0.05 | 0.47 | 6.0 | 0.35 | ND | 0.73 | 1.12 | 0.23 | 0.91 | ND | ND | 9.86 |
| Coalfish | 0.51 | 0.02 | ND | 1.54 | 0.02 | ND | 0.46 | 0.13 | 0.03 | 0.03 | NA | 0.42 | 2.66 |
| Pike-perch | 0.56 | 0.08 | 0.23 | 20.5 | 0.64 | 0.10 | 4.17 | 4.22 | 0.85 | 3.85 | 0.11 | 2.79 | 37.6 |
| Victoria perch | 1.8 | ND | ND | 0.67 | 0.01 | ND | 0.15 | 0.10 | 0.10 | 0.25 | 0.21 | 1.04 | 2.53 |
| Catfish | 3.1 | ND | 0.21 | 3.77 | 0.27 | ND | 1.45 | 0.73 | 0.16 | 0.38 | 0.12 | 1.18 | 8.27 |

From Päpke et al. (2004)

ND, not detected; NA, not analysed

*Figure 6. Levels and congener profiles of PBDEs in fish samples*




Taken from Ashizuka, Y., Nakagawa, R., Hori, T., Tobiishi, K. & Iida, T. (2004) Levels of polybrominated diphenyl ethers and polybrominated dioxins in fish, total diet study food groups and Japanese meals. *Organohalogen Compd.*, **66**, 2553–2559.

***Table 24. PBDE concentrations in food samples collected in the city of Hirakata, Japan***

| Food | PBDE (pg/g fresh weight) | Food | PBDE (pg/g fresh weight) |
|---|---|---|---|
| Young yellowtail | 1650 | Salmon | 593 |
| Young yellowtail | 1580 | Yellow tuna | 18.5 |
| Young yellowtail | 1720 | Yellow tuna | 17.7 |
| Young yellowtail | 1620 | Yellow tuna | 26.2 |
| Mackerel | 1550 | Short-necked clam | 61.3 |
| Mackerel | 1400 | Short-necked clam | 43.5 |
| Mackerel | 1540 | Short-necked clam | 52.4 |
| Mackerel | 1280 | Spinach | 134 |
| Yellowtail | 1320 | Potato | 47.6 |
| Yellowtail | 985 | Carrot | 38.4 |
| Salmon | 1040 | Pork | 63.6 |
| Salmon | 897 | Beef | 16.2 |
| Salmon | 813 | Chicken | 6.25 |

From Ohta et al. (2002)

### 6.1.5 The Netherlands

The Netherlands Institute of Fisheries Research (RIVO) investigated background concentrations of PBDEs in 91 samples of food products consumed by the Dutch population. Table 25 lists the number of samples analysed per food group, and Table 26 summarizes the concentrations in these foods.

***Table 25. Food products analysed by RIVO***

| Category | Product | Number of (pooled) samples |
|---|---|---|
| Dairy and dairy products | Blue-veined cheese | 11 |
| | Hard cheese | 2 |
| | Milk | 6 |
| | Whipping cream | 2 |
| | Coffee creamer | 1 |
| Eggs | Egg | 9 |
| Meat and poultry | Beef | 7 |
| | Pork | 5 |
| | Poultry | 9 |
| Animal fats | Fat of cattle | 4 |
| | Fat of pigs | 3 |
| Fish | Plaice | 1 |
| | Salmon | 1 |
| | Mackerel | 2 |
| | Herring | 2 |
| | Eel | 8[a] |
| | Mussel | 2 |
| | Shrimp | 1 |
| Vegetable oil | Oil | 2 |
| | Sunflower olive oil | 6 |

From de Winter-Sorkina et al. (2003)

[a] Smoked eel ($n$ = 1), IJsselmeer eel ($n$ = 2), hatched eel ($n$ = 3) and imported eel ($n$ = 2).

***Table 26. Mean concentrations per food category, according to scenario 1 (<LOD = 0.5 × LOD) and 2 (<LOD = 0)***

| Category | $n$ > LOD | Mean concentration (ng/g) | |
|---|---|---|---|
| | | Scenario 1 | Scenario 2 |
| Cheese | 2 | 0.3 | 0.04 |
| Beef | 4 | 0.7 | 0.08 |
| Pork | 2 | 2.1 | 0.08 |
| Poultry | 5 | 0.3 | 0.04 |
| Herring | 2 | 12.9 | 2.14 |
| Salmon | 1 | 3.4 | 0.57 |

From de Winter-Sorkina et al. (2003)

### 6.1.6 Spain

Food samples — from local markets, big supermarkets and grocery stores from seven cities (Barcelona, Tarragona, Lleida, Girona, L'Hospitalet de Llobregat, Badalona and Terrassa) of Catalonia — were collected between June and August 2000. For collection of samples, two groups were made up. The first group included meat of beef (steak, hamburger), pork (loin, sausage), chicken (breast) and lamb (steak); fish (hake, sardine) and shellfish (mussel); vegetables and tubers (lettuce, tomato, potato, green beans, cauliflower); fresh fruits (apple, orange, pear); and eggs. The second group included cow milk (whole, semi-skimmed) and dairy products (yoghurt, cheese); cereals (bread, pasta, rice); pulses (lentils, beans); fats (margarine) and oils (olive, sunflower); tinned fish (tuna, sardine); and meat products (ham, hot dogs, salami). Two composite samples were analysed for each food item in group 1. Each composite was made up of 10 individual samples, which were collected in five different places. For foods in group 2, only one composite sample was analysed for each food item. This composite was made up of eight individual samples of similar weights, which were collected in four different places of the same city. The sums of the tetra- to octa-brominated congeners were determined for each sample. In total, 54 samples were analysed. The detection limits varied from 5 to 40 ng/kg dry weight, depending on the specific food and the respective congeners. Tables 27 and 28 summarize the measured concentrations. The highest concentrations of total PBDEs were found in oils and fats, followed by fish and shellfish, meats and meat products and eggs (Bocio et al., 2003).

### 6.1.7 United Kingdom

A survey was conducted in late 2001 to determine the concentrations of PBDEs in brown trout and eels from locations upstream and downstream from a site known to have manufactured both penta- and octaBDE until the late 1990s. Table 46 in section 7.3.1 summarizes the detected concentrations (UK COT, 2004). In addition, a survey of the concentrations of PBDE congeners in food samples from the 2001 TDS was conducted. None of the congeners measured was detectable in this analysis.

### 6.1.8 United States

A market basket survey has been performed by Schecter et al. (2004a). Thirty-two food samples purchased from three Dallas, Texas, supermarket chains in 2003 were analysed for 13 individual PBDE congeners (Table 29).

Further data on meat samples and dairy products from Schecter et al. (2004c) are presented in Tables 30 and 31.

In addition, data on PBDE concentrations in meat and meat products were reported by Huwe (2004) (Table 32). Individual values below the limit of detection (LOD = 3 times the standard deviation of the blanks) were considered non-

*Table 27. PBDE concentrations (ng/kg wet weight) in food samples collected in Catalonia, Spain*[a]

| BDE | Vegetables ($n$ = 8)[b] | Tubers ($n$ = 2) | Pulses ($n$ = 2) | Cereals ($n$ = 4) | Fruits ($n$ = 6) | Fish and shellfish ($n$ = 8) | Meat and meat products ($n$ = 15) | Eggs ($n$ = 2) | Milk ($n$ = 2) | Dairy products ($n$ = 2) | Fats and oils ($n$ = 3) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tetra | 4.0 (3.9) | 0.5 (0) | 2.3 (2.0) | 2.2 (0) | 0.4 (0) | 158.3 (158.2) | 23.5 (23.3) | 17.3 (17.3) | 8.0 (8.0) | 10.7 (10.7) | 169.7 (169.7) |
| Penta | 1.4 (1.3) | 0.5 (0) | 0.6 80 | 2.2 (0) | 0.4 (0) | 115.9 (115.8) | 24.9 (24.7) | 25.8 (25.8) | 5.2 (5.2) | 23.4 (23.4) | 157.7 (157.7) |
| Hexa | 0.4 (0) | 0.9 (0) | 1.1 (0) | 4.5 (0) | 0.7 (0) | 47.4 (47.0) | 13.5 (12.8) | 11.9 (11.9) | 0.5 (0) | 2.0 (0) | 139.7 (138.0) |
| Hepta | 0.7 (0) | 1.8 (0) | 2.2 (0) | 8.9 (0) | 1.4 (0) | 5.4 (3.0) | 23.9 (22.5) | 4.4 (3.3) | 1.1 (0) | 4.0 (0) | 77.0 (73.7) |
| Octa | 1.4 (0) | 3.7 (0) | 17.9 (0) | 17.9 (0) | 2.9 (0) | 6.8 (1.4) | 23.4 (19.1) | 4.7 (0) | 2.1 (0) | 7.9 (0) | 43.7 (30.3) |
| Sum | 7.9 (5.2) | 7.4 (0) | 10.7 (2.0) | 35.7 (0) | 5.8 (0) | 33.9 (325.3) | 109.2 (102.4) | 64.5 (58.3) | 16.9 (13.2) | 47.9 (34.1) | 587.7 (669.3) |

From Bocio et al. (2003)

[a] For each food group, two values are given. The first and second (in parentheses) values were calculated assuming that when a congener was below the LOD, the concentration was equal to one-half of the respective LOD (first value) or zero (second value).

[b] $n$ = number of composite samples analysed.

detects (ND) and set to either LOD/2 or zero (in parentheses) before the averages were calculated.

*Table 28. PBDE concentrations in food samples collected in Catalonia, Spain*

| Food | PBDE concentration[a] | |
|---|---|---|
| | ng/kg, lipid weight | ng/kg, wet weight |
| Vegetables | | 8 (5) |
| Tubers | | 7 (0) |
| Pulses | | 11 (2) |
| Cereals | | 36 (0) |
| Fruits | | 6 (0) |
| Whitefish | 2359 (2052) | 88 (37) |
| Shellfish | 3140 (2961) | 88 (83) |
| Tinned fish | 2117 (1997) | 260 (246) |
| Bluefish | 10 839 (10 804) | 1019 (1016) |
| Pork and pork products | 597 (565) | 172 (166) |
| Chicken | 247 (0) | 10 (0) |
| Beef and beef products | 290 (248) | 42 (36) |
| Lamb | 261 (182) | 31 (21) |
| Eggs | 530 (482) | 64 (58) |
| Dairy products | 677 (557) | 48 (34) |
| Whole milk | 630 (525) | 24 (20) |
| Unskimmed milk | 618 (402) | 10 (6) |
| Vegetable oils and fats | 805 (795) | 804 (794) |
| Margarine | 188 (145) | 155 (120) |

From Bocio et al. (2003)

[a] Data were calculated assuming that when a congener was below the LOD, the concentration was equal to one-half of the respective LOD. Values in parentheses were calculated assuming that ND = 0.

Further data for meat samples collected in three northern California markets were published by Luksemburg et al. (2004) and are summarized in Table 33.

### 6.1.9 Other data

Hites et al. (2004) is another important source of data on PBDE contamination of fish. Hites et al. (2004) analysed farmed and wild salmon produced and bought worldwide. The highest PBDE concentrations were found in farmed salmon.

Figure 7 and Table 34 summarize the PBDE concentrations detected in fish from Europe and the United States. The total BDE mean values from fish samples collected in the United States were 10 times higher than those detected in fish samples collected in Europe. This difference may be due to the fact that the samples from the United States were mainly from rivers and lakes, while the fish samples from Europe were mainly marine fish.

***Table 29. PBDE concentrations in 32 food samples purchased in Dallas, Texas***

| Food | PBDE concentration (pg/g wet weight) | Food | PBDE concentration (pg/g wet weight) |
|---|---|---|---|
| Margarine | 0.9 | Salmon fillet 2 | 3078 |
| Evaporated milk 1 | 28.2 | Catfish | 2450 |
| Evaporated milk 2 | 29.6 | Bacon 1 | 0 |
| Milk formula | 30.3 | Pork | 41 |
| Low-fat yoghurt | 31.5 | Ground beef | 78.3 |
| Ice cream | 149 | Bacon 2 | 104 |
| Evaporated goat milk | 290 | Chicken breast | 283 |
| Butter | 412 | Ground turkey | 713 |
| Cheese | 679 | Duck | 1282 |
| Tilapia fillets | 8.5 | Wieners | 1333 |
| Texas shrimps | 106 | Pork sausage | 1373 |
| Rainbow trout | 536 | Non-fat milk | 0 |
| Catfish fillet | 1547 | Soya formula | 16.9 |
| Salmon | 1752 | Chicken eggs | 73.7 |
| Shark | 1920 | Calf liver | 115 |
| Salmon fillet 1 | 1994 | Chicken liver | 2835 |

Adapted from graphs in Schecter et al. (2004c)

Another collection of PBDE data in fish samples of different origins is given in Table 35. Mean concentrations for samples collected from different countries range between 14 and 2200 ng/g lipid.

Tritscher et al. (2003) reported on PBDE values for different types of fish, one egg sample and five cow milk samples. The concentration of total PBDEs in fish ranged between 1.1 and 5.4 ng/g lipid. The lowest value of all six samples was found in Whiting, Peru, the only sample originating from the Southern Hemisphere (Figure 8). The highest concentration in the egg yolk sample was found for BDE-99 and BDE-47, at 1.1 and 0.5 ng/g lipid, respectively; the total BDE concentration was reported to be 2.2 ng/g lipid. The total PBDE values for the five milk samples

*Table 30. PBDE concentration in meat and meat products*

| BDE congener number | PBDE concentration[a] (ng/g lipid) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Sliced bacon | Sliced bacon | Butcher block pork | Ground pork | Beef tenderloin filet | Extra lean ground beef | Chicken breast | Fresh ground chicken |
| | (35% fat) | (43% fat) | (8.9% fat) | (21.5% fat) | (13.7% fat) | (14% fat) | (4.9% fat) | (7.25% fat) |
| 17 | 0.0020 | ND (0.01) | 0.0016 | ND (0.01) | ND (0.01) | 0.0018 | ND (0.01) | ND (0.01) |
| 28 | ND (0.01) | ND (0.01) | ND (0.01) | ND (0.02) | ND (0.01) | ND (0.01) | 0.0093 | ND (0.02) |
| 47 | 0.085 | ND (0.05) | 0.078 | 0.25 | 0.26 | 0.17 | 1.2 | 0.15 |
| 66 | ND | ND (0.01) | NA | ND (0.01) | ND (0.01) | 0.0040 | NA | ND (0.01) |
| 85 | 0.0039 | NA | NA | 0.014 | 0.013 | NA | NA | ND (0.01) |
| 99 | 0.048 | ND (0.04) | 0.18 | 0.35 | 0.29 | 0.24 | 2.6 | 0.26 |
| 100 | 0.014 | ND (0.01) | 0.020 | 0.060 | 0.050 | 0.033 | 0.35 | 0.064 |
| 138 | ND (0.01) | ND (0.01) | 0.0018 | 0.020 | ND (0.01) | 0.0030 | 0.046 | ND (0.01) |
| 153 | 0.013 | ND (0.01) | 0.011 | 0.087 | 0.036 | 0.035 | 0.25 | 0.056 |
| 154 | 0.0080 | ND (0.01) | 0.014 | 0.070 | 0.027 | 0.018 | 0.22 | 0.035 |

*Table 30.* (contd)

| BDE congener number | PBDE concentration[a] (ng/g lipid) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Sliced bacon | Sliced bacon | Butcher block pork | Ground pork | Beef tenderloin filet | Extra lean ground beef | Chicken breast | Fresh ground chicken |
| | (35% fat) | (43% fat) | (8.9% fat) | (21.5% fat) | (13.7% fat) | (14% fat) | (4.9% fat) | (7.25% fat) |
| 183 | 0.040 | ND (0.01) | 0.015 | 0.092 | 0.028 | ND | 0.066 | 0.080 |
| 209 | 0.080 | ND (0.08) | 0.13 | ND (0.01) | ND (0.08) | 0.072 | 1.00 | 1.1 |
| Total[b] | 0.29 | ND | 0.46 | 0.94 | 0.70 | 0.58 | 5.8 | 1.8 |

***Table 30. PBDE concentration in meat and meat products (contd)***

| BDE congener number | PBDE concentration[a] (ng/g lipid) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Young duck with giblets | Fresh ground turkey | Calf liver sliced | Chicken liver | Wieners | Chinese style sausage | Pork sausage |
| | (75% fat) | (11% fat) | (6.4% fat) | (13% fat) | (33% fat) | (26.2% fat) | (24% fat) |
| 17 | ND (0.01) | 0.0018 | 0.0019 | 0.0023 | ND (0.01) | ND (0.01) | ND (0.01) |
| 28 | ND (0.01) | ND (0.01) | 0.0070 | 0.0080 | ND (0.01) | ND (0.01) | ND (0.03) |
| 47 | 0.38 | 0.88 | 0.14 | 5.2 | 1.2 | ND (0.1) | 1.6 |
| 66 | 0.0036 | 0.0076 | NA | 0.041 | 0.0043 | ND (0.01) | ND (0.01) |
| 85 | 0.020 | NA | 0.0075 | 0.21 | 0.034 | 0.012 | 0.071 |

*Table 30.* (contd)

| BDE congener number | PBDE concentration[a] (ng/g lipid) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Young duck with giblets | Fresh ground turkey | Calf liver sliced | Chicken liver | Wieners | Chinese style sausage | Pork sausage |
| | (75% fat) | (11% fat) | (6.4% fat) | (13% fat) | (33% fat) | (26.2% fat) | (24% fat) |
| 99 | 0.81 | 2.0 | 0.16 | 9.6 | 2.1 | 0.15 | 2.9 |
| 100 | 0.16 | 0.49 | 0.025 | 2.0 | 0.16 | 0.024 | 0.31 |
| 138 | 0.0097 | 0.035 | ND (0.01) | 0.14 | 0.022 | ND (0.01) | 0.024 |
| 153 | 0.070 | 0.30 | 0.045 | 1.1 | 0.32 | 0.023 | 0.34 |
| 154 | 0.057 | 0.22 | 0.028 | 0.99 | 0.15 | 0.019 | 0.23 |
| 183 | 0.042 | 0.33 | 0.098 | 0.088 | 0.043 | 0.026 | 0.062 |
| 209 | 0.15 | 2.2 | 1.3 | 2.2 | ND (0.09) | ND (0.2) | 0.21 |
| Total[b] | 1.7 | 6.4 | 1.8 | 22 | 4.1 | 0.53 | 5.8 |

From Schecter at al. (2004c)

NA, not analysed; ND, not detected

[a] For PBDEs that were not detected, the LOD is provided in parentheses, where available.
[b] In calculating the totals, ND was assumed to be equal to 0.

***Table 31. PBDE concentration in milk and milk products***

| BDE congener number | PBDE concentration[a] (ng/g lipid) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Evap-orated milk | Evap-orated milk | Evap-orated goat milk | Milk-based instant formula | Low-fat yoghurt | Sweet cream salted, butter | Original cream cheese | Pas-teurized process cheese | Natural cheese gouda | Pasteur-ized prepared cheese | Cottage cheese |
| | (6.6% fat) | (6.3% fat) | (6.7% fat) | (3.4% fat) | (1.3% fat) | (78% fat) | (39% fat) | (19% fat) | (26.2% fat) | (11.6% fat) | (4.72% fat) |
| 17 | ND (0.01) | ND (0.01) | 0.0030 | ND (0.01) | 0.016 | ND (0.01) | 0.00095 | ND (0.01) | ND (0.01) | ND (0.01) | ND (0.01) |
| 28 | ND (0.01) | ND (0.01) | 0.038 | ND (0.01) | 0.074 | ND (0.01) | ND (0.01) | ND (0.01) | ND (0.01) | ND (0.02) | ND (0.03) |
| 47 | 0.24 | 0.19 | 1.6 | ND (0.01) | 0.72 | 0.21 | 0.25 | 0.24 | 0.29 | 0.24 | 0.29 |
| 66 | NA | NA | 0.027 | ND (0.09) | 0.019 | ND (0.01) | 0.0040 | ND (0.01) | ND (0.01) | 0.0069 | ND (0.01) |
| 85 | NA | NA | NA | NA | NA | NA | NA | ND (0.01) | 0.021 | ND (0.01) | ND (0.01) |
| 99 | 0.13 | 0.20 | 1.5 | 0.36 | 0.62 | 0.22 | 0.20 | 0.18 | 0.22 | 0.20 | 0.30 |
| 100 | 0.029 | 0.036 | 0.41 | 0.032 | 0.11 | 0.052 | 0.031 | 0.031 | 0.047 | 0.036 | 0.056 |
| 138 | ND (0.01) | 0.0031 | ND | 0.0079 | 0.0042 | ND (0.01) | NA | ND (0.01) | ND (0.01) | ND (0.01) | ND (0.01) |
| 153 | 0.020 | 0.030 | 0.44 | 0.042 | 0.077 | 0.021 | 0.015 | 0.019 | 0.032 | 0.020 | 0.029 |
| 154 | 0.0067 | 0.013 | 0.12 | 0.032 | 0.032 | 0.016 | 0.0073 | 0.014 | 0.018 | 0.014 | 0.021 |

*Table 31.* (contd)

| BDE congener number | PBDE concentration[a] (ng/g lipid) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Evap-orated milk | Evap-orated milk | Evap-orated goat milk | Milk-based instant formula | Low-fat yoghurt | Sweet cream salted, butter | Original cream cheese | Pas-teurized process cheese | Natural cheese gouda | Pasteur-ized prepared cheese | Cottage cheese |
| | (6.6% fat) | (6.3% fat) | (6.7% fat) | (3.4% fat) | (1.3% fat) | (78% fat) | (39% fat) | (19% fat) | (26.2% fat) | (11.6% fat) | (4.72% fat) |
| 183 | 0.0033 | ND (0.01) | 0.18 | 0.0059 | 0.11 | 0.0067 | ND (0.01) | 0.011 | 0.0060 | ND (0.01) | ND (0.02) |
| 209 | ND (0.03) | ND (0.03) | 0.085 | 0.41 | 0.72 | ND (0.2) | 1.2 | 0.077 | ND (0.09) | 0.15 | ND (0.3) |
| Total[b] | 0.43 | 0.47 | 4.4 | 0.89 | 2.5 | 0.53 | 1.7 | 0.58 | 0.63 | 0.67 | 0.69 |

From Schecter et al. (2004a)

NA, not analysed; ND, not detected

[a] For PBDEs that were not detected, the LOD is provided in parentheses, where available.
[b] In calculating the totals, ND was assumed to be equal to 0.

***Table 32. Concentrations of major PBDEs in blanks, bacon and meat trimmings[a]***

| BDE | PBDE concentration (pg/sample) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Blanks, *n* = 7 | | Bacon, *n* = 11 | | Chicken fat, *n* = 17 | | Pork fat, *n* = 11 | | Beef fat, *n* = 9 | |
| | Average | LOD (3 × SD) | Average | Range | Average | Range | Average | Range | Average | Range |
| 28/33 | 1.5 | 2.6 | 1.7 (0.7) | ND–4.6 | 1.7 (0.5) | ND–6 | 3.3 (2.1) | ND–23 | 1.3 (0) | ND |
| 47 | 31.8 | 56.9 | 83.0 (62.3) | ND–454 | 424.0 (419) | ND–2764 | 518.0 (513) | ND–3897 | 50.4 (28) | ND–178 |
| 85 | 1.7 | 4.2 | 3.3 (1.4) | ND–15 | 22.9 (22.4) | ND–182 | 13.2 (12.2) | ND–66 | 2.5 (0.6) | ND–5.3 |
| 99 | 31.2 | 52.5 | 104.9 (88.2) | ND–624 | 742.7 (742) | 60–4447 | 510 (508) | ND–2972 | 70.6 (53) | ND–279 |
| 100 | 4.4 | 5.9 | 14.0 (12.7) | ND–85 | 151.8 (151) | 10–859 | 85.7 (85.7) | 9–559 | 11.4 (9.8) | ND–48 |
| 153 | 2.6 | 7.3 | 27.4 (26.4) | ND–140 | 126.1 (126) | 17–576 | 61.6 (61.6) | 8–178 | 13.9 (13) | ND–42 |
| 154 | 2.4 | 5.6 | 14.8 (13.5) | ND–85 | 38.9 (37.9) | ND–126 | 43.2 (43.0) | ND–137 | 7.5 (6.3) | ND–24 |
| 183 | 3.1 | 14.7 | 46.9 (42.9) | ND–135 | 84.9 (82.7) | ND–469 | 46.8 (43.5) | ND–134 | 7.3 (0) | ND |
| 209 | 914 | 3385 | 1693 (0) | ND | 1845 (251) | ND–4275 | 1913 (374) | ND–4120 | 1693 (0) | ND |
| Σtri to hepta BDEs | | | 296 (248) | ND–7831 | 1593 (1582) | 86–8965 | 1282 (1269) | 17–7831 | 165 (111) | ND–586 |
| Σtri to hepta BDEs, lipid weight | | | 818 (634) | ND–4642 | 2508 (2412) | 124–15 139 | 2603 (2488) | 35–16 329 | 251 (178) | ND–835 |
| % lipid | | | 39.1 | 30.7–46.3 | 65.6 | 56.0–71.6 | 51.0 | 37.2–71.6 | 62.3 | 45.2–73.4 |

From Huwe (2004)

LOD, limit of detection; ND, not detected; SD, standard deviation

[a] Sample data are blank-subtracted.

*Table 33. Concentration of PBDEs in beef and fowl meat purchased in three food markets in northern California, USA*

| | PBDE concentration (pg/g wet weight) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Meat products | | | Fowl products | | | | | |
| | Ground beef (grain fed) | Ground beef (free range) | Ground deer | Chicken thighs | Chicken thighs (free range) | Duck | Goose | Ground turkey | Pheasant |
| BDE-7 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| BDE-13 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| BDE-15 | ND | ND | ND | ND | ND | 0.60 | ND | ND | ND |
| Total diBDE | ND | ND | ND | ND | ND | 0.60 | ND | ND | ND |
| BDE-17 | ND | ND | ND | ND | ND | 1.3 | ND | ND | ND |
| BDE-25 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| BDE-28 | ND | 0.36 | ND | ND | ND | 4.2 | 0.40 | 0.36 | 0.55 |
| BDE-35 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Total triBDE | ND | 0.36 | ND | ND | ND | 5.4 | 0.40 | 0.36 | 0.55 |
| BDE-47 | 45 | 10 | 120 | 37 | 12 | 187 | 20 | 77 | 26 |
| BDE-49 | ND | 0.61 | ND | ND | ND | 7.3 | ND | 1.7 | 0.75 |
| BDE-65 | ND | ND | ND | ND | ND | 2.8 | ND | ND | ND |
| BDE-75 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Total tetraBDE | 45 | 11 | 120 | 37 | 12 | 195 | 20 | 79 | 26 |
| BDE-85 | ND | ND | 6.5 | 1.3 | ND | ND | 1.3 | 2.9 | 1.2 |
| BDE-99 | 75 | 17 | 179 | 53 | 21 | 209 | 29 | 165 | 34 |

***Table 33.*** (contd)

| | PBDE concentration (pg/g wet weight) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Meat products | | | Fowl products | | | | | |
| | Ground beef (grain fed) | Ground beef (free range) | Ground deer | Chicken thighs | Chicken thighs (free range) | Duck | Goose | Ground turkey | Pheasant |
| BDE-100 | ND | 3.4 | 33 | 13 | 5.2 | 144 | 5.4 | 47 | 7.3 |
| BDE-126 | ND | ND | ND | ND | ND | ND | ND | ND | ND |
| Total pentaBDE | 95 | 20 | 218 | 68 | 26 | 370 | 36 | 216 | 42 |
| BDE-138 | ND | ND | ND | ND | ND | 44 | ND | 2.3 | ND |
| BDE-153 | ND | 2.8 | 27 | 33 | 3.4 | 1220 | 5.3 | 38 | 5.9 |
| BDE-154 | ND | 1.2 | 14 | 7.8 | 1.9 | 170 | 1.9 | 21 | 2.9 |
| BDE-155 | ND | ND | ND | ND | ND | ND | ND | 1.3 | ND |
| Total hexaBDE | ND | 4.8 | 41 | 41 | 5.3 | 1440 | 7.2 | 66 | 8.8 |
| BDE-181 | ND | ND | ND | ND | ND | 11 | ND | ND | ND |
| BDE-183 | 14 | 5.1 | ND | 112 | 5.3 | 146 | 2.5 | 71 | 3.5 |
| Total heptaBDE | 24 | 5.1 | ND | 112 | 5.3 | 174 | 2.5 | 71 | 3.5 |
| BDE-197 | ND | 5.5 | ND | 35 | ND | 46 | 1.6 | 26 | 5.8 |
| BDE-203 | ND | 1.5 | ND | ND | ND | 17 | ND | 9.0 | ND |
| Total octaBDE | ND | 7.0 | ND | 46 | ND | 110 | 1.6 | 45 | 5.8 |
| BDE-207 | ND | 11 | ND | 30 | 16 | 23 | 5.9 | 26 | 8.7 |
| Total nonaBDE | ND | 15 | ND | 30 | 21 | 33 | 5.9 | 32 | 14 |

*Table 33.* (contd)

| | PBDE concentration (pg/g wet weight) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Meat products | | | Fowl products | | | | | |
| | Ground beef (grain fed) | Ground beef (free range) | Ground deer | Chicken thighs | Chicken thighs (free range) | Duck | Goose | Ground turkey | Pheasant |
| BDE-209 | ND | 113 | ND | 284 | 417 | 188 | 123 | 147 | 106 |
| Total BDEs[a] | 164 | 177 | 379 | 618 | 486 | 2516 | 196 | 656 | 207 |

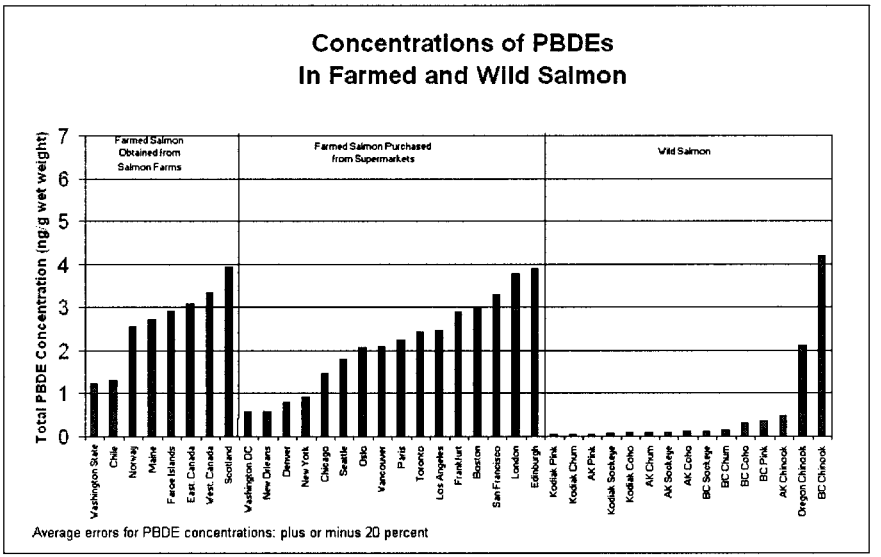
From Luksemburg et al. (2004)

ND, not detected

[a] In calculating the totals, ND is assumed to be equal to the LOQ (where LOQ varies from 10 to 250 pg/g for all congeners).

from northern France ranged between 0.12 and 0.55 ng/g lipid. In all cases, the highest concentration was found for BDE-47.

***Figure 7. Concentrations of PBDEs in farmed and wild salmon***




Taken from Hites, R., Foran, J., Schwager, S., Knuth, B., Hamilton, C. & Carpenter, D. (2004) Global assessment of polybrominated diphenyl ethers in farmed and wild salmon. *Environ. Sci. Technol.*, **38** (19), 4945–4949.

### *6.2 Distribution curves*

There were large differences in the amount, detail and quality of the data from the various countries. In particular, the data available differed with respect to the number of congeners analysed, whether concentrations were reported on a lipid or a wet weight basis and the sensitivity of the method used. Some data were available only as the sum of the congeners, and in some instances it was not clear which congeners were included in these sums. Further, in some cases, an upper-bound approach was used, i.e. substituting the LOQ (or LOD) for those congeners that were not quantified, in calculating total PBDEs. In other cases, the concentration of the contaminants may have been underestimated, when a lower-bound approach, with a zero value used for those congeners that were not quantified, was used. In some cases, the reported summaries did not clarify which approach was used. When data were available on a per lipid basis, they were converted to a per wet weight basis if the associated percent lipid information was available in the database or publication. Several studies summarizing concentrations expressed concentrations on a per fat basis and did not provide an estimate of the fat content of the food samples. For these studies, an average estimate based on the fat content of similar foods from the other studies was used. It was not always possible to determine which congeners were analysed; however, when that information was

*Table 34. PBDE concentrations and congener distributions in fish*

| Location | Type | Date | Repetitions | PBDE concentration (ng/g lipid) | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 47 | 99 | 100 | 153 | 154 | ΣPBDE | |
| Germany | Eel, river | 2001 | 5 | 4.50 | 0.14 | 0.98 | 0.21 | 0.48 | 6.31 | Lepom et al. (2002) |
| Netherlands | Mackerel | 1997 | 1 | 5.40 | 1.90 | 1.80 | | | 9.10 | de Boer & Denneman (1998) |
| Baltic Sea | Herring | 1985 | 4 | 10.3 | 1.70 | 1.57 | | | 13.6 | Haglund et al. (1997) |
| Baltic Sea | Three species | 1998 | 22 | 10.8 | 1.47 | 1.60 | 0.95 | 0.48 | 15.3 | Burreau et al. (1999) |
| Switzerland | Rainbow trout | 2002 | 4 | 11.5 | 2.27 | 1.70 | 0.27 | 0.36 | 16.1 | Zennegg et al. (2003) |
| Baltic Sea | Herring | 1998 | 3 | 12.4 | 4.14 | | 0.75 | | 17.3 | Strandman et al. (1999) |
| Greenland | Three species | 2000 | 36 | 15.6 | 0.69 | 1.28 | | | 17.6 | Christensen et al. (2002) |
| Scotland and Belgium | Salmon | 2001 | 13 | 10.9 | 2.87 | 3.56 | 1.01 | 0.81 | 19.2 | Jacobs et al. (2002) |
| Sweden | Whitefish | 1986 | 35 | 15.0 | 7.20 | 3.90 | | | 26.1 | Sellström et al. (1993) |
| Sweden | Herring | 1987 | 50 | 24.1 | 9.33 | 4.01 | | | 37.4 | Sellström et al. (1993) |
| Baltic Sea | Sprat | 1998 | 9 | 49.4 | 6.34 | | 1.03 | | 56.7 | Strandman et al. (1999) |
| Switzerland | Whitefish | 2002 | 8 | 44.3 | 24.0 | 4.63 | 1.21 | 1.52 | 75.6 | Zennegg et al. (2003) |
| North Sea | Several species | 1999 | 28 | 47.6 | 11.2 | 13.5 | 1.17 | 3.36 | 76.8 | Boon et al. (2002) |
| Sweden | Herring | 1987 | 260 | 130 | 23.0 | 13.0 | | | 166 | Sellström et al. (1993) |
| Germany | Bream, river | 2001 | 22 | 127 | 0.49 | 31.8 | 4.80 | 18.2 | 182 | Lepom et al. (2002) |
| Baltic Sea | Salmon | 1995 | 8 | 132 | 35.0 | 37.0 | 3.20 | 6.00 | 213 | Asplund et al. (1999) |
| Baltic Sea | Salmon fillet | 1991 | 1 | 167 | 52.0 | 44.0 | 4.20 | 11.0 | 278 | Haglund et al. (1997) |

*Table 34.* (contd)

| Location | Type | Date | Repetitions | PBDE concentration (ng/g lipid) | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 47 | 99 | 100 | 153 | 154 | ΣPBDE | |
| Sweden | Several species | 1987 | 12 | 269 | 41.8 | 34.5 | | | 345 | Sellström (1996) |
| Sweden | Pike, rivers | 1995 | 14 | 226 | 128 | 53.9 | | | 408 | Sellström et al. (1998) |
| Sweden | Arctic char | 1987 | 15 | 400 | 64.0 | 51.0 | | | 515 | Sellström et al. (1993) |
| European means | | | | 81.8 | 19.9 | 16.0 | 1.58 | 4.27 | 119 | |
| SD | | | | 23.4 | 6.77 | 4.38 | 0.46 | 1.89 | 32.9 | |
| Geometric means | | | | 33.6 | 5.54 | 6.23 | 0.97 | 1.71 | 49.1 | |
| Slocan River, USA | Whitefish | 1996 | 3 | 4.20 | 4.70 | 1.50 | 0.93 | 0.76 | 12.1 | Rayne et al. (2003) |
| British Columbia, Canada | Sole | 1992 | 26 | 14.7 | 7.36 | 4.45 | 6.16 | 1.51 | 34.2 | Ikonomou et al. (2002) |
| Columbia River, USA | Whitefish | 1992 | 4 | 16.8 | 22.8 | 5.20 | 3.00 | 2.00 | 49.8 | Rayne et al. (2003) |
| Columbia River, USA | Whitefish | 1992 | 2 | 20.0 | 27.7 | 8.20 | 4.10 | 2.90 | 62.9 | Rayne et al. (2003) |
| Michigan & Illinois, USA | Two species | 1999 | 36 | 34.0 | 7.28 | 6.83 | 8.96 | 11.4 | 68.4 | Rice et al. (2002) |
| British Columbia, Canada | Sole | 2000 | 60 | 48.5 | 16.8 | 15.4 | 6.21 | 4.93 | 91.8 | Ikonomou et al. (2002) |

*Table 34.* (contd)

| Location | Type | Date | Repetitions | PBDE concentration (ng/g lipid) | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 47 | 99 | 100 | 153 | 154 | ΣPBDE | |
| Columbia River, USA | Whitefish | 2000 | 9 | 63.4 | 83.4 | 22.3 | 12.9 | 7.40 | 189 | Rayne et al. (2003) |
| Great Lakes, Canada and USA | Lake trout | 2000 | 40 | 151 | 37.0 | 19.9 | 9.96 | | 217 | Luross et al. (2002) |
| Kootenay Lake, USA | Whitefish | 1998 | 5 | 125 | 135 | 38.2 | 17.0 | 13.8 | 330 | Rayne et al. (2003) |
| Great Lakes | Several species | 1999 | 20 | 208 | 59.0 | 45.5 | 14.7 | 40.4 | 368 | Dodder et al. (2002) |
| Columbia River, USA | Whitefish | 1996 | 1 | 132 | 184 | 43.5 | 23.8 | 14.8 | 398 | Rayne et al. (2003) |
| Columbia River, USA | Whitefish | 2000 | 12 | 179 | 227 | 68.8 | 32.9 | 20.0 | 527 | Rayne et al. (2003) |
| Columbia River, USA | Whitefish | 1994 | 1 | 185 | 263 | 71.6 | 40.6 | 30.2 | 590 | Rayne et al. (2003) |
| Columbia River, USA | Whitefish | 1995 | 4 | 325 | 479 | 148 | 63.7 | 44.0 | 1060 | Rayne et al. (2003) |
| Lake Michigan | Salmonids | 1996 | 21 | 1340 | 239 | 249 | 30.3 | 116 | 1970 | Manchester-Neesvig et al. (2001) |
| Kootenay River, USA | Suckers | 2000 | 6 | 2110 | 6.60 | 461 | 24.4 | 168 | 2770 | Rayne et al. (2003) |
| Lake Michigan, Canada and USA | Trout | 1996 | 6 | 1700 | 600 | 360 | 110 | 200 | 2970 | Asplund et al. (1999) |

*Table 34.* (contd)

| Location | Type | Date | Repetitions | PBDE concentration (ng/g lipid) | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 47 | 99 | 100 | 153 | 154 | ΣPBDE | |
| Virginia, eastern | Three species | 1998 | 25 | 4540 | 783 | 1410 | 235 | 235 | 7200 | Hale et al. (2001) |
| North American means | | | | 622 | 177 | 165 | 35.8 | 53.7 | 1050 | |
| SD | | | | 275 | 53.7 | 79.5 | 13.3 | 18.5 | 423 | |
| Geometric means | | | | 136 | 63.1 | 38.9 | 16.0 | 16.6 | 308 | |

From Hites et al. (2004)

SD, standard deviation

available, the BDE-28, BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154 congeners were the ones most reported analysed. Therefore, the following analyses assume that, at a minimum, these six congeners were analysed in all studies. For the studies in which additional congeners were analysed and concentrations of the individual congeners were available, the assessment restricted the analyses to the six congeners listed above.

***Table 35. PBDEs in fish samples, various studies***

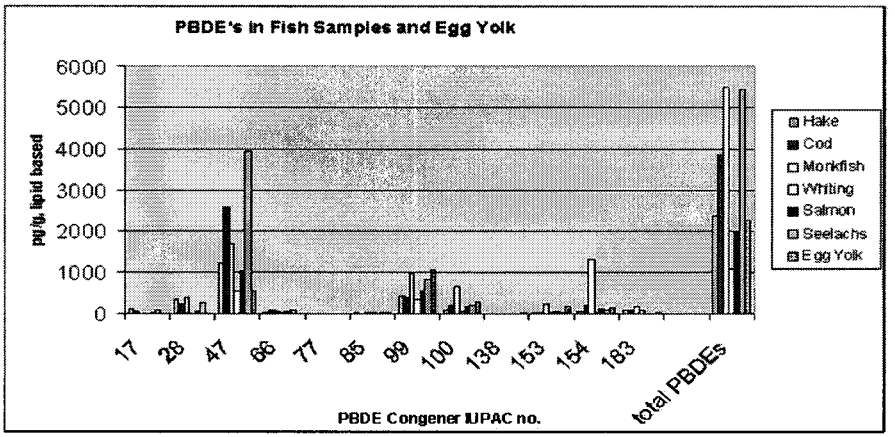
| Area | Reference | Year of collection | Sample | *n* | Mean values (range) (ng/g lipid weight) |
|---|---|---|---|---|---|
| Norway (13 lakes) | Schlabach et al. (2001) | 1999 | Trout | 1/lake | 43.2 (7.9–124)[a] |
| Baltic Sea (7 sites) | Nylund et al. (2001) | 1999 | Herring | 12–20/site | 17.0 (12–30.7)[b] |
| German market | CVUA (2001) | 2001 | Plaice | 44 | 30 (151)[c] |
| | | | Rosefish | 64 | 14 (196)[c] |
| Scotland | Jacobs et al. (2002) | 1999 | Salmon | 8 | 53.6 (1.1–85.2)[a] |
| Belgian market | | 2001 | | 5 | 19.6 (3.1–52.1)[a] |
| San Francisco Bay area | Holden et al. (2003) | 2002 | Perch | 6 | 696 |
| | | | Halibut | 4 | 2235 |
| | | | Bass | 4 | 1925 |
| | | | Shark | 1 | 489 |
| River Elbe | Lepom et al. (2002) | 2001 | Bream | 22 | 198 (26–728)[a] |
| | | | Eel | 5 | 6.3 (3.6–21.4)[a] |

[a] Range of individual data.
[b] Range of means.
[c] Maximum.

Concentration data available on fish samples collected in the United Kingdom were clearly identified as targeted samples and were therefore excluded from the analyses. It was impossible to identify analytical results for targeted samples for the other countries; all the remaining data were therefore considered representative of total contamination of foods.

Foods for which PBDE contamination data were available were grouped in six food groups: Meats and products (including beef, pork, poultry and game), Dairy and dairy products, Fish and shellfish, Fats and oils, Eggs and Fruits and vegetables.

*Figure 8. PBDEs in fish samples and egg yolk*




Taken from Tritscher, A., Stadler, R., Scanlan, F., Collingro, C. & Päpke O. (2003) Determination of polychlorinated diphenylethers in samples of raw cow's milk, fish and egg. *Organohalogen Compd.*, **61**, 131–134.

Data were generally available in an aggregated form; although individual data were available from some studies, there were not enough samples per study to allow the generation of a full curve for the distribution of concentrations. As agreed at the FAO/WHO workshop on exposure assessment of contaminants (WHO, 2000), the data from the various studies were grouped by geographical region, and a lognormal distribution was assumed for each food group and each region. To estimate the mean of the distribution, the aggregated data were weighted as a function of the number of initial samples. Each result was multiplied by the number of individual samples in the original survey, and the sum of the products was then divided by the total number of individual samples to obtain a weighted mean of the contamination of foods by PBDEs. In a second step, the geometric standard deviation (GSD) of the distribution was derived by calculating the weighted standard deviation of the log-transformed means available for each country and food group. An average GSD of 2 was used to represent variability between countries within a given geographical region.

In addition, a GSD was estimated from the studies for which data on individual samples were available. An average GSD of 5.6 was used for fish and shellfish, whereas an average standard deviation of 2.6 was used for the other food groups. The within-food component of the variation represents variation in concentrations in different portions of one food group bought in one area. This component is not used in estimating long-term intakes, because the long averaging time for PBDE intake renders "meal-to-meal" variation irrelevant to the consideration of long-term risk. In the case of long-term intakes, it is assumed that consumers choose food randomly with respect to the distribution of concentrations of contaminants and will therefore have an intake over time that is an approximation of the

true mean of that distribution. This component, however, would be used, in conjunction with the between-countries variation, in the calculation of short-term intakes if acute exposures to PBDEs are considered of interest.

National data were aggregated by region when sufficient data were available: Western Europe, North America and Far East. There were no data for countries in other regions. Two sets of distributions were generated and used in the regional intake assessments: "lower-bound" distributions, where estimates were derived from studies setting non-detects at zero; and "upper-bound" distributions, where estimates were derived from studies setting non-detects at the LOD. The percentiles of these distribution curves were determined, and the median values and 90th percentiles are presented in Tables 36 and 37. In addition, Figures 9 to 12 illustrate these distributions for two food groups and two regions.

## *7. DIETARY INTAKE ASSESSMENT*

### *7.1 Introduction and background*

PBDEs have been detected at low levels in food, human milk, outdoor air, indoor air, water, household dust, human blood and human fat tissue. The main sources of exposure of humans to PBDEs are through food, human breast milk and dust (Health Canada, 2004f). In 1979 and 1980, the first record of the occurrence of PBDEs in fish samples was published by Andersson & Blomkvist (1981). Concentrations between 950 and 27 000 ng/g lipid were found in fish sampled along the Swedish river Viskan, where numerous textile industries are located. These industries have used various brominated flame retardants in the production of textiles. Due to the importance of fish in the diet worldwide, a number of fish studies have been undertaken. PBDEs accumulate in fatty tissues and fluids such as milk due to their physicochemical properties.

### *7.2 Methods*

#### *7.2.1 Definitions*

The following definitions were adopted:

- *Dietary intake*: The dietary intake of PBDEs is defined as the amount of these contaminants that is ingested in food per unit time. Dietary intake is expressed in one of two ways: intake per unit of time, or intake per kilogram body weight per unit of time. The latter measure requires that data on body weight be available. In the current assessment, intake is expressed as picograms of total PBDEs per capita per day.
- *Region*: When applied to concentrations and diets, region is an area composed of individual nations or other geopolitical units that are likely to have separate food sources and markets but common dietary characteristics. The five Global Environment Monitoring System Food Contamination Monitoring and Assessment Programme (GEMS/Food) regional diets fit this definition.

***Table 36. Weighted mean and derived median and 90th percentile of the simulated concentration distributions of PBDEs used in the long-term intake assessment***

| Region | Parameter | PBDE concentrations (ng/g of fresh weight) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Dairy & dairy products | Eggs | Fish & shellfish | Fruits & vegetables | Meat & poultry | Fats & oils |
| *Derived using summaries with ND = 0* | | | | | | | |
| Europe | Weighted mean | 0.030 | 0.048 | 1.782 | 0.007 | 0.078 | 0.267 |
| | GSD | 2 | 2 | 2 | 2 | 2 | 2 |
| | Median | 0.023 | 0.037 | 1.364 | 0.005 | 0.060 | 0.204 |
| | 90th percentile | 0.055 | 0.090 | 3.316 | 0.013 | 0.146 | 0.496 |
| North America | Weighted mean | 0.100 | 0.207 | 0.918 | 0.007[a] | 0.351 | 0.925 |
| | GSD | 2 | 2 | 2 | 2 | 2 | 2 |
| | Median | 0.077 | 0.158 | 0.703 | 0.005 | 0.269 | 0.708 |
| | 90th percentile | 0.187 | 0.384 | 1.708 | 0.013 | 0.654 | 1.722 |
| *Derived using summaries with ND = LOD* | | | | | | | |
| Europe | Weighted mean | 0.249 | 0.128 | 1.872 | 0.010 | 0.232 | 0.944 |
| | GSD | 2 | 2 | 2 | 2 | 2 | 2 |
| | Median | 0.190 | 0.098 | 1.433 | 0.007 | 0.178 | 0.723 |
| | 90th percentile | 0.463 | 0.239 | 3.484 | 0.018 | 0.433 | 1.757 |

*Table 36.* (contd)

| Region | Parameter | PBDE concentrations (ng/g of fresh weight) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Dairy & dairy products | Eggs | Fish & shellfish | Fruits & vegetables | Meat & poultry | Fats & oils |
| North America | Weighted mean | 0.249[a] | 0.128[a] | 1.872[a] | 0.010[a] | 0.246 | 1.083 |
| | GSD | 2 | 2 | 2 | 2 | 2 | 2 |
| | Median | 0.190 | 0.098 | 1.433 | 0.007 | 0.188 | 0.829 |
| | 90th percentile | 0.463 | 0.239 | 3.484 | 0.018 | 0.457 | 2.016 |
| Far East | Weighted mean | 0.249[b] | 0.128[b] | 0.910 | 0.073 | 0.029 | 0.944[b] |
| | GSD | 2 | 2 | 2 | 2 | 2 | 2 |
| | Median | 0.190 | 0.098 | 0.697 | 0.056 | 0.022 | 0.723 |
| | 90th percentile | 0.463 | 0.239 | 1.694 | 0.136 | 0.053 | 1.757 |

GSD, geometric standard deviation; LOD, limit of detection; ND, not detected

[a] No data available for the North American region; data from the Western European region used instead.
[b] No data available for the Far Eastern region; data from the Western European region used instead.

***Table 37. Weighted mean and derived median and 90th percentile of the simulated concentration distributions of PBDEs used in the acute intake assessment***

| Region | Parameter | PBDE concentrations (ng/g of fresh weight) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Dairy & dairy products | Eggs | Fish & shellfish | Fruits & vegetables | Meat & poultry | Fats & oils |
| *Derived using summaries with ND = 0* | | | | | | | |
| Europe | Weighted mean | 0.030 | 0.048 | 1.782 | 0.007 | 0.078 | 0.267 |
| | GSD | 3.26 | 3.26 | 6.40 | 3.26 | 3.26 | 3.26 |
| | Median | 0.015 | 0.024 | 0.314 | 0.003 | 0.039 | 0.132 |
| | 90th percentile | 0.066 | 0.108 | 3.393 | 0.015 | 0.176 | 0.598 |
| North America | Weighted mean | 0.100 | 0.207 | 0.918 | 0.007[a] | 0.351 | 0.925 |
| | GSD | 3.26 | 3.26 | 6.40 | 3.26 | 3.26 | 3.26 |
| | Median | 0.050 | 0.102 | 0.162 | 0.003 | 0.173 | 0.457 |
| | 90th percentile | 0.225 | 0.463 | 1.748 | 0.015 | 0.787 | 2.074 |
| *Derived using summaries with ND = LOD* | | | | | | | |
| Europe | Weighted mean | 0.249 | 0.128 | 1.872 | 0.010 | 0.232 | 0.944 |
| | GSD | 3.26 | 3.26 | 6.40 | 3.26 | 3.26 | 3.26 |
| | Median | 0.123 | 0.063 | 0.330 | 0.005 | 0.115 | 0.466 |
| | 90th percentile | 0.557 | 0.288 | 3.565 | 0.022 | 0.521 | 2.116 |

*Table 37.* (contd)

| Region | Parameter | PBDE concentrations (ng/g of fresh weight) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Dairy & dairy products | Eggs | Fish & shellfish | Fruits & vegetables | Meat & poultry | Fats & oils |
| North America | Weighted mean | 0.249[a] | 0.128[a] | 1.872[a] | 0.010[a] | 0.246 | 1.083 |
| | GSD | 3.26 | 3.26 | 6.40 | 3.26 | 3.26 | 3.26 |
| | Median | 0.123 | 0.063 | 0.330 | 0.005 | 0.121 | 0.535 |
| | 90th percentile | 0.557 | 0.288 | 3.565 | 0.022 | 0.551 | 2.428 |
| Far East | Weighted mean | 0.249[b] | 0.128[b] | 0.910 | 0.073 | 0.029 | 0.944[b] |
| | GSD | 3.26 | 3.26 | 6.40 | 3.26 | 3.26 | 3.26 |
| | Median | 0.123 | 0.063 | 0.161 | 0.036 | 0.014 | 0.466 |
| | 90th percentile | 0.557 | 0.288 | 1.734 | 0.164 | 0.064 | 2.116 |

GSD, geometric standard deviation; LOD, limit of detection; ND, not detected

[a] No data available for the North American region; data from the Western European region used instead.
[b] No data available for the Far Eastern region; data from the Western European region used instead.

*Figure 9. Simulated distributions of PBDEs in dairy products for use in the long-term intake assessment for the Western European region*

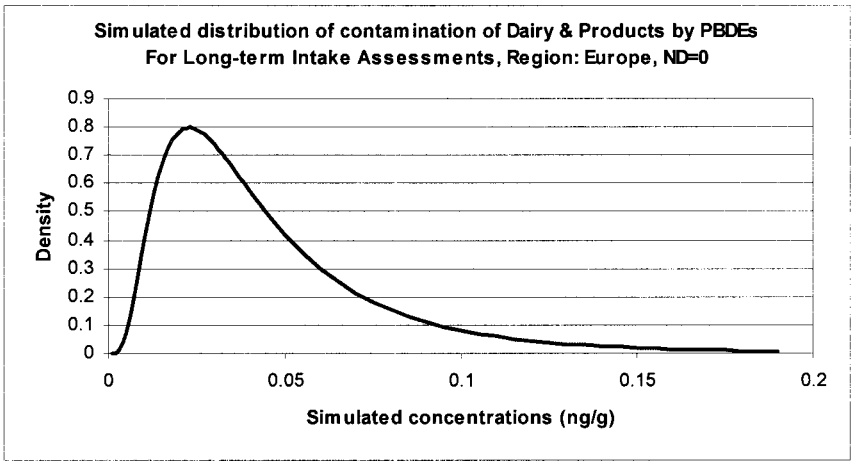
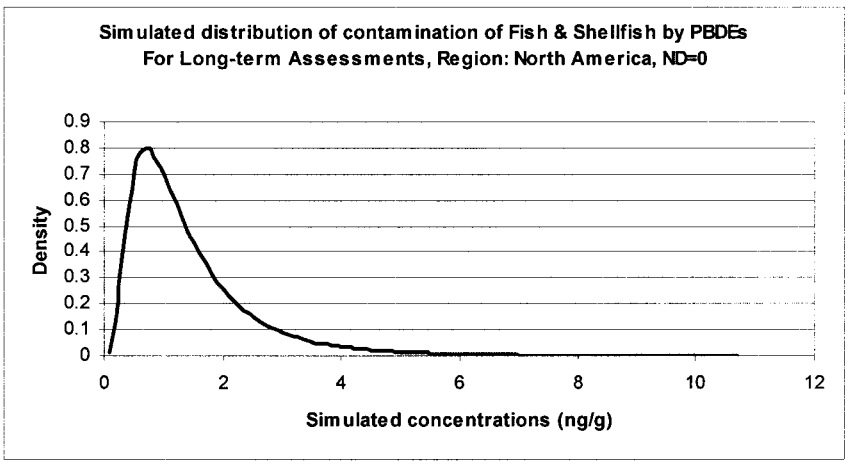



*Figure 10. Simulated distributions of PBDEs in fish and shellfish for use in the long-term intake assessment for the Northern American region*




- *Between-person variation*: When applied to intake and food consumption, between-person variation is defined as variation between individuals in a population within a nation or other geopolitical unit that is likely to have common food sources and markets.

- *Between-country variation*: When applied to concentrations, between-country variation is defined as variation between long-term mean concentrations in

*Figure 11. Simulated distributions of PBDEs in dairy products for use in the acute intake assessment for the Western European region*

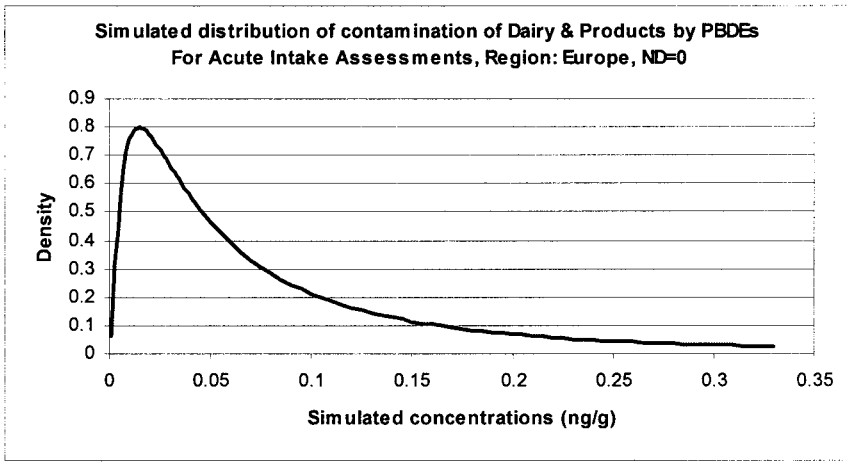
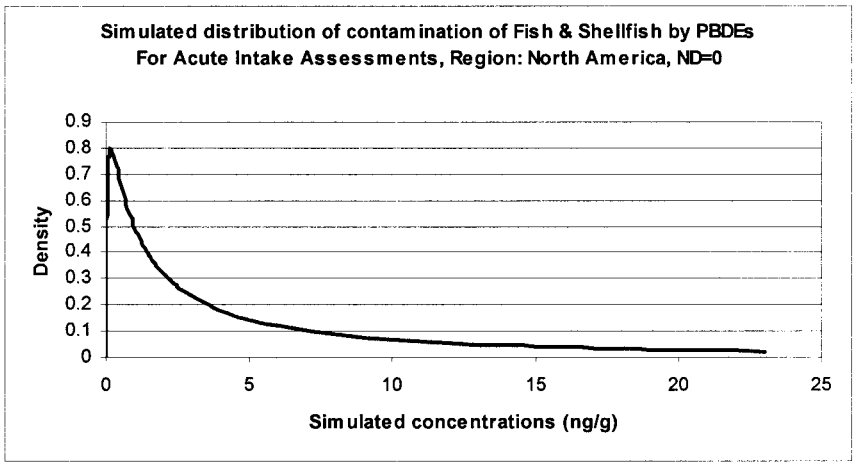



*Figure 12. Simulated distributions of PBDEs in fish and shellfish for use in the acute intake assessment for the Western European region*




specific food groups in areas that predominantly do not share food sources or markets. National boundaries are assumed to define these populations within an acceptable degree of error for this analysis.

- *Within-food variation*: When applied to concentrations, within-food variation is defined as variation between consumed portions of a given food group during the period considered in the analysis. For example, the within-food variation in

PBDE concentration for the group "Fish" would comprise the variation in PBDE concentration from one meal to the next during the period of exposure (lifetime or other) of that individual. This variation is composed of variation due to differences between species and variation related to differences between fish of the same species. The within-food variation in PBDE concentration is assumed to be equivalent to the between-sample variation for the samples considered for each food group in this analysis.

### 7.2.2 *Intake calculations*

Mean intake per person can be calculated from mean food consumption, the composition of the diet and the mean concentrations of PBDE in food from a local market, as follows:

Equation 1:

$$\bar{J}_T = \bar{I}_f \sum_{i=1}^{N} \bar{C}_i f_i$$

where $\bar{J}_t$ is the long-term mean personal intake of a contaminant, $\bar{C}_i$ is the mean concentration (in different portions) of the contaminant in food group *i*, $\bar{I}_f$ is the mean food consumption (g/day), *N* is the number of food groups considered and $f_i$ is the fraction of food group *i* that contributes to total food consumption.

The contribution of a food group *i* to the total intake of PBDEs is obtained from the partial intake, $J_i$ for group *i*, as follows:

Equation 2:

$$\bar{J}_i = \bar{I}_t \bar{C}_i f_i$$

If the mean food consumption per person and the mean concentration are considered random variables, it becomes possible to evaluate the distribution of the dietary intake by a certain population. The approach used corresponds to the method for assessing intake of contaminants and toxins in food recommended by an FAO/WHO workshop on the topic (WHO, 2000). In short, the following procedure was followed:

1. Concentration distributions indicating between-country variation in the mean were constructed for various regions and food groups from the data on occurrence submitted by the countries. These distributions were assumed to be lognormal (see section 6.2).
2. Data on food consumption were used to estimate mean consumption and the between-person variation in food consumption in different diets. Lognormal food consumption distributions were constructed for each diet. Additionally,

the contribution of the recognized food groups to total food consumption in these diets was derived from data on food consumption.

3. The dietary intake of a particular population was assessed by combining the concentration and the food consumption distributions for that population by Monte Carlo simulations (with 10 000 trials for each simulation). In each Monte Carlo trial, dietary intake was estimated by multiplying random realizations of food consumption and concentrations in different food groups sampled from their distributions (Eq. 1). The concentrations were weighted according to the fraction that each food group contributes to total food intake (Eqs. 1 and 2). The collective intake estimates obtained by the Monte Carlo approach thus form a distribution of dietary intake for each population studied. The distributions are characterized by the median intake and two high percentiles (80th and 90th). Note that the 90th percentile is a realistic estimate corresponding to the mean intake that is exceeded by 10% of the population considered.

### *7.2.3 Compounds*

Dietary intake was calculated for the sum of the following PBDEs: BDE-28, BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154.

### *7.2.4 Distributions of concentrations*

Data on occurrence were available for various countries (see section 6.1), and these data were used to compile regional distributions of concentrations, each distribution characterized by two parameters, the median (see Table 38) and a GSD. Two sets of distributions were derived: the first was derived assuming non-detects are set at zero, while the second was derived assuming non-detects are set at the LOD. Since the data available from the various countries were not always derived using the same sets of assumptions, different countries were included in the two sets of distributions. In order to construct complete data series for each region, missing data are typically replaced by data for the closest region, e.g. Western European data for North America. However, since the fish concentration data were shown to be different between the two regions when non-detects were set at 0, it was not possible to use the Western European data as a surrogate for the missing North America data when non-detects were set at the LOD. Since Japan was the only country in the Far Eastern region for which data were available, data from Western Europe had to be used as a surrogate for the foods missing data in the Far Eastern region. Essentially, the variation in concentrations within each food group and region consists of a "between-country" and a "within-food" component.

#### *(a) Between-country variation*

In calculating long-term intakes, only the between-country component of the variation in concentration is relevant. Such variation implies that each region has areas with less and more contaminated areas. In other words, it is assumed that

persons living in a country where there is higher contamination will not "dilute" their daily intake of PBDEs by eating food from a country where there is less contamination, nor will persons living in a less contaminated area frequently consume foods from a more contaminated area. The between-country variation was estimated from the results available for this assessment, which consisted mainly of means of aggregated data, i.e. measurements in pooled samples or means of series of individual measurements (see section 6.2). The GSD of a data series of means thus refers to the variation between those means.

The GSD values ranged from 1.2 to 10.8 and clustered around 2. On the basis of these results, a universal between-country GSD of 2 was assumed.

*(b) Within-food variation*

The within-food component of the variation represents variation in concentrations in different portions of one food group bought in one area. This component is not used in long-term intake estimates, because the long averaging time for PBDE intake renders "meal-to-meal" variation irrelevant to the consideration of long-term risk. In the long-term intake assessment, it is assumed that consumers choose food randomly with respect to the distribution of concentrations of contaminants and will therefore have an intake over time that is an approximation of the true mean of that distribution.

An accurate estimate of the GSD for within-food variation requires measurement of concentrations in a set of individual products within one food group and one area. Some of the data available were on a per individual sample. The GSDs varied from 4.7 to 7.0 in the case of fish and shellfish and from 1.2 to 5.2 for the other foods. On the basis of these results, an average within-food GSD of 5.6 was assumed for fish and shellfish and of 2.6 for the other foods. The within-food variation should be used in estimation of acute (short-term) intakes.

### *7.2.5 National diets*

National diet estimates were summarized by the various intake studies available. Some were based on TDS, others on national consumption surveys. Only mean intake estimates were provided.

### *7.2.6 International diets*

Calculations were also performed for the GEMS/Food regional diets (WHO, 1998). These diets are derived not from data on food consumption but from food production and import and export balances, as summarized by the FAO in their Food Balance Sheets. Comparison with the detailed results of national food consumption surveys shows that this type of data on food consumption provides estimates that are more than 15% higher than actual mean food consumption (WHO, 1998). The same estimate of between-person variation in total food consumption that was assumed for dioxins (1.3) was assumed here.

## 7.3 Estimates of dietary intake

### 7.3.1 National estimates for adults

National intake estimates were submitted by Australia, Canada, The Netherlands and New Zealand. The Canadian estimate was based on the Canadian TDS. The Australian and New Zealand estimates were derived using concentration data from the Canadian TDS and consumption estimates from Australia and New Zealand. The Netherlands estimate was based on a report prepared by RIVO and consumption data from the Dutch National Food Consumption Survey. In addition, estimates for other countries were available in published reports and studies.

*(a) Australia*

No Australian or Codex maximum permitted levels or Australian analytical data exist for PBDE concentrations in foods at present. Australia submitted estimated exposures calculated using the concentration levels of PBDEs in Canadian foods, analysed in samples of the food groups reported in the Canadian 1998 Whitehorse and 2002 Vancouver TDS (Health Canada, 2004a, 2004b) and Australian food consumption data. Specifically, the exposure assessment was conducted using Australian food consumption data with Canadian mean and maximum concentration data derived from the two Canadian TDS.

Estimated dietary exposures to PBDEs based on Canadian concentration data and Australian food consumption data are presented in Table 38.

***Table 38. Estimated dietary exposure to PBDEs using Canadian concentration data and Australian food consumption data***

| Exposure units | All respondents[a] ($n$ = 13 858) | | Consumers only[b] ($n$ = 13 810) | | |
|---|---|---|---|---|---|
| | Mean | Median | Mean | Median | 95th percentile |
| *Using mean concentrations* | | | | | |
| pg/day | 37.1 | 27.0 | 37.2 | 27.2 | 103.9 |
| pg/kg bw per day | 0.6 | 0.4 | 0.6 | 0.4 | 1.8 |
| *Using maximum concentrations* | | | | | |
| pg/day | 48.8 | 33.6 | 49.0 | 33.7 | 142.0 |
| pg/kg bw per day | 0.8 | 0.5 | 0.8 | 0.6 | 2.4 |

[a] Respondents: This includes all members of the survey population whether or not they consumed a food that contains the contaminant.

[b] Consumers only: This includes only the people who have consumed a food that contains the contaminant.

*(b) Canada*

Intake estimates for Canada are available from Ryan & Patry (2001) and from Health Canada (2004d, 2004e). Ryan & Patry (2001) estimated the PBDE intake of Canadian adults by sampling commercial foods from an ongoing total diet market basket study. This resulted in a daily intake of total PBDEs of about 44 ng. The main intake of PBDEs was observed to be correlated with the intake of meat. Health Canada estimated the total diet PBDE intake based on food composites collected from Whitehorse in the winter of 1998 and from Vancouver in the spring of 2002. The intake estimate is based on an average consumption rate for all ages and both sexes using a 60-kg person (Table 39). On inspection of the data, it appears that the intake of PBDEs by Canadians from consumption of commercial foods is about 30–40 ng total. Based on limited information, this value does not appear to have changed substantially from 1998 to 2002.

***Table 39. Dietary intakes of total PBDEs in two Canadian cities in 1998 and 2002***

| Food group | PBDE intake (ng/day) | |
|---|---|---|
| | Vancouver 2002 | Whitehorse 1998 |
| Dairy | 5.9 | 3 |
| Meat | 12.5 | 29.6 |
| Fish | 8.6 | 1.2 |
| Other | 3.4 | 4.5 |
| All foods | 30.4 | 38.2 |

*(c) Finland*

Kiviranta et al. (2004) measured the concentrations of PBDEs in 10 market baskets consisting of almost 4000 individual food samples representing 228 different food items, as well as in the total diet basket. The fish basket contributed most to the concentrations of PBDEs, in which the lower-bound range was from 0.82 to 850 pg/g. The associated average daily intake of these substances by the Finnish adult population was 44 ng/day (Table 40). Fish contributed most to the PBDE intake.

*(d) Japan*

For Japan, two independent intake studies have been reported by Ashizuka et al. (2004). They compared the results of their market basket food study and the duplicate study. The average composition of the total diet for Fukuoka residents is given in Table 41. The total dietary PBDE intakes per day and per person for the two estimating methods are calculated as follows:

Market basket study: 114 ng/day

*Table 40. Average intakes of PBDEs in Finland based on 10 market baskets and total diet basket*

| Market baskets | NQ = 0 | | NQ = LOQ | |
|---|---|---|---|---|
| | PBDE intake (ng/day) | % | PBDE intake (ng/day) | % |
| (1) Liquid milk products | 0.35 | 0.8 | 0.86 | 0.9 |
| (2) Solid milk products | 1.1 | 2.6 | 1.3 | 2.9 |
| (3) Fish | 23 | 55 | 23 | 52 |
| (4) Meat and eggs | 1.8 | 4.2 | 2 | 4.5 |
| (5) Fats | 6.5 | 15 | 7.9 | 18 |
| (6) Cereal products | 2.8 | 6.6 | 2.8 | 6.2 |
| (7) Potato products | 0.16 | 0.4 | 0.17 | 0.4 |
| (8) Vegetables | 1.9 | 4.5 | 1.9 | 4.3 |
| (9) Fruits and berries | 0.85 | 2 | 0.93 | 2.1 |
| (10) Beverages, spices, sweets | 3.9 | 9.2 | 4 | 8.8 |
| Sum of baskets | 43 | | 45 | |
| Total diet basket | 44 | | 44 | |

LOQ, limit of quantification; NQ, not quantified

Meal samples study (duplicate study): 68.2 ng/day (range: 10.8–212.7 ng/day)

*(e) The Netherlands*

Mean dietary intakes of PBDEs were estimated by de Winter-Sorkina et al. (2003) using data collected by RIVO (section 6.1) and the consumption data from the third Dutch National Food Consumption Survey. The calculated mean dietary intakes of the "middle" scenario (derived assuming ND = LOD/2) are 3.2–3.5 ng/kg bw per day. When the ND was set at zero (the "low" scenario), the estimated intake is 0.2 ng/kg bw per day (Table 42).

*(f) New Zealand*

No New Zealand or Codex maximum permitted levels or New Zealand analytical data exist for PBDE concentrations in foods at present. New Zealand submitted estimated exposures calculated using the concentration levels of PBDEs in Canadian foods, analysed in samples of the food groups reported in the Canadian 1998 Whitehorse and 2002 Vancouver TDS (Health Canada, 2004a, 2004b) and New Zealand food consumption data. Estimated dietary exposures to PBDE based on mean and maximum Canadian concentration data and New Zealand food consumption data are presented in Table 43.

*Table 41. Average composition of total diet of average person in Fukuoka, Japan*

| Food group | Average weight (g/day) | % (by weight) of total diet |
|---|---|---|
| Rice and rice products | 409.0 | 25.6 |
| Grains, seeds and potatoes | 192.8 | 12.1 |
| Sugar and confectionaries | 32.6 | 2.0 |
| Oils | 15.2 | 1.0 |
| Legumes and legume products | 73.2 | 4.6 |
| Fruits | 113.9 | 7.1 |
| Carrots and green leafy vegetables | 86.9 | 5.4 |
| White leafy vegetables, mushrooms and seaweeds | 184.6 | 11.5 |
| Fish and fish products | 172.2 | 10.8 |
| Meat and eggs | 82.1 | 5.1 |
| Milk and milk products | 107.9 | 6.8 |
| Other processed foods | 122.5 | 7.7 |
| Water | 5.6 | 0.4 |
| Total | 1598.5 | 100.0 |

From Ashizuka et al. (2004)

*(g) Spain*

The dietary intake of PBDEs for an adult male was 97.3 ng/day (ND = 0.5 × LOD) or 81.9 ng/day (ND = 0), as given in Table 44. The greatest contribution to these values corresponds to fish and shellfish, with approximately one third of the total intake.

*(h) Sweden*

Darnerud et al. (1998b), using primarily Nordic data, estimated the exposure of the Swedish population to PBDEs from food in a report to the Nordic Council of Ministers. Their estimates were based on the upper range of total PBDE levels in herring caught in the Baltic Sea (528 ng/g lipid). The total PBDE intake was estimated by assuming a similar relative intake from different dietary sources as described earlier in a Swedish estimation for PCBs (Wicklund-Glynn et al., 1996). Consequently, according to this very approximate calculation, the total PBDE intake for the Nordic consumer would be 200–700 ng/day.

A more detailed Swedish intake estimate was published by Darnerud et al. (2000), on the basis of PBDE levels (BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154) in market basket samples collected in 1999. Analyses of food group homogenates were performed, and not detected values were recognized as 0.5 ×

LOD. Total PBDE intake was obtained by adding intake from fish, meat, dairy products, eggs, fats/oils and pastry food groups. Using this method, total intake in Sweden was estimated to be 51 ng/day. About 50% of the intake originated from fish. All data given above are summarized by Darnerud et al. (2001).

***Table 42. Total average dietary intake of PBDEs by the Dutch population, according to scenario 1 (ND = 0.5 × LOD) and scenario 2 (ND = 0)***

| Compound | Mean intake (ng/kg bw per day)[a] | |
|---|---|---|
| | Scenario 1 | Scenario 2 |
| BDE-28 | 0.01 | 0.01 |
| BDE-47 | 0.7 | 0.5 |
| BDE-99 | 0.5 | 0.3 |
| BDE-100 | 0.2 | 0.1 |
| BDE-153 | 1.0 | 0.1 |
| BDE-154 | 0.5 | 0.2 |
| Sum PBDEs | 3.2 (scenario A)[b] | 0.2 (scenario A) |
| | 3.5 (scenario B)[c] | 0.2 (scenario B) |

From de Winter-Sorkina et al. (2003)

[a] The mean body weight of Dutch National Food Consumption Survey participants was 65.8 kg.
[b] Scenario A: congener scenario.
[c] Scenario B: food group scenario.

***Table 43. Estimated dietary exposure to PBDE using Canadian concentration data and New Zealand food consumption data***

| Exposure units | All respondents[a] ($n$ = 4636) | | Consumers only[b] ($n$ = 4624) | | |
|---|---|---|---|---|---|
| | Mean | Median | Mean | Median | 95th percentile |
| *Using mean concentrations* | | | | | |
| pg/day | 48.7 | 33.1 | 48.8 | 33.2 | 140.8 |
| pg/kg bw per day | 0.7 | 0.5 | 0.7 | 0.5 | 1.9 |
| *Using maximum concentrations* | | | | | |
| pg/day | 65.4 | 41.8 | 65.6 | 41.9 | 199.4 |
| pg/kg bw per day | 0.9 | 0.6 | 0.9 | 0.6 | 2.7 |

[a] Respondents: This includes all members of the survey population whether or not they consumed a food that contains the contaminant.
[b] Consumers only: This includes only the people who have consumed a food that contains the contaminant.

*Table 44. Estimated dietary intake of PBDEs by adult population of Catalonia, Spain*[a]

| Food group | Daily consumption (g) | PBDE intake (ng/day) |
|---|---|---|
| Vegetable | 226 (15.7) | 1.8 (1.2) |
| Pulses | 24 (1.7) | 0.3 (0.05) |
| Cereals | 206 (14.3) | 7.4 (–) |
| Tubers | 74 (5.1) | 0.6 (–) |
| Fruits | 239 (16.6) | 1.4 (–) |
| Fish and shellfish | 92 (6.4) | 30.7 (29.9) |
| Meat and meat products | 185 (12.8) | 20.2 (18.9) |
| Eggs | 34 (2.4) | 2.2 (2.0) |
| Dairy products | 106 (7.3) | 5.1 (3.6) |
| Milk | 217 (15.0) | 3.7 (2.9) |
| Fats and oils | 41 (2.8) | 24.1 (23.3) |
| Total intake | 1444 (100) | 97.3 (81.9) |
| | | 1.4 (1.2)[b] |

From Bocio et al. (2003)

[a] Results are given for a male adult of 70 kg bw. In parentheses are percentages of total consumption. Data were calculated assuming that when a congener was below the LOD, the concentration was equal to one half of the respective LOD. Values in parentheses were calculated assuming that ND = 0.

[b] Total intake expressed in ng/kg bw per day.

The latest intake study for Sweden was presented by Lind et al. (2002). The intake data of total PBDEs in female Swedish subjects are shown in Table 45. For females, a mean daily intake of 0.63 ng/kg bw (40.8 ng/day) was found. The intake data for male individuals are quite similar to the female data, at a mean of 0.58 ng/kg bw per day.

*(i) United Kingdom*

Table 46 summarizes the intake of PBDEs from brown trout and eels from locations upstream and downstream from a site known to have manufactured both penta- and octaBDE until the late 1990s.

A preliminary assessment of human exposure to PBDEs in the United Kingdom is given by Wijesekera et al. (2002). They reported data on a duplicate-diet study for 10 individuals. The daily dietary intake of total PBDEs (total of BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154) was calculated using data on the total content of the diet samples and food mass ingestion data for the individuals consuming each sample. The estimated median lower-bound value of 90.5 ng had a range between 37.2 and 235 ng/person per day.

*Table 45. Intake of PBDEs from different food groups in Sweden, females age 17–74*

| Food group | *n* | PBDE intake (ng/day) | | | |
|---|---|---|---|---|---|
| | | Mean | Median | Range | 95th percentile |
| All fish | 629 | 30.2 | 17.1 | 0.0–654 | 87.5 |
| Fatty Baltic fish | 629 | 9.37 | 2.02 | 0.0–551 | 43.5 |
| Other fatty fish | 629 | 18.8 | 9.90 | 0.0–598 | 64.1 |
| Other fish | 629 | 4.87 | 2.79 | 0.0–48.9 | 12.5 |
| Meats, chicken | 626 | 2.38 | 2.28 | 0.0–8.15 | 4.74 |
| Dairy products | 626 | 3.38 | 3.15 | 0.0–12.4 | 6.75 |
| Vegetable fats | 626 | 1.60 | 1.26 | 0.0–12.1 | 4.17 |
| Other fats | 626 | 2.76 | 2.51 | 0.0–11.6 | 6.02 |
| Eggs | 626 | 0.52 | 0.31 | 0.0–3.77 | 1.88 |
| *Total intake* | | | | | |
| ng/day | 621 | 40.8 | 28.1 | 1.28–666 | 96.4 |
| ng/kg bw per day | 621 | 0.63 | 0.43 | 0.02–11.7 | 1.42 |

From Lind et al. (2002)

*(j) United States*

Intake estimates for the United States are based on concentration data detected in the market basket survey conducted by Schecter et al. (2004a) (section 6.1.8). Figure 13 summarizes the estimated daily intake of PBDEs for 20- to 49-year-old males and females. The estimated intakes, 2.0 ng/kg bw and 1.4 ng kg/bw, are about 2–3 times higher than the daily intake in Europe.

*(k) Summary of national intake estimates*

A summary of the eight dietary PBDE intake studies performed worldwide to date is given in Table 47.

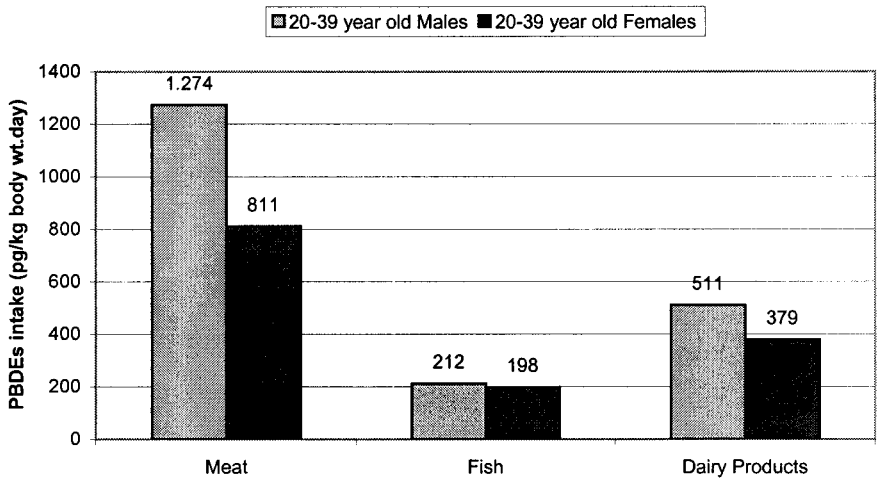
***Table 46. Estimated average dietary intake of PBDEs following consumption of trout or eels from the Skerne-Tees river system***

| Sampling location | Species | Number of samples | Concentration range[a] (µg/kg fresh weight) | Maximum intake (µg/portion)[b] | Maximum average intake (µg/kg bw per day)[c] |
|---|---|---|---|---|---|
| Ricknall Grange[d] | Trout | 5 | 12–14 | 1.6 | 0.003 |
| Haughton Road[e] | Trout | 7 | 59–197 | 24 | 0.056 |
| Ricknall Grange[d] | Eels | 1 | 53 | 3.7 | 0.0088 |
| Oxenfield Bridge[e] | Eels | 5 | 164–288 | 20.2 | 0.048 |

From UK COT (2004)

[a] Reported as sum of BDE-28, BDE-47, BDE-99, BDE-100, BDE-153 and BDE-154.
[b] Portion sizes were assumed to be 120 g trout or 70 g eels, as cited in the United Kingdom Ministry of Agriculture, Fisheries and Food's Food Portion Sizes.
[c] Average daily intake was calculated assuming consumption of one portion of trout or eels per week and an adult body weight of 60 kg.
[d] Control site for Skerne River.
[e] Test site showing the highest concentration of PBDEs in trout or eels.

***Figure 13. Daily PBDE intake estimate for adults in the United States, 2003***




Taken from Schecter, A., Päpke, O., Tung, K.C., Staskal, D. & Birnbaum, L. (2004a) Polybrominated diphenyl ethers contamination of United States food. *Environ. Sci. Technol.*, **38** (20), 5306–5311.

*Table 47. Summary of data on human exposure to PBDEs through the diet*

| Country | Characteristics of the study | PBDE intake (ng/day) | Remarks | Reference |
|---|---|---|---|---|
| Australia | Canadian total diet study, Australian food consumption (per capita) | Mean intake: 37.1 pg/day<br>Maximum intake: 48.8 pg/day | ND = 0 | Food Standards Australia New Zealand (2004) |
| Canada | Food basket study, most food samples of animal origin | 44 | | Ryan & Patry (2001) |
| | TDS conducted in Whitehorse in 1998 and Vancouver in 2002 | 38.2 (Whitehorse)<br>30.4 (Vancouver) | Calculations for intake were done assuming that ND = 0 | Health Canada (2004a, 2004b) |
| Catalonia (Spain) | TDS<br>54 samples<br>11 food groups | 81.9 (lower)<br>97.3 (upper)<br>sum of tetra- to octaBDEs | ND = 0<br>ND = LOD | Bocio et al. (2003) |
| Finland | 10 market baskets and total diet basket | Market baskets<br>43<br>45<br>Total diet basket<br>44<br>44 | <br>ND = 0<br>ND = LOD<br><br>ND = 0<br>ND = LOD | Kiviranta et al. (2004) |
| Japan | a) Market basket study<br>b) Duplicate-diet study | a) 114<br>b) 68.2 (10.8–212.7) | | Ashizuka et al. (2004) |
| Netherlands | TDS<br>84 samples<br>6 food groups | 13 (low estimate)<br>213 (middle estimate) | ND = 0<br>ND = ½ LOD | de Winter-Sorkina et al. (2003) |
| New Zealand | Canadian TDS, New Zealand food consumption | Mean intake: 48.7 pg/day<br>Maximum intake: 65.4 pg/day | ND = 0 | Food Standards Australia New Zealand (2004) |

*Table 47.* (contd)

| Country | Characteristics of the study | PBDE intake (ng/day) | Remarks | Reference |
|---|---|---|---|---|
| Sweden | Market basket samples: fish, meat, dairy products, eggs, fats/oils, pastry | 51<br>sum of congeners 47, 99, 100, 153, 154 | Calculations for intake were done assuming that ND = ½ LOD | Darnerud et al. (2001) |
| Sweden | Food of animal origin, National Swedish Diet Inventory | 40.8 (mean)<br>females (18–74 years)<br>sum of congeners 47, 99, 100, 153, 154 | Calculations for intake were done assuming that ND = 0 | Lind et al. (2002) |
| United Kingdom | Duplicate-diet samples | 90.5 (median)<br>sum of congeners 47, 99, 100, 153, 154 | Calculations for intake were done assuming that ND = 0 | Wijesekera et al. (2002) |
| United States | Food basket study, 49 individual samples, most food samples of animal origin | Females: 1.4 ng/kg bw<br>Males: 2.0 ng/kg bw | ND = 0 | Schecter et al. (2004a) |

LOD, limit of detection; ND, non-detects; TDS, total diet study

### *7.3.2 Regional estimates*

The regional estimates for dietary intake presented use the concentration distributions derived by adjusting only for between-country variability and represent long-term intake estimates. The concentration distributions used in the assessment are those for Western Europe, the Far East (data from Japan) and North America (data from Canada and the United States).

Consumption data for the regional estimates were based on GEMS/Food regional diets. As these diets provide only point estimates of intakes, distributions of intake (representing interperson variability) assumed a lognormal distribution with a GSD of 1.3. Table 48 summarizes these distributions.

The estimated median long-term intakes from the GEMS/Food regional diets are listed in Table 49.

The estimated long-term intakes of PBDEs in the GEMS/Food regional diets (Tables 49 and 50) are considerably higher than those for the national diets summarized in section 7.3.1, particularly for the Western European region and the

Northern American region. This difference is driven by the fact that food consumption is overestimated in the GEMS/Food regional diets, as they are based on food production balances instead of actual food consumption.

***Table 48. Statistical descriptors of the food consumption distributions used in the assessment (based on the GEMS/Food regional diets)***

| Region | Parameter | Per capita food consumption estimate (g/day) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Dairy & dairy products | Eggs | Fish & shellfish | Fruits, vegetables, roots & tubers | Meat & poultry | Fats & oils |
| Europe and North America | Mean | 336.1 | 37.6 | 46.8 | 826.0 | 217.3 | 49.4 |
| | GSD | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 |
| | Median | 303.7 | 34.0 | 42.3 | 746.6 | 196.4 | 44.6 |
| | 90th percentile | 425.1 | 47.6 | 59.2 | 1045.0 | 274.8 | 62.5 |
| Far East | Mean | 32.8 | 13.1 | 31.5 | 372.8 | 47.0 | 16.0 |
| | GSD | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 |
| | Median | 29.6 | 11.8 | 28.5 | 337.0 | 42.5 | 14.5 |
| | 90th percentile | 41.5 | 16.6 | 39.9 | 471.6 | 59.5 | 20.3 |

GSD, geometric standard deviation

***Table 49. Statistical descriptors (median, 80th and 90th percentiles) of estimated distributions of long-term PBDE intake in GEMS/Food regional diets***

| Source of concentration data | Diet | Total PBDE intake (ng/day per person), using distributions derived assuming ND = 0 | | | Total PBDE intake (ng/day per person), using distributions derived assuming ND = LOD | | |
|---|---|---|---|---|---|---|---|
| | | Median | P80 | P90 | Median | P80 | P90 |
| Western Europe | European | 109 | 166 | 210 | 250 | 350 | 420 |
| North America | European | 189 | 264 | 318 | 259 | 361 | 433 |
| Far East | Far Eastern | NA | NA | NA | 73 | 103 | 125 |

LOD, limit of detection; NA, not available; ND, not detected; P80, 80th percentile; P90, 90th percentile

A large difference is observed between the estimates using the lower-bound concentration distributions (generated with ND = 0) and those derived using the upper-bound concentration distributions (generated with ND = LOD), reflecting the large uncertainty in the concentration estimates due to the large number of non-detects in the data and to the fact that different studies were used in the

generation of these sets of distributions. When estimates using the lower-bound distributions are considered, the Western European intake estimates are driven by the fish and shellfish intakes, whereas meat, fat and oil and fish and shellfish intakes drive the North American intake estimates (Table 50). On the other hand, when estimates using the upper-bound distributions are considered, the Western European intake estimates are driven by the fish and shellfish and dairy intakes, whereas dairy intakes drive the North American intake estimates and fish and shellfish and fruit and vegetable intakes drive the Far Eastern intake estimates (Table 50). It should be noted that these estimates are based in some instances on a very small number of studies and are therefore largely uncertain.

***Table 50. Contribution of the various food groups to the mean long-term intake in the GEMS/Food regional diets***

| Diet | Dairy & dairy products | Eggs | Fish & shellfish | Fruits & vegetables | Meat & poultry | Fats & oils | Total |
|---|---|---|---|---|---|---|---|
| | Contributions to total diet at the mean level (ng/day) (ND = 0) | | | | | | |
| Western Europe | 10 | 2 | 81 | 6 | 17 | 13 | 128 |
| North America | 25 | 8 | 42 | 6 | 63 | 46 | 188 |
| Far East | NA | NA | NA | NA | NA | NA | NA |
| | Per cent contributions to total diet at the mean level (ND = 0) | | | | | | |
| Western Europe | 8% | 1% | 64% | 4% | 13% | 10% | 100% |
| North America | 13% | 4% | 22% | 3% | 33% | 24% | 100% |
| Far East | NA | NA | NA | NA | NA | NA | NA |
| | Contributions to total diet at the mean level (ng/day) (ND = LOD) | | | | | | |
| Western Europe | 81 | 5 | 85 | 8 | 49 | 45 | 274 |
| North America | 81 | 5 | 42 | 8 | 52 | 52 | 240 |
| Far East | 8 | 2 | 28 | 27 | 1 | 13 | 79 |
| | Per cent contributions to total diet at the mean level (ND = LOD) | | | | | | |
| Western Europe | 30% | 2% | 31% | 3% | 18% | 17% | 100% |
| North America | 34% | 2% | 17% | 3% | 22% | 22% | 100% |
| Far East | 10% | 2% | 36% | 34% | 2% | 17% | 100% |

LOD, limit of detection; NA, not available; ND, non-detects

### 7.3.3 Dietary intake for infants

Nearly all PBDE intake studies are calculated for adults. In Table 51, preliminary estimates of the daily PBDE intake by nursing infants via human milk are presented. On the basis of this information, it can be concluded that the daily intake for breastfed infants is between 1 and 2 orders of magnitude higher than that for adults.

*Table 51. Daily PBDE intake in nursing infants (calculation made under the assumption of consumption of 800 ml milk per day with a lipid content of 3%)*

| | Germany | United States | Viet Nam |
|---|---|---|---|
| PBDE concentration in human milk (ng/g lipid) | 2.3[a] | 30[b] | 0.48[b] |
| Total PBDE intake per day (ng) | 48.3 | 630 | 10 |
| Total PBDE intake per day (ng/kg bw) | 9.7 | 126 | 2 |

[a] Fürst (2001).
[b] Schecter et al. (2004c).

## 7.4 Potential sources of intake other than food

The knowledge of pathways/sources other than food for the daily intake of PBDEs is quite limited. Potential additional pathways for intake are inhalation of air and the uptake of dust (especially household dust). Detailed information on the importance of these pathways is difficult to obtain. Wijesekera et al. (2002) analysed nine indoor air samples for PBDEs (presented in Table 52).

*Table 52. PBDE concentrations in indoor air samples*

| Location | Sum PBDEs (ng/m$^3$)[a] | Location | Sum PBDEs (ng/m$^3$) |
|---|---|---|---|
| 1W | 0.77 | 3D | 2.35 |
| 2W | 15.9 | 7D | 1.62 |
| 4W | 17.9 | 9D | 0.91 |
| 5W | 1.43 | | |
| 6W | 5.73 | | |
| 8W | 9.1 | | |
| Median W | 2.3 | Median D | 1.62 |

From Wijesekera et al. (2002)

D, domestic; W, workplace

[a] Total of BDE-47, BDE-99, BDE-100, BDE-153, BDE-154.

The adult respiration rate was estimated as 20 m$^3$/day. Due to the low level of outdoor air PBDE concentrations (low pg/m$^3$ range; de Wit, 2002), no remarkable

influence was expected. Using the measured data, assuming a 100% absorption of intake and taking into account a 40-h weekly working time, a daily human exposure to PBDEs via inhalation was calculated at 32.9 ng/person. The intake via contaminated dust is more difficult to estimate. Various authors have described wide ranges of contamination of household dust. Data from Leonards et al. (2001), Knoth et al. (2002, 2003), Sjödin et al. (2004b), Stapelton et al. (2004), Schecter et al. (2005) and Wilford et al. (2005) are presented in Table 53.

***Table 53. PBDE concentrations in household dust***

| Area | Author | Year of collection | *n* | Mean values (range) (ng/g) |
|---|---|---|---|---|
| EU | Leonards et al. (2001) | 1995 | 7[a] | 195 |
| Germany | Knoth et al. (2002, 2003) | 2000–2001 | 40 | 63 |
| United States | Stapelton et al. (2004) | 2004 | 17 | 5563 (780–29 700) |
| United States | Schecter et al. (2005) | 2004 | 9 | 12 136 (705–69 283) |
| Canada | Wilford et al. (2005) | 2002–2003 | 68 | 5500 (170–170 000) |
| United States | Sjödin et al. (2004b) | 2004 | 10 | 4240 (534–28 763) |
| Australia | Sjödin et al. (2004b) | 2004 | 10 | 1166 (506–12 772) |
| United Kingdom | Sjödin et al. (2004b) | 2004 | 10 | 10 292 (952–54 313) |
| Germany | Sjödin et al. (2004b) | 2004 | 10 | 17 (74–552) |

[a] Includes The Netherlands, Finland, Denmark ($n$ = 2), Sweden, Italy ($n$ = 2).

## 8. PREVENTION AND CONTROL

As with other lipophilic contaminants, control of PBDE residues in animal feed is likely to have an impact on the concentrations of PBDEs found in meat, poultry, farmed fish and other animal-derived products. In addition, indoor air and dust are currently being investigated as possible significant sources of human exposure to PBDEs from consumer products (Wilford et al., 2004; Jones-Otazo et al., 2005).

## 9. LEVELS AND PATTERNS OF CONTAMINATION OF HUMANS

### 9.1 Comparison of analytical data in different tissues

With respect to comparability of PBDE data determined in different samples, it is important to have data for concentrations in various tissues. As will be seen, a comparison is possible only in the case of lipid-based data. Hirai et al. (2003)

analysed the distribution of PBDEs among bile, blood, liver and adipose tissue. Table 54 gives the relationship between PBDE concentrations in these tissues.

***Table 54. Comparison of PBDE congener levels among different tissues in Japan: Bile, blood, liver and adipose tissue***

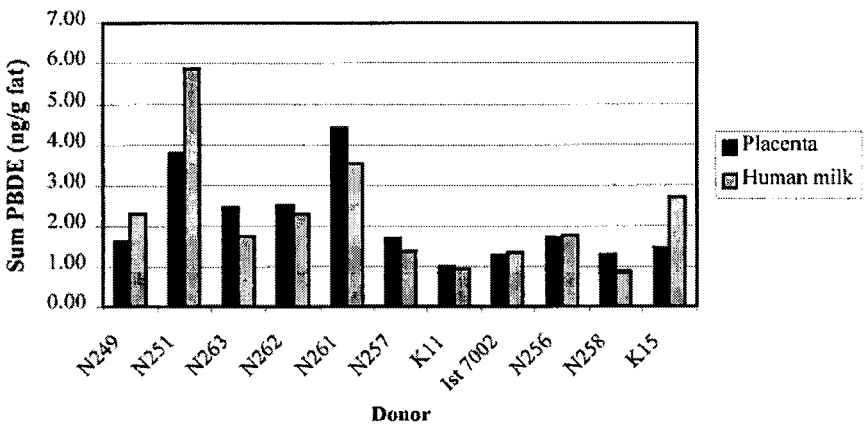
| BDE | Mean ± SD | | | | | |
|---|---|---|---|---|---|---|
| | Bile/ blood | Liver/ blood | Adipose tissue/ blood | Liver/ bile | Adipose tissue/ bile | Liver/ adipose tissue |
| 71 | 1.1 ± 0.6 | 1.5 ± 0.6 | 1.4 ± 0.8 | 2.7 ± 3.1 | 2.3 ± 1.8 | 1.2 ± 0.7 |
| 47 | 1.6 ± 1.5 | 1.2 ± 0.4 | 1.6 ± 0.7 | 3.3 ± 3.6 | 4.3 ± 5.9 | 1.0 ± 1.2 |
| 100 | 1.6 ± 1.5 | 1.1 ± 0.4 | 1.7 ± 0.7 | 2.3 ± 2.3 | 3.9 ± 3.8 | 0.7 ± 0.5 |
| 99 | 2.2 ± 2.6 | 1.3 ± 0.6 | 1.6 ± 0.7 | 3.4 ± 3.0 | 4.6 ± 4.6 | 0.9 ± 0.9 |
| 153 | 1.5 ± 1.3 | 1.1 ± 0.5 | 1.8 ± 1.1 | 2.3 ± 2.2 | 4.2 ± 5.9 | 0.7 ± 0.4 |
| Total (25 congeners) | 1.3 ± 1.0 | 1.2 ± 0.4 | 1.7 ± 0.9 | 2.4 ± 2.4 | 3.8 ± 5.1 | 0.8 ± 0.6 |

From Hirai et al. (2003)

SD, standard deviation

A comparison of the PBDE distribution between human milk and placenta was undertaken for sum PBDEs (BDE-28, BDE-47, BDE-99 and BDE-153) by Strandman et al. (2000). As can be seen in Figure 14, the concentrations are similar in both tissues.

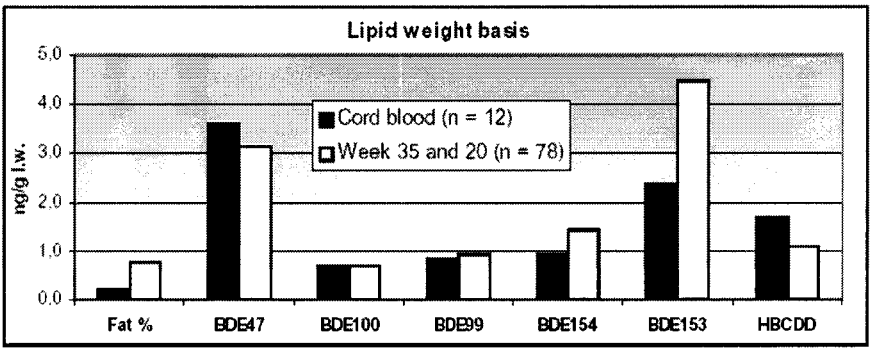
***Figure 14. Sum of PBDEs in human milk and placenta from 11 donors***




Taken from Strandman, T., Koistinen, J. & Vartiainen, T. (2000) Polybrominated diphenyl ethers (PBDEs) in placenta and human milk. *Organohalogen Compd.*, **47**, 61–64.

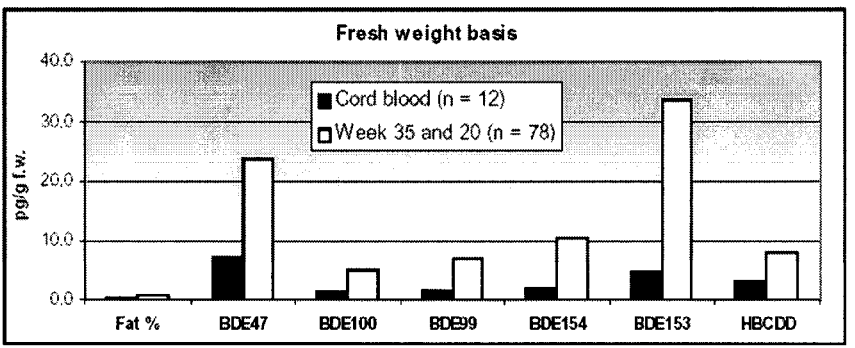
Weiss et al. (2004a, 2004b) compared PBDE concentrations in serum samples from Dutch mothers and from infants. As can be seen in Figures 15 and 16, the higher brominated congeners tend to have higher concentrations in the maternal samples when comparing the lipid-based values. Due to the low lipid content of cord blood, all values are significantly lower when reported on a fresh weight basis.

***Figure 15. Mean PBDE concentrations on a lipid weight basis in Dutch mothers and infants***




Taken from Weiss, J., Meijer, L., Sauer, P., Linderholm, L., Athanasiadis, I. & Bergman, A. (2004a) PBDE and HBCDD levels in blood from Dutch mothers and infants. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 71–74 (http://www.bfr2004.com).

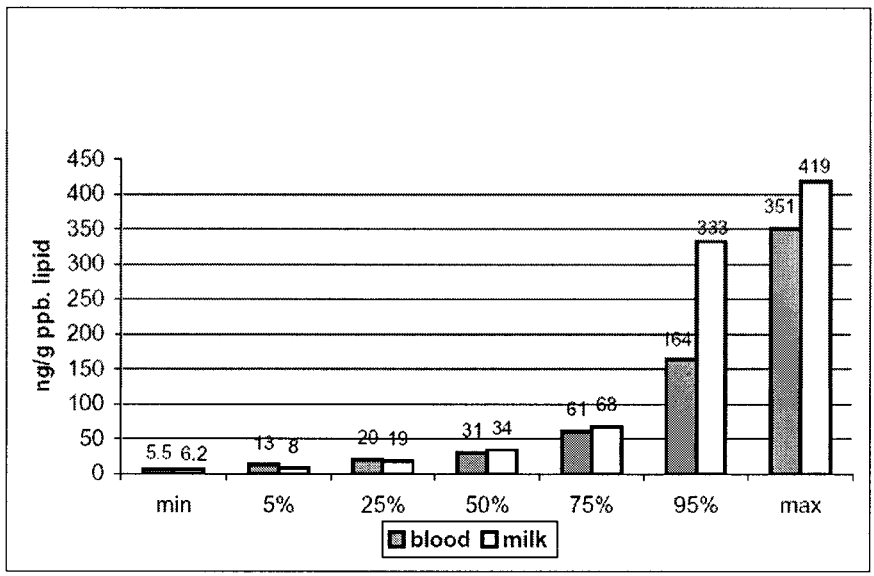
***Figure 16. Mean PBDE concentrations on a wet weight basis in Dutch mothers and infants***




Taken from Weiss, J., Meijer, L., Sauer, P., Linderholm, L., Athanasiadis, I. & Bergman, A. (2004a) PBDE and HBCDD levels in blood from Dutch mothers and infants. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 71–74 (http://www.bfr2004.com).

A comparison of PBDE concentrations in blood and human milk was reported by Schecter et al. (2004b). They analysed 52 milk samples and 29 blood samples collected in 2003. When looking at the total PBDEs, presented in Figure 17, a great similarity can be observed in both tissues. On the other hand, it is important to mention that the samples analysed are from different individuals.

***Figure 17. PBDE levels in human milk (n = 52) and blood (n = 29) from the United States***



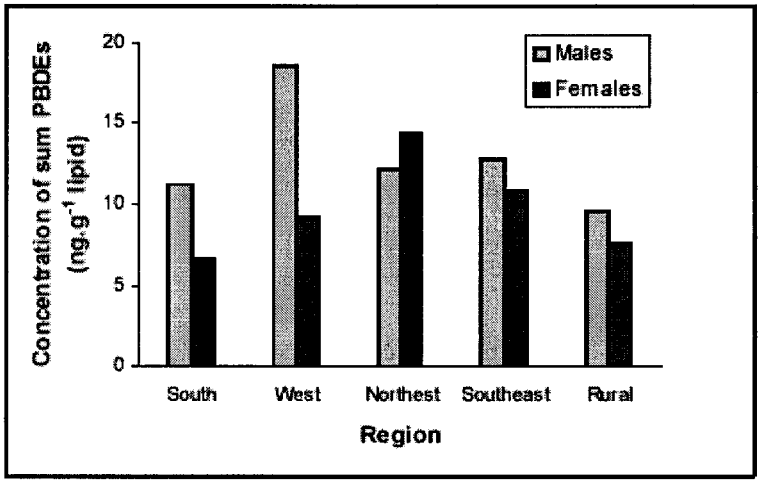

Taken from Schecter, A., Päpke, O., Tung, K.C., Joseph, J., Dahlgren, J. & Harris, T.R. (2005) Polybrominated diphenylether (PBDE) flame retardants in the US population: current levels, temporal trends, and comparison with dioxins, dibenzofurans and polychlorinated biphenyls. *J. Occup. Environ. Med.*, **47** (3), 199–211.

## *9.3 Different countries*

### *9.3.1 Australia*

The first data for PBDEs in the Australian population were provided by Harden et al. (2004). They analysed pooled samples collected in 2003 for different areas from Australia for males and females. Each pool consisted of about 100 individual samples. The age of the participants was between 31 and 45 years. Results of the study are given in Figure 18. The average total concentration (sum of 13 PBDEs) across all samples was 11.0 ± 3.9 ng/g lipid. Overall concentrations ranged from 6.7 ng/g lipid in a pooled sample collected from females from the South region to a maximum of 19 ng/g lipid in a pooled sample collected from males in the West region.

*Figure 18. Concentration of PBDE congeners in blood sera from Australians aged 31–45 years*




Taken from Harden, F., Toms, L.M., Ryan, J.J. & Müller, J. (2004) Determination of the levels of polybrominated diphenylethers (PBDEs) in pooled blood sera obtained from Australians aged 31–45 years. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 59–62 (http://www.bfr2004.com).

### 9.3.2 Belgium

Levels of selected PBDEs in Belgian human milk were published by Pirard et al. (2003). The samples, 14 from primiparous and multiparous women between the ages of 26 and 38 years, were collected between 2000 and 2001. The values are given in Table 55.

*Table 55. BDE concentrations in investigated Belgian breast milk samples*

| BDE congener | Concentrations (ng/g lipid weight) | SD |
|---|---|---|
| BDE-28 | 0.09 | 0.17 |
| BDE-47 | 1.69 | 1.90 |
| BDE-100 | 0.17 | 0.209 |
| BDE-99 | 0.35 | 0.319 |
| BDE-154 | 0.12 | 0.082 |
| BDE-153 | 0.43 | 0.388 |
| Total BDEs | 2.85 | |

From Pirard et al. (2003)

SD, standard deviation

### *9.3.3 Canada*

For Canada, 10 individual human milk samples were obtained in 1992 as part of a countrywide survey of concentrations of organochlorines in Canadian women. The results of this study are shown in Table 56.

***Table 56. Concentrations of PBDEs in individual human milk (n = 10) collected in 1992 from Ontario and Quebec***

| Sample no. | Concentration (ng/g, lipid basis) | | | | | | |
|---|---|---|---|---|---|---|---|
| | BDE-28 | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-183 | ∑6 BDEs |
| 1 | 0.10 | 1.64 | 1.11 | 0.25 | 0.30 | 0.15 | 3.55 |
| 2 | 0.12 | 2.09 | 1.26 | 0.36 | 0.27 | 0.08 | 4.18 |
| 3 | ND (0.05) | 0.31 | 0.10 | 0.07 | 0.21 | 0.10 | 0.79 |
| 4 | 0.07 | 0.91 | 0.24 | 0.10 | 0.14 | ND (0.05) | 1.46 |
| 5 | 0.13 | 0.70 | 0.30 | 0.16 | 0.34 | ND (0.05) | 1.63 |
| 6 | 0.15 | 2.46 | 0.87 | 0.42 | 0.23 | 0.10 | 4.23 |
| 7 | 0.26 | 4.57 | 1.70 | 0.65 | 1.31 | 0.71 | 9.20 |
| 8 | 1.22 | 18.72 | 5.63 | 2.14 | 0.76 | ND (0.05) | 28.47 |
| 9 | ND (0.05) | 0.65 | 0.22 | 0.12 | 0.35 | 0.39 | 1.73 |
| 10 | 0.10 | 1.85 | 0.43 | 0.16 | 0.14 | ND (0.05) | 2.68 |
| Median | 0.13 | 1.75 | 0.65 | 0.21 | 0.29 | 0.13 | 3.14 |
| Average | 0.22 | 3.39 | 1.19 | 0.44 | 0.41 | 0.15 | 5.79 |

From Ryan & Patry (2000)

ND, not detected

At the same time, pooled milk samples were also prepared by combining samples from 20 individuals from each of five geographic regions and from 100 and 200 individuals across Canada. The data are reported in Table 57.

Further information on levels of PBDEs in maternal human blood from ethnic groups living in different areas is presented by Ryan & van Oostdam (2004) (Table 58).

### *9.3.4 Czech Republic*

Crhova et al. (2002) analysed adipose tissue samples collected postmortem between 2000 and 2001 from 24 individuals. The age of the donors ranged between 23 and 78 years. Concentrations are given in Table 59. In the groups studied, lower concentrations of PBDEs were observed in women than in men.

*Table 57. Variation of PBDEs in composite samples of Canadian human milk samples*

| Region of origin | Time collected | No. of individual milk samples | BDE concentration (sum of six congeners) (ng/g milk lipid) |
|---|---|---|---|
| Maritimes | 1992 | 20 | 19.08 |
| Quebec | 1992 | 20 | 18.75 |
| Ontario | 1992 | 20 | 2.57 |
| Prairies | 1992 | 20 | 5.70 |
| Canada-wide | 1992 | 100 | 16.24 |
| Canada-wide | 1981–1982 | 200 | 0.21 |

From Ryan & Patry (2000)

### 9.3.5 Faroe Islands

The aim of the study of Fängström et al. (2004b) was to determine the temporal trend for PBDEs in human milk samples from the Faroe Islands. It was demonstrated that an ongoing increase is taking place (Table 60).

### 9.3.6 Finland

The first measurements for the Finnish population were performed by Strandman et al. (1999), as given in Table 61. The tissue samples were randomly selected from an epidemiological population study. The range for the sum of three PBDE congeners was between 6.15 and 18.72 ng/g lipid.

Strandman et al. (2000) analysed pairs of placenta and human milk from 11 mothers in Finland, collected between 1994 and 1998. The data for the human milk samples are presented in Table 62.

### 9.3.7 Germany

The first PBDE data for Germany have been published by Schröter-Kermani et al. (2000). The study was conducted with blood samples archived by the German environmental specimen bank. Whole blood samples from 20 subjects (10 male and 10 female) participating in the monitoring programmes were chosen. The age of the participants ranged between 20 and 30 years. As can be seen in Table 63, a time-related increase was found. During the period 1985–1999, median PBDE concentrations in blood increased from 3.08 to 4.69 ng/g lipid.

Fürst (2001) compared PBDE data in human milk collected in 1992 and 2000. The values for most congeners were quite similar in the samples of either collection period. Slightly higher values were found only for BDE-153 and BDE-183 in the samples collected in 2000.

*Table 58. PBDE congeners in maternal human blood plasma composites collected from northern populations*

| Code | Year of sampling | Ethnicity | Region | No. of individuals | Concentrations (ng/g, lipid basis) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | #28 | #47 | #85 | #99 | #100 | #153 | #154 | #183 | ΣPBDE |
| M1 | 1998–1999 | Caucasian | Inuvik | 19 | 0.8 | 15.1 | 0.4 | 4.2 | 1.6 | 2.1 | 0.2 | 1.4 | 25.8 |
| M2 | 1998–1999 | Dene/Metis | Inuvik | 40 | 1.2 | 12.6 | 0.8 | 4.9 | 4.1 | 6.7 | 0.7 | 1.1 | 31.9 |
| M3 | 1994–1995 | Inuit | Kitikmeot | 13 | 0.2 | 4.8 | 0.8 | 7.6 | 2.1 | 2.5 | 0.9 | 0.8 | 19.6 |
| M4 | 1994–1995 | Inuit | Kitikmeot | 34 | 0.3 | 5.5 | 0.9 | 9.5 | 1.7 | 1.9 | 0.7 | 0.5 | 21.0 |
| M5 | 1994–1999 | Caucasian | Mackenzie | 24 | 0.5 | 6.7 | 0.2 | 3.0 | 0.9 | 0.8 | ND (0.4) | 0.9 | 13.1 |
| M6 | 1994–1999 | Caucasian | Mackenzie | 29 | 1.4 | 23.5 | 1.1 | 11.5 | 4.1 | 3.3 | 0.9 | 0.8 | 46.5 |
| M7 | 1994–1999 | Caucasian | Mackenzie | 29 | 1.1 | 7.2 | 0.2 | 2.8 | 1.1 | 1.5 | 0.3 | 1.1 | 15.3 |
| M8 | 1994–1995 | Dene/Metis | Mackenzie | 21 | 0.9 | 7.9 | ND (0.5) | 3.7 | 1.0 | 0.8 | ND (0.4) | 0.6 | 14.9 |
| M9 | 1994–1995 | Dene/Metis | Mackenzie | 10 | 0.8 | 10.3 | 0.2 | 3.7 | 1.1 | 1.0 | 0.3 | 0.5 | 18.0 |
| M10 | 1994–1999 | Inuit | Several | 23 | 1.1 | 15.6 | 0.4 | 4.8 | 2.3 | 2.0 | 0.5 | 0.6 | 27.2 |
| | | | | Mean | 0.8 | 10.9 | 0.5 | 5.6 | 2.0 | 2.3 | 0.5 | 0.8 | 23.3 |
| | | | | Range | 0.2–1.4 | 4.8–23.5 | ND–1.1 | 2.8–11.5 | 1.0–4.1 | 0.8–6.7 | ND–0.9 | 0.5–1.4 | 13.1–46.5 |

From Ryan & van Oostdam (2004)

ND, not detected (LOD given in parentheses, where available)

*Table 59. Concentration of PBDE congeners in human adipose tissue*

| PBDE congener | Concentration (ng/g fat) | | | | | |
|---|---|---|---|---|---|---|
| | Male ($n$ = 10) | | | Female ($n$ = 14) | | |
| | Mean | Minimum | Maximum | Mean | Minimum | Maximum |
| BDE-28 | 0.13 | 0.028 | 0.53 | 0.034 | 0.004 | 0.145 |
| BDE-47 | 1.18 | 0.230 | 3.69 | 0.400 | 0.087 | 0.821 |
| BDE-99 | 0.340 | 0.075 | 1.14 | 0.117 | 0.015 | 0.233 |
| BDE-100 | 0.590 | 0.088 | 2.35 | 0.132 | 0.013 | 0.330 |
| BDE-154 | 0.055 | 0.012 | 0.110 | 0.026 | 0.002 | 0.054 |
| BDE-153 | 0.520 | 0.520 | 1.89 | 0.413 | 0.080 | 1.47 |
| BDE-183 | 0.440 | 0.075 | 1.59 | 0.320 | 0.049 | 1.74 |
| Total PBDEs | 3.26 | 1.03 | 11.3 | 1.44 | 0.25 | 4.79 |

From Crhova et al. (2002)

*Table 60. Concentrations of congeners identified in human milk from the Faroe Islands*[a]

| | Concentrations (ng/g lipid weight) | | |
|---|---|---|---|
| | 1987 ($n$ = 10) | 1994–1995 ($n$ = 10) | 1998–1999 ($n$ = 10) |
| BDE-47 | 0.5 | 1.2 | 1.7 |
| BDE-99 | 0.20 | 0.50 | 1.0 |
| BDE-100 | 0.25 | 0.60 | 1.0 |
| BDE-153 | 0.60 | 1.4 | 3.6 |
| Sum PBDE | 1.5 | 3.6 | 7.2 |

From Fängström et al. (2004b)

[a] The samples were pooled with samples in each pool.

Very recent data for German mothers are reported by Vieth et al. (2004), with milk samples collected in 2001–2003. Statistical data from this investigation are presented in Table 64.

Significantly lower PBDE levels were observed in the group of mothers preferring a vegetarian or vegan diet and in the mothers nursing their second or third child. However, it should be pointed out that the sample size of mothers nursing their second or third child is higher in the group of vegetarians/vegans. BDE-209 was quantified in 40% of the human milk samples corresponding to background level.

*Table 61. Concentration of three PBDE congeners in Finnish human adipose tissue*

| Age (years) | Concentration (ng/g fat) | | | |
|---|---|---|---|---|
| | BDE-47 | BDE-99 | BDE-153 | Total BDEs (three congeners) |
| 36 | 3.07 | 0.80 | 3.05 | 6.92 |
| 45 | 6.17 | 2.77 | 2.88 | 11.82 |
| 47 | 8.76 | 5.51 | 3.74 | 18.0 |
| 54 | 3.94 | 0.74 | 1.47 | 6.15 |
| 57 | 6.55 | 1.55 | 3.25 | 11.35 |
| 62 | 16.75 | 3.27 | 1.68 | 21.7 |
| 64 | 6.23 | 1.31 | 1.26 | 8.8 |
| 69 | 14.46 | 2.45 | 1.81 | 18.72 |
| 82 | 3.48 | 1.40 | 1.61 | 6.49 |
| 84 | 3.39 | 0.88 | 2.54 | 6.81 |
| | | | | 11.7 (mean) |

From Strandman et al. (1999)

*Table 62. Concentrations of PBDEs in human milk (n = 11)*

| | Concentration (ng/g lipid) | | | | |
|---|---|---|---|---|---|
| | BDE-28 | BDE-47 | BDE-99 | BDE-153 | Total BDEs (four congeners) |
| Mean | 0.16 | 1.31 | 0.39 | 0.39 | 2.25 |
| SD | 0.15 | 1.15 | 0.23 | 0.20 | 1.73 |
| Median | 0.13 | 0.85 | 0.35 | 0.29 | 1.62 |
| Minimum | 0.04 | 0.30 | 0.14 | 0.19 | 0.67 |
| Maximum | 0.59 | 4.25 | 0.94 | 0.72 | 6.5 |

From Strandman et al. (2000)

SD, standard deviation

*Table 63. Statistical data on ΣPBDE levels in human blood, time trend, Germany*

| Year | *n* | Concentrations (ng/g lipid) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Maximum | 25th percentile | Median | Arithmetic mean | Geometric mean | 75th percentile |
| 1985 | 20 | 15.72 | 1.94 | 3.08 | 3.91 | 2.86 | 4.03 |
| 1990 | 20 | 12.35 | 1.73 | 3.88 | 4.89 | 3.57 | 6.82 |
| 1995 | 19 | 17.56 | 3.30 | 3.90 | 5.55 | 4.59 | 5.9 |
| 1999 | 20 | 12.61 | 3.98 | 4.69 | 5.57 | 4.87 | 7.27 |

From Schröter-Kermani et al. (2000)

***Table 64. PBDE concentrations in human milk from Germany (ng/g fat) sampled between November 2001 and December 2003***

| BDE | Omnivores and vegetarians/vegans together | | | | | | Omnivores | Vegetarians/vegans |
|---|---|---|---|---|---|---|---|---|
| | 1st sampling period | | | | | 2nd sampling period | 1st sampling period | 1st sampling period |
| | *n* = 62 | | | | | *n* = 31 | *n* = 37 | *n* = 25 |
| | Mean | Median | 95th percentile | Maximum | *n* < LOQ[a] | Mean | Mean | Mean |
| BDE-28 | 0.04 | 0.04 | 0.12 | 0.17 | 9 | 0.04 | 0.05 | 0.04 |
| BDE-47 | 0.82 | 0.54 | 3.52 | 4.50 | 1 | 0.78 | 0.99 | 0.58 |
| BDE-66 | 0.01 | 0.01 | 0.03 | 0.06 | 14 | 0.01 | 0.02 | 0.01 |
| BDE-99 | 0.25 | 0.17 | 0.92 | 1.30 | 2 | 0.25 | 0.30 | 0.16 |
| BDE-100 | 0.21 | 0.17 | 0.67 | 1.10 | 0 | 0.19 | 0.23 | 0.18 |
| BDE-153 | 0.63 | 0.53 | 1.54 | 1.90 | 0 | 0.50 | 0.66 | 0.57 |
| BDE-154 | 0.02 | 0.02 | 0.06 | 0.07 | 0 | 0.02 | 0.03 | 0.02 |
| BDE-183 | 0.09 | 0.04 | 0.34 | 0.63 | 12 | 0.06 | 0.10 | 0.07 |
| BDE-209 | 0.17 | 0.10 | 0.59 | 1.00 | 37 | 0.11 | 0.17 | 0.17 |
| Sum PBDEs | 2.23 | 1.78 | 6.69 | 7.25 | | 1.95 | 2.54 | 1.78 |

From Vieth et al. (2004)

[a] Non-detects are set at one half the LOQ.

### 9.3.8 Italy

The first data of the PBDE concentrations in Italian nulliparous women of reproductive age were reported by De Felip et al. (2003). They analysed blood samples originating from three pools consisting of 10, 6 and 6 individuals, respectively. The mean concentration, as a sum of six congeners, was 2.0 ng/g lipid.

Ingelido et al. (2004) reported data on PBDE levels in human milk from mothers from the general population of Rome and Venice and its surroundings. The mean values, as presented in Table 65, range between 1.6 and 4.1 ng/g lipid. A positive correlation with the fish consumption was not observed.

***Table 65. PBDE congener concentrations and distribution in pooled human milk samples from Venice and Rome***

| PBDE | Concentrations (ng/g lipid) | | | |
|---|---|---|---|---|
| | Venice (LC)[a] | Venice (MC)[b] | Venice (HC)[c] | Rome |
| | (*n* = 10) | (*n* = 13) | (*n* = 6) | (*n* = 10) |
| BDE-17 | 0.004 | 0.004 | <0.002 | 0.004 |
| BDE-28 | 0.065 | 0.064 | 0.036 | 0.082 |
| BDE-47 | 1.5 | 0.90 | 0.55 | 1.9 |
| BDE-66 | 0.015 | 0.037 | <0.006 | 0.019 |
| BDE-85 | 0.035 | 0.045 | 0.018 | 0.074 |
| BDE-99 | 0.41 | 0.51 | 0.14 | 0.97 |
| BDE-100 | 0.28 | 0.19 | 0.15 | 0.48 |
| BDE-138 | <0.01 | 0.020 | <0.01 | 0.013 |
| BDE-153 | 0.41 | 0.47 | 0.60 | 0.47 |
| BDE-154 | 0.025 | 0.047 | 0.020 | 0.070 |
| BDE-183 | 0.061 | 0.19 | 0.050 | 0.092 |
| ΣPBDEs | 2.8 | 2.5 | 1.6 | 4.1 |

From Ingelido et al. (2004)

[a] LC= low fish consumption.
[b] MC = medium fish consumption.
[c] HC = high fish consumption.

### 9.3.9 Japan

Human adipose tissue samples from around the Tokyo area in Japan were collected in 1970 (*n* = 10) and 2000 (*n* = 10) from 40- to 50-year-old female individuals (Choi et al., 2002). As can be seen in Table 66, a dramatic increase over time can be observed for all congeners.

***Table 66. Concentrations of seven PBDE congeners and total PBDEs from Japanese human adipose tissue in 1970 and 2000***

| Compound | Concentrations (pg/g fat) | | | |
|---|---|---|---|---|
| | 1970 ($n$ = 10) | | 2000 ($n$ = 10) | |
| | Median | Range | Median | Range |
| BDE-28 | 2.3 | <1.0–7.6 | 76 | 47–487 |
| BDE-47 | 17.0 | 4.4–60.4 | 459 | 109–979 |
| BDE-100 | 2.1 | <2.5–6.1 | 250 | 41–527 |
| BDE-99 | 3.9 | <2.5–13.9 | 118 | 42–362 |
| BDE-154 | <6.3 | <6.3 | 60 | 14–104 |
| BDE-153 | <6.3 | <6.3 | 382 | 122–631 |
| Total PBDEs | 29.2 | 6.8–78.4 | 1288 | 466–2753 |

From Choi et al. (2002)

Takasuga et al. (2002) published human PBDE residue data from a study for the development of halogenated components. Nine married couples, 37–48 years old, participated in the study. Concentrations for PBDEs are given in Table 67. The mean and median values are 3550 and 1902 pg/g lipid, respectively.

***Table 67. PBDE concentrations in Japanese human blood for a 2-year study period***

| PBDE | Concentration (pg/g fat weight) | | | |
|---|---|---|---|---|
| | Average | Median | Minimum | Maximum |
| BDE-15 | 770 | 100 | 53 | 20 000 |
| BDE-28 | 410 | 125 | 65 | 8 600 |
| BDE-47 | 830 | 1200 | 100 | 14 000 |
| BDE-99 | 210 | 670 | 130 | 63 000 |
| BDE-100 | 260 | 140 | 57 | 1200 |
| BDE-153 | 670 | 510 | 370 | 2100 |
| BDE-183 | 160 | 140 | 56 | 520 |
| Total PBDEs | 3550 | 1902 | 951 | 37 250 |

From Takasuga et al. (2002)

### *9.3.10 Mexico*

The first data on PBDE contamination of Mexican women were reported by Lopez et al. (2004). They analysed blood and milk samples originating from two different areas, 300 km apart. The authors stated that in some samples, BDE-209

was the dominant congener or was a significant contributor to the sum of PBDEs. As presented in Table 68, the concentrations are significantly higher in plasma than in milk.

***Table 68. Concentrations of individual PBDEs and total PBDEs in plasma and milk samples from Mexico***

| Analyte | Concentration (ng/g lipid weight) | | | |
|---|---|---|---|---|
| | Plasma (San Luis Potosi City) ($n$ = 5) | | Milk (La Huastecha Potosina) ($n$ = 7) | |
| | Mean | Range | Mean | Range |
| BDE-47 | 9.0 | 3.0–14.5 | 1.7 | 1.1–4.3 |
| BDE-99 | 2.0 | 0.6–3.6 | 0.6 | 0.3–1.2 |
| BDE-100 | 3.7 | 1.8–7.4 | 0.8 | 0.5–1.3 |
| BDE-154 | 1.0 | 0.5–1.3 | 0.2 | 0.1–0.3 |
| BDE-153 | 3.9 | 0.9–6.6 | 0.8 | 0.4–1.6 |
| BDE-209 | 9.5 | 4.8–14.6 | 0.3 | 0.1–0.6 |
| Sum PBDEs | 29.7 | 21.5–37.5 | 2.1 | 0.8–5.4 |

From Lopez et al. (2004)

### *9.3.11 The Netherlands*

In 1998, 108 breast milk samples were obtained from Dutch primiparous women and analysed for PBDEs (de Winter-Sorkina et al., 2003). The results of the study are given in Table 69.

Weiss et al. (2004a, 2004b) analysed a number of blood samples collected from Dutch mothers and infants. The data measured for the adults are given in Table 70.

### *9.3.12 Norway*

For four different areas of Norway, Polder et al. (2004) analysed human milk samples collected in 2003 (Table 71). The median values found for Norway range between 1.66 and 2.52 ng/g lipid.

A time trend-related study on PBDEs in serum samples from the general population in Norway was performed by Thomsen et al. (2001). As with other countries, a time trend was observed in Norway as well (Figure 19).

Additional data from Norway on a congener-specific basis are presented in another study from Thomsen et al. (2004). The samples ($n$ = 130) were obtained from individuals reporting a normal consumption of fish and game. The samples collected in 1999 are presented in Table 72.

*Table 69. Statistical summary of PBDE congener concentrations measured in 103 Dutch breast milk samples taken in 1998*

| Congener | Number > LOD | Concentration (ng/g fat) | | | | |
|---|---|---|---|---|---|---|
| | | Minimum | Maximum | Median | Mean | Relative standard deviation |
| BDE-17 | 10 | <0.03 | 0.13 | <0.03 | | |
| BDE-28 | 108 | 0.05 | 0.43 | 0.11 | 0.13 | 0.50 |
| BDE-47 | 108 | 0.45 | 6.50 | 1.23 | 1.56 | 0.70 |
| BDE-66 | 36 | <0.06 | 0.32 | <0.06 | | |
| BDE-85 | 13 | <0.08 | 0.17 | <0.08 | | |
| BDE-99 | 108 | 0.17 | 2.70 | 0.40 | 0.50 | 0.76 |
| BDE-100 | 108 | 0.09 | 1.72 | 0.31 | 0.37 | 0.67 |
| BDE-153 | 108 | 0.33 | 3.88 | 0.91 | 1.02 | 0.51 |
| BDE-154 | 51 | <0.08 | 0.26 | <0.08 | | |
| BDE-183 | 105 | <0.09 | 1.90 | 0.42 | 0.45 | 0.61 |
| Total PBDEs | | 1.43 | 18.01 | 3.63 | | |

From de Winter-Sorkina et al. (2003)

*Table 70. PBDE concentrations in maternal serum collected at gestation week 20 (n = 8) and week 35 (n = 70)*

| | PBDE concentration (ng/g lipid weight)[a] | | |
|---|---|---|---|
| | Mean | Median | Range |
| BDE-47 | 3.2 | 2.4 | 0.6–13 |
| BDE-99 | 0.92 | 0.76 | <0.12–4.3 |
| BDE-100 | 0.69 | 0.69 | 0.11–2.9 |
| BDE-153 | 4.5 | 4.5 | 0.79–39 |
| BDE-154 | 1.5 | 1.1 | 0.26–6. |

From Weiss et al. (2004a, 2004b)

[a] Fat percentage: mean 0.77%, median 0.74%, range 0.4–1.8%.

### 9.3.13 Republic of Korea

Lee et al. (2002) reported a study of potential exposure of Korean municipal waste incinerator workers, with the comparison group taken from the general population living near the incinerator. The total value found for the total of five congeners was 41.577 and 24.695 ng/g lipid for the incinerator workers and general population, respectively (Table 73).

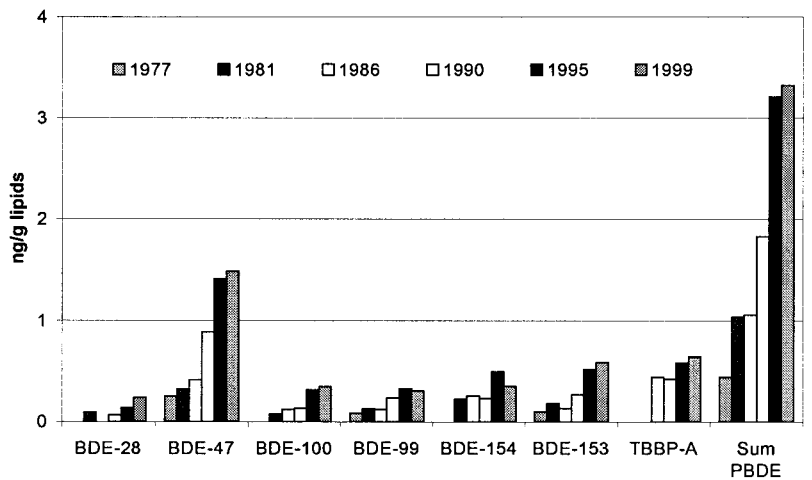
***Table 71. Median concentrations and ranges of sum PBDEs in human milk from four different areas in Norway***

| | Sum PBDE[a] concentration (ng/g milk fat) | | | |
|---|---|---|---|---|
| | Rogaland ($n$ = 17) | Telemark ($n$ = 4) | Troms ($n$ = 8) | Östfold ($n$ = 3) |
| Median | 2.47 | 1.66 | 2.52 | 1.95 |
| Minimum | 1.00 | 1.06 | 1.41 | 1.73 |
| Maximum | 10.79 | 2.55 | 10.56 | 3.76 |

From Polder et al. (2004)

[a] Sum PBDEs: sum of BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154.

***Figure 19. Concentration of individual PBDE congeners and sum PBDEs in pooled serum samples from Norwegian men age 40–50 years sampled between 1977 and 1999***




Taken from Thomsen, C., Lundanes, E. & Becher, G. (2001) A time trend study on brominated flame retardants in serum samples from the general population in Norway. *Organohalogen Compd.*, **52**, 206–209.

### *9.3.14 Spain*

Schumacher et al. (2004) analysed milk samples collected in 2002 from women living near and far from a hazardous waste incinerator in Spain. They concluded that living in the vicinity of the hazardous waste incinerator did not suggest any additional exposure to PBDEs (or PCBs) for the general population of the area. The PBDE data are given in Table 74.

*Table 72. PBDEs in blood, Norway, n = 123*

| | #28 | #47 | #99 | #100 | #153 | #154 | #183 | Total |
|---|---|---|---|---|---|---|---|---|
| Mean (ng/g lipid) | 0.30 | 2.98 | 1.00 | 0.56 | 1.45 | 0.58 | 0.29 | 6.84 |
| Median (ng/g lipid) | 0.18 | 1.68 | 0.69 | 0.34 | 1.11 | 0.41 | 0.22 | 4.71 |
| RSD[a] (%) | 187 | 268 | 119 | 190 | 87 | 82 | 76 | 162 |
| Minimum (ng/g lipid) | 0.05 | 0.25 | 0.27 | 0.04 | 0.02 | 0.10 | 0.009 | 1.40 |
| Maximum (ng/g lipid) | 4.56 | 87.93 | 10.60 | 11.2 | 9.56 | 2.91 | 1.09 | 121.7 |
| Number of detects | 66 | 123 | 123 | 119 | 123 | 122 | 61 | 123 |

From Thomsen et al. (2004)

RSD, relative standard deviation of the mean

[a] Seven samples have been excluded from calculation due to high blank value.

*Table 73. Comparison of the concentrations of PBDE congeners in blood between this study and previous studies in general population (n = 11), Republic of Korea*

| Congener | Concentration (ng/g lipid based) | |
|---|---|---|
| | Waste incinerator workers | General population |
| BDE-33 | 1.163 | |
| BDE- 47 | 15.860 | 9.842 |
| BDE-99 | 5.468 | 4.316 |
| BDE-100 | 2.655 | 1.692 |
| BDE-153 | 7.321 | 5.217 |
| BDE-154 | 0.487 | |
| BDE-183 | 8.603 | 3.628 |
| Total PBDEs | 41.557 | 24.695 |

From Lee et al. (2002)

### *9.3.15 Sweden*

For Swedish human milk, decreasing levels of certain organochlorine compounds have been found by Norén & Meironyté Guvenius (2000). In contrast, levels for PBDEs have increased continuously since 1972. Recently, Meironyté Guvenius & Norén (2001) reported that after the peak level found for Swedish human milk in 1997, a decline for the years 1998–2000 was observed (Figure 20).

In 1998, Darnerud et al. (1998a) reported on PBDE values in 39 individual samples of breast milk from primiparous woman from Uppsala County (Table 75). The values are provided on both a fresh weight and lipid weight basis.

Further data for Uppsala County are given in Table 76.

*Table 74. Levels of total PBDEs and percent fat in samples of human milk from women living near a hazardous waste incinerator, Catalonia, Spain*

| Sample code | Total PBDE concentration (ng/g fat) | Fat content (%) |
|---|---|---|
| 1 | 5.6 | 3.2 |
| 2 | 2.5 | 3.1 |
| 3 | 3.7 | 1.6 |
| 4 | 2.6 | 1.6 |
| 5 | 1.8 | 3.0 |
| 6 | 1.5 | 1.7 |
| 7 | 1.2 | 4.1 |
| 8 | 1.5 | 1.6 |
| 9 | 1.4 | 3.0 |
| 10 | 1.4 | 4.7 |
| 11 | 1.0 | 3.6 |
| 12 | 6.6 | 2.5 |
| 13 | 2.3 | 4.1 |
| 14 | 1.3 | 4.3 |
| 15 | 1.7 | 3.4 |
| Mean | 2.4 | 3.0 |

From Schumacher et al. (2004)

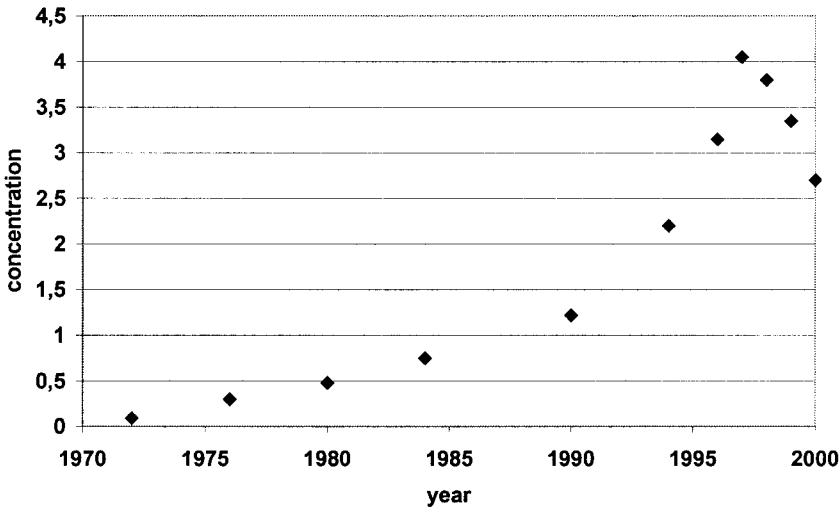
In the study of Lind et al. (2001), the authors stated that the PBDE levels in human milk are associated with factors other than age, body mass index, alcohol consumption, smoking habits and dietary intake of PBDEs.

Important information on the distribution of PBDEs in the general population was given by van Bavel et al. (2002). They collected blood from a cohort of 220 persons from Sweden. The distribution of selected samples is shown in Figure 21. A normal distribution can be seen between 1.0 and 13 ng/g lipid, with a mean value of 4.9 ng/g lipid. However, in 10 of the remaining samples, extremely high values for PBDEs were found, with one exceeding 1000 ng/g lipid.

### *9.3.16 United Kingdom*

Kalantzi et al. (2004) collected human milk samples between late 2001 and early 2003 from 54 mothers in the United Kingdom. Of these, 27 originated from southeast England (London) and the other 27 from northwest England (Lancaster). For BDE-47 and ΣPBDEs, a difference could be found for the investigated areas, as presented in Table 77.

***Figure 20. Mean concentration of PBDEs (ng/g lipid) in Swedish human milk from 1972 to 2000***




Taken from Meironyté Guvenius, D. & Norén, K. (2001) Polybrominated diphenyl ethers in Swedish human milk. The follow-up study. In: *The Second International Workshop on Brominated Flame Retardants.* BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, pp. 303–305.

***Table 75. PBDE levels in breast milk from primiparous women in Uppsala County, Sweden***

| | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-154 | Sum PBDEs |
|---|---|---|---|---|---|---|
| *pg PBDE/g fat weight* | | | | | | |
| Mean | 2516 | 717 | 475 | 648 | 70 | 4452 |
| Median | 1830 | 442 | 340 | 478 | 60 | 3373 |
| Minimum | 331 | 181 | 60 | 255 | 30 | 1139 |
| Maximum | 16 100 | 4470 | 5140 | 4320 | 270 | 28 170 |
| *pg PBDE/g fresh weight* | | | | | | |
| Mean | 77 | 24 | 14 | 19 | 2.1 | 137 |
| Median | 58 | 16 | 10 | 14 | 1.5 | 102 |
| Minimum | 8 | 4 | 1.5 | 8 | 1.5 | 28 |
| Maximum | 358 | 222 | 114 | 96 | 6 | 626 |

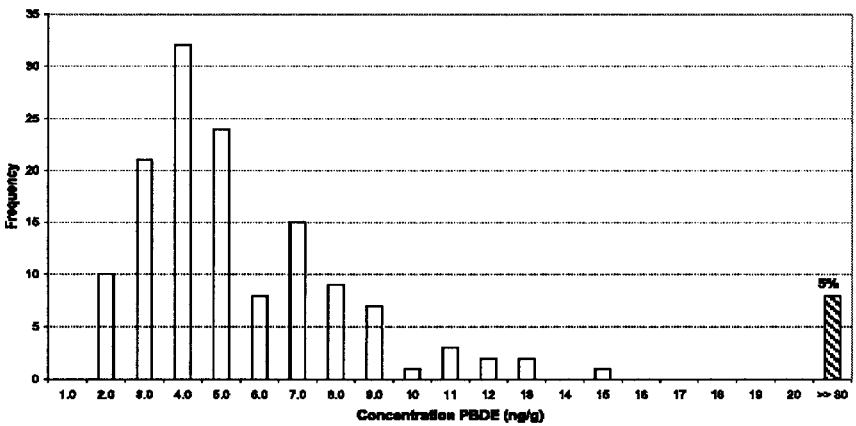
From Darnerud et al. (1998a)

***Table 76. PBDE levels in breast milk from primiparous women (n = 93) in Uppsala County, Sweden***

| | PBDE concentration (ng/g fat weight) | | | | | |
|---|---|---|---|---|---|---|
| | BDE-47 | BDE-99 | BDE-100 | BDE-153 | BDE-154 | ΣPBDEs |
| Mean | 2.35 | 0.619 | 0.377 | 0.597 | 0.068 | 4.01 |
| Median | 1.78 | 0.432 | 0.269 | 0.496 | 0.060 | 3.15 |
| Minimum | 0.20 | 0.100 | 0.050 | 0.197 | 0.030 | 0.906 |
| Maximum | 16.1 | 4.47 | 5.14 | 4.32 | 0.270 | 28.2 |

From Lind et al. (2001)

***Figure 21. The distribution of 143 samples rerun using negative chemical ionization to enhance LOD for PBDEs; 5% of the samples showed levels of PBDEs above 30 ng/g lipid***




Taken from van Bavel, B., Hardell, L., Kitti, A., Lijedahl, M., Karlsson, M., Petterson, A., Tysklind, M. & Lindström, G. (2002) High levels of PBDEs in 5 % of 220 blood samples from the Swedish population. *Organohalogen Compd.*, **58**, 161–164.

### *9.3.17 United States*

The first data on PBDEs in adipose samples collected in 1987 were published by Stanley et al. (1991). The study essentially confirmed the presence of PBDEs in adipose tissue. The full-scan analysis demonstrated the presence of a hexa-BDE, which was estimated to exceed 1 ng/g lipid. The presence of other PBDEs was confirmed by additional HRMS–selected ion monitoring (SIM) analysis, although it was not possible to confirm the concentrations from this preliminary study due to a lack of standards for individual PBDE isomers.

*Table 77. Comparison of concentrations of PBDE congeners in human milk from London and Lancaster, United Kingdom*

| Congener | Geometric mean (median; range) (ng/g milk fat) | | Significance (*P*-value) |
|---|---|---|---|
| | London | Lancaster | |
| BDE-47 | 3.9 (4.6; 1.0–36) | 1.8 (2.2; 0.1–17) | Yes |
| BDE-99 | 0.9 (1.0; ND–12) | 0.8 (0.6; ND–6.8) | No |
| BDE-100 | 0.6 (0.5; 0.7–7.0) | 0.5 (0.4; ND–4.5) | No |
| BDE-153 | 1.4 (1.2; ND–4.9) | 1.4 (1.4; ND–3.5) | No |
| BDE-154 | 0.5 (0.5; ND–2.1) | 0.4 (0.3; ND–2.4) | No |
| ΣPBDE | 7.8 (8.1; 3.1–69) | 4.6 (5.0; 0.3–34) | Yes |

From Kalantzi et al. (2004)

ND, not detected

Approximately 10 years later, five adipose tissue samples were collected in the late 1990s from northern California women and analysed for PBDEs (She et al., 2000). The authors suggested that from these preliminary limited data, it was reasonable to conclude that the background level of PBDEs in the general population is in the low ng/g range (less than 100 ng/g). The data are given in Table 78.

*Table 78. Concentration of PBDEs in human adipose tissue samples*

| Sample no. | % lipid | Concentration (ng/g lipid) | | | |
|---|---|---|---|---|---|
| | | BDE-47 | BDE-99 | BDE-153 | Total PBDEs |
| 1 | 44.6 | 23 | 7.3 | 2.3 | 32.6 |
| 2 | 50.8 | 11 | 3.6 | 1.6 | 16.2 |
| 3 | 85.6 | 7.0 | 3.1 | 1.5 | 11.6 |
| 4 | 89 | 28 | 6.6 | 2.4 | 37 |
| 5 | 84.5 | 20 | 4.1 | 3.2 | 27.3 |
| Mean | 70.9 | 18 | 4.9 | 2.2 | 25.1 |
| SD | 21.3 | 8.6 | 1.9 | 0.69 | |

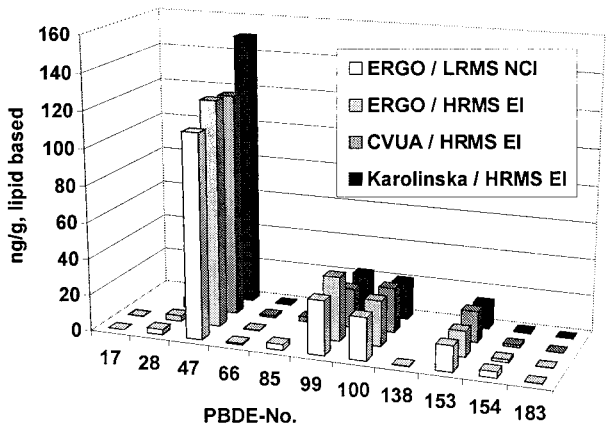
From She et al. (2000)

SD, standard deviation

Due to unexpectedly high PBDE concentrations found in a pooled human milk sample in the United States (Päpke et al., 2001), the pooled material was analysed in three laboratories with extensive experience in determination of halogenated contaminants in human samples: ERGO in Hamburg (O. Päpke), Chemical and Veterinary Control Laboratory in Münster (P. Fürst) and Karolinska

Institute in Stockholm (K. Norén). Comparing the HRMS results from the three laboratories, the differences in concentrations for most congeners are quite low, and the total PBDE concentrations of 204, 196 and 217 ng/g lipid are similar. Due to the relatively difficult determination of compounds with high boiling points such as PBDEs, the results of this comparison were helpful (Figure 22).

***Figure 22. PBDEs in human milk (comparison of data from three laboratories with different analytical methods)***




Adapted from Päpke, O., Bathe, L., Bergman, Å., Fürst, P., Meironyté Guvenius, D., Herrmann, T. & Norén, K. (2001) Determination of PBDEs in human milk from the United States, comparison of results from three laboratories. *Organohalogen Compd.*, **52**, 197–200.

Congener BDE-47 occurred at the highest level, followed by BDE-99, BDE-100 and BDE-153. These compounds contributed approximately 61–69%, 11–17%, 10–13% and 5–9%, respectively, to the total PBDEs in the pooled milk sample in the United States. It is striking that a concentration of PBDEs as high as almost 200 ng/g lipid weight is indicated for human milk in the United States. The first study on individual samples of human milk in the United States was published by Schecter et al. (2004c). They analysed 47 milk samples collected in 2002. The data are given in Table 79 and in Figure 23. The mean and median values for total PBDEs are 73.9 and 34 ng/g lipid, respectively.

Archived serum samples from the United States have been analysed by Petreas et al. (2002) and Schecter et al. (2004b). They did not find significant concentrations of PBDEs in pooled samples collected in the 1960s and 1973, respectively.

Sjödin et al. (2004a) analysed archived serum samples from the United States collected at four different time periods. The concentration of most of the PBDEs had significant positive correlations with time of sample collection, showing that PBDEs are increasing in serum collected in the United States. The data are given in Table 80.

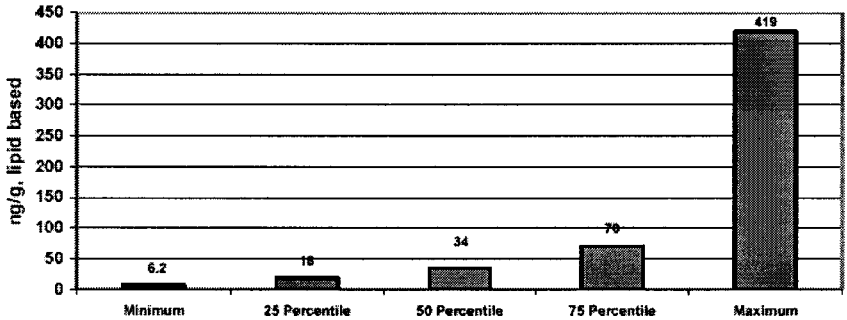
*Table 79. Levels of PBDE congeners in human milk from Texas, USA, in 2002, n = 47*

| | Age | Nursing (weeks) | Concentration (ng/g lipid) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 17 | 28 | 47 | 66 | 77 | 85 | 99 | 100 | 138 | 153 | 154 | 183 | 209 | Sum BDE |
| Mean | 28.6 | 24.6 | 0.02 | 2.4 | 40.8 | 0.65 | 0.01 | 1.15 | 14.0 | 8.2 | 0.60 | 5.3 | 0.76 | 0.13 | 0.92 | 73.9 |
| Median | 29 | 20 | 0.01 | 1.2 | 18.4 | 0.14 | NA | 0.41 | 5.7 | 2.9 | 0.09 | 2.0 | 0.22 | 0.07 | NA | 34.0 |
| SD | 5.70 | 22.26 | 0.04 | 3.1 | 59.4 | 1.19 | 0.04 | 1.89 | 24.6 | 10.8 | 1.37 | 6.1 | 1.30 | 0.23 | 1.96 | 103.0 |
| Minimum | 20 | 2 | ND | 0.2 | 2.9 | ND | ND | 0.08 | 0.7 | 0.5 | ND | 0.4 | 0.06 | ND | ND | 6.2 |
| Maximum | 41 | 109 | 0.18 | 16.1 | 271.5 | 6.67 | 0.16 | 7.73 | 111.0 | 47.4 | 6.86 | 21.8 | 7.21 | 1.32 | 8.24 | 418.8 |

From Schecter et al. (2004c)

NA, not analysed; ND, not detected; SD, standard deviation

***Figure 23. PBDEs in breast milk from Texas, USA, collected in 2002, n = 47***




Taken from Schecter, A., Pavuk, M., Päpke, O., Ryan, J.J., Birnbaum, L. & Rosen, R. (2004c) Polybrominated diphenyl ethers (PBDEs) in US mothers' milk. *Environ. Health Perspect.*, **111** (14), 1723–1729.

***Table 80. Concentration of selected PBDEs in archived serum pools from the United States, stratified according to 5-year collection periods***

| Compound | Median concentration (range) (ng/g lipid) | | | |
|---|---|---|---|---|
| | 1985–1989 | 1990–1994 | 1995–1999 | 2000–2002 |
| | (*n* = 9) | (*n* = 14) | (*n* = 10) | (*n* = 7) |
| BDE-47 | 5.4 (<1–44) | 28 (3.7–49) | 46 (24–68) | 34 (29–98) |
| BDE-85 | <0.5 (<0.5–1.08) | 0.61 (0.50–1.4) | 0.78 (0.50–1.9) | 0.70 (0.50–1.4) |
| BDE-99 | <2 (<2–15) | 10 (1.3–18) | 13 (9.1–29) | 11 (6.8–26) |
| BDE-100 | 0.81 (<0.5–7.3) | 4.0 (0.63–7.7) | 6.7 (3.8–14) | 5.9 (3.5–18) |
| BDE-153 | 0.84 (<0.5–7.3) | 1.6 (0.67–15) | 4.2 (2.5–16) | 7.3 (1.8–17) |
| BDE-154 | <0.5 (<0.5–0.94) | <0.5 (<0.5–1.07) | 0.88 (0.52–1.8) | 0.95 (0.50–1.8) |
| ΣPBDEs | 9.6 (4.6–74) | 48 (7.5–86) | 71 (42–120) | 61 (47–160) |

From Sjödin et al. (2004a)

She et al. (2004) analysed 16 recently collected human milk samples from residents of the Pacific Northwest of the United States. The total BDE values and the lipid content are given in Table 81.

The congener profiles for the 16 Northwest United States human milk samples, using means of individual PBDE congeners, are shown in Figure 24.

***Table 81. Summary results of PBDE concentrations in 16 Northwest United States human milk samples***

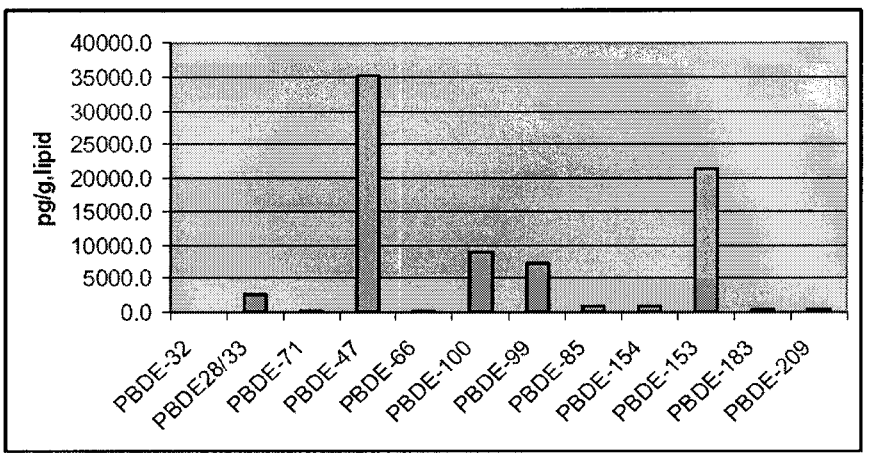
| | Minimum | Maximum | Mean | Median | SD |
|---|---|---|---|---|---|
| % fat | 2.78 | 5.06 | 4.19 | 4.50 | 0.69 |
| ΣPBDEs[a] (ng/g lipid) | 6.34 | 309 | 77.5 | 48.5 | 79.6 |

From She et al. (2004)

SD, standard deviation

[a] Total of BDE-28/33, BDE-32, BDE-47, BDE-66, BDE-71, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-209.

***Figure 24. Pattern of 12 PBDE congeners analysed in Northwest United States human milk, n = 16, mean***




Taken from She, J., Holden, A., Sharp, M., Tanner, M., Williams-Derry, C. & Hooper, K. (2004) Unusual pattern of polybrominated diphenyl ethers (PBDEs) in US breast milk. *Organohalogen Compd.*, **66**, 3945–3950.

### *9.3.18 Summary*

Human PBDE data are available for a number of countries. Typical values found for human samples such as human milk, blood and adipose tissue collected in various regions are shown in Tables 82 and 83.

## *9.4 Data on time trends for PBDEs*

The first data on the observation of an increasing time trend for PBDE concentrations in humans were published by Norén & Meironyté Guvenius (1998). Subsequently, similar time trend data for PBDEs have been observed in many countries. In Table 84, observations on this time trend are summarized.

***Table 82. PBDEs in human milk from Europe, North America and Asia***

| Country | Collection year | Sample type[a]; number | Total PBDEs (ng/g, lipid) | | References |
|---|---|---|---|---|---|
| | | | Median | Range | |
| Canada | 1982 | P; *n* = 200 | <0.2 | – | Ryan & Patry (2000) |
| | 1986 | P; *n* = 100 | 0.6 | – | Ryan & Patry (2000) |
| | 1992 | I; *n* = 72 | 3.0 | 0.6–580 | Ryan & Patry (2001) |
| | 2001–2002 | I; *n* = 98 | 22 | 0.8–956 | Ryan et al. (2002); Pereg et al. (2003) |
| Canadian Arctic (Nunavik) | 1989–1991 | I; *n* = 20 | 1.7 | ND–14 | Pereg et al. (2003) |
| | 1996–2000 | I; *n* = 20 | 6.8 | 0.2–318 | |
| Faroe Island | 1987 | P; *n* = 10 | 1.5 | – | Fängström et al. (2004b) |
| | 1994–1995 | P; *n* = 10 | 3.6 | – | |
| | 1998–1999 | P; *n* = 10 | 7.2 | – | |
| Finland | 1994–1998 | I; *n* = 11 | 1.6 | 0.9–5.9 | Strandman et al. (2000) |
| Germany | 1992 | P; *n* > 500 | 1.7 | – | Fürst (2001) |
| | 2000 | I; *n* = 7 | 1.8 | – | |
| | 2002 | I; *n* = 8 | 6.6 | 4.3–12 | Weber & Heseker (2004) |
| | 2001–2003 | I; *n* = 62 | 1.78 | max. 7.25 | Vieth et al. (2004) |
| Italy | 1998–2001 | P; *n* = 39 | – | 1.6–4.1 | Ingelido et al. (2004) |
| Japan | late 1990s | I; *n* = 12 | 1.3 | 0.7–1.8 | Ohta et al. (2002) |
| Japan | 1973 | P; *n* = 21 | <0.1 | – | Akutsu et al. (2003) |
| | 1983 | P; *n* = 19 | 0.6 | – | |
| | 1993 | P; *n* = 35 | 2.3 | – | |
| | 2000 | P; *n* = 27 | 1.4 | – | |
| | 1999 | I; *n* = 13 | 1.6 | 0.6–4.0 (single sample = 291) | |

*Table 82.* (contd)

| Country | Collection year | Sample type[a]; number | Total PBDEs (ng/g, lipid) | | References |
|---|---|---|---|---|---|
| | | | Median | Range | |
| Mexico | not given | I; *n* = 7 | 2.1 (mean) | 0.8–5.4 | Lopez et al. (2004) |
| Netherlands | 1998 | I; *n* = 103 | 3.3 | 1.0–13 | Baumann et al. (2003) |
| Norway | 1993, 2001 | P; *n* = 10–12 | 1.9, 2.9 | – | Thomsen et al. (2003) |
| | 2001 | I; *n* = 9 | 2.8 | 2.0–10 | |
| Spain | 2002 | I ; *n* = 15 | 2.4 | 1.2–6.6 | Schumacher et al. (2004) |
| Sweden | 1972 | P; *n* = 227 | 0.1 | – | Meironyté Guvenius et al. (1998, 1999, 2003); Norén & Meironyté Guvenius (2000) |
| | 1984–1985 | P; *n* = 102 | 0.7 | – | |
| | 1994 | P; *n* = 20 | 2.2 | – | |
| | 1997 | P; *n* = 40 | 4.0 | – | |
| | 2000–2001 | I; *n* = 15 | 2.1 | 0.6–7.7 | |
| Sweden | 1996–1999 | I; *n* = 93 | 3.2 | 0.9–28 | Lind et al. (2003) |
| | 2000–2001 | I; *n* = 31 | 2.9 | 1.5–1.8 | |
| United Kingdom | 2001–2002 | I; *n* = 52 | 6.6 | 0.3–69 | Kalantzi et al. (2004) |
| USA; New York | 1997 | I; *n* = 17 | 147 | – | Ryan et al. (2002) |
| USA | 2000 | P; *n* = 20 | 196 | – | Päpke et al. (2001) |
| USA; Texas | 2002 | I; *n* = 47 | 34 | 6.2–419 | Schecter et al. (2003) |
| USA | 2002–2003 | I; *n* = 20 | 58 | 10–1080 | Lunder & Sharp (2003) |
| USA; west coast | 2003 | I; *n* = 9 | 50 | 13–156 | Northwest Environment Watch (2004) |

max., maximum; ND, not detected

[a] P = pooled sample, I = individual samples.

***Table 83. Total PBDE concentration in different tissues from various countries***

| Country | Year of collection | Sample type | Total PBDE concentration (ng/g, lipid based) | | *n* | Reference |
|---|---|---|---|---|---|---|
| | | | Mean | Range | | |
| Australia | 2003 | Blood | 11 | 6.7–18 | 10 pools (98–100 samples/ pool) | Harden et al. (2004) |
| Belgium | Not given | Adipose | 3.7 | 1.7–10.1 | 20 | Covaci & Schepens (2001) |
| Canada | 1994–1999 | Blood | 23.3 | 13.1–46.4 | | Ryan & van Oostdam (2004) |
| Czech Republic | 2000–2001 | Adipose | 3.26/ 1.44 | 1.03–11.3<br>0.25–4.79 | 10/14 | Crhova et al. (2002) |
| Finland | Unknown, from ongoing study | Adipose | 11.7 | 6.49–21.7 | 10 | Strandman et al. (1999) |
| Germany | 1999 | Blood | 5.8 | 0.9–12.6 | 20 | Schröter-Kermani et al. (2000) |
| Italy | 2001 | Blood | 2.0 | | 22 | De Felip et al. (2003) |
| Japan | 1970 | Adipose | 0.03 | 0.01–0.08 | 10 | Choi et al. (2002) |
| | 2000 | Adipose | 1.29 | 0.47–2.75 | 10 | |
| Mexico | Not given | Blood | 29.7 | 21.5–37.5 | 5 | Lopez et al. (2004) |
| Republic of Korea | 2001 | Blood | 24.7 | | 11 | Lee et al. (2002) |
| Spain | Not given | Adipose | 1.4 | 0.2–5.8 | 13 | Meneses et al. (1999) |
| USA | 1998 | Adipose | 25.1 | 11.6–37.0 | 5 | She et al. (2000) |

*Table 84. Total PBDE concentration in different tissues from various countries*

| Country | First year of collection | Latest year of collection | Sample type | Increasing effect | Reference |
|---|---|---|---|---|---|
| Canada | 1982 | 2001–2002 | Human milk | Strong effect | Ryan & Patry (2000); Ryan et al. (2002) |
| Faroe Islands | 1987 ($n$ =10) | 1998–1999 ($n$ = 10) | Milk | Strong effect | Fängström et al. (2004a, 2004b) |
| Germany | 1992 | 2000 | Milk | Moderate effect | Schröter-Kermani et al. (2000) |
| | | | | No effect | Fürst (2001) |
| Japan | 1970 ($n$ =10) | 2000 ($n$ =10) | Adipose | Strong effect | Choi et al. (2002) |
| Norway | 1977 | 1999 | Serum | Strong effect | Thomsen et al. (2001) |
| Sweden | 1972 | 2001 | Milk | | Meironyté Guvenius & Norén (2001) |
| United States | 1973 | 2003 | Milk | Strong effect | Schecter et al. (2004c) |
| | 1985–1989 | 2000–2002 | Serum | Strong effect | Sjödin et al. (2004a) |

## *10. DOSE–RESPONSE ANALYSIS AND ESTIMATION OF RISK*

### *10.1 Contribution of above data to assessment of risk*

#### *10.1.1 Pivotal data from biochemical and toxicological studies*

*(a) DecaBDE*

In repeat-dose short-term oral studies, DecaBDE appears to induce limited toxic effects in experimental animals. In a well conducted chronic feeding student in rodents (NTP, 1986), DecaBDE (94–97% purity) caused a variety of non-neoplastic and neoplastic organ changes, mainly in the liver and thyroid gland, when administered in the diet (2.5% or 5.0%) over 2 years. In rats, the incidence of neoplastic nodules (hepatoproliferative lesions) was significantly increased compared with controls in males (both dose groups) and females (high dose only), while in male mice, the combined incidence of hepatic adenomas and carcinomas was significantly increased (low dose group) along with thyroid gland follicular cell adenomas or carcinomas (combined) in both dose groups. Overall, NTP (1986) classified the cancer potential for DecaBDE as equivocal for male mice and

suggestive for rats. IARC estimated a $TD_{50}$ value, defined as the chronic dose that results in one half of animals developing tumours, of 2220 mg/kg bw per day based on the male rat neoplastic nodule response (McGregor, 1992), but has placed DecaBDE in its Group 3 category (not classifiable as to its carcinogenicity to humans). Comparison of the $TD_{50}$ value with an estimated lifetime average oral daily intake of 0.7 µg/kg bw per day for DecaBDE (NAS, 2000) would suggest a low to negligible cancer risk (Gold et al., 1992).

Regarding non-cancer end-points, a recent study has suggested that BDE-209 can induce behavioural alterations in mice, similar to effects seen with less brominated congeners. Exposure of newborn NMRI male mice to a single oral BDE-209 dose of 20.1 mg/kg bw on PND 3 caused persistent changes in spontaneous behaviour with testing up to 6 months after dosing (Viberg et al., 2003b). No consistent effects were observed in mice with a dose of 2.22 mg/kg bw on PND 3 or similar doses when administered on PND 10 or PND 19. While the mode of action is not fully understood, it does not appear to require solely the presence of BDE-209 and/or metabolites in the brain. Similar amounts of radioactivity associated with a gavage dose of [U-$^{14}$C]BDE-209 were seen in the brains of neonatal mice 24 h and 7 days after dosing on either PND 3 or 10, whereas behavioural alterations were associated with dosing only on PND 3. In contrast to these findings, treatment of NMRI mice with BDE-99 on either PND 3 or PND 10 was effective in causing neurobehavioural alterations (Eriksson et al., 2002). Although this represents a single experimental observation with BDE-209 in one strain of mice, similar changes in spontaneous behaviour have been induced with lower brominated congeners in both NMRI and C57BL mice and Sprague-Dawley rats.

Timing of the dose in this experimental model appears to be critical for effects and is likely related to the brain growth spurt period, which in rodents occurs 2–3 weeks after parturition (peaks on PND 10). For the human infant, this critical period begins in the third trimester of pregnancy and extends into the first 2–3 years after birth (Eriksson & Talts, 2000).

Gestational exposure of rats to doses of BDE-209 up to 1000 mg/kg bw per day had no significant effect on fetal survival or development (Hardy et al., 2002). Based on fetal liver bromine analysis, it has been reported that there is no significant in utero transfer of decaBDE after maternal exposure to doses up to 1000 mg/kg bw per day during gestation (GD 6–15) (Norris et al., 1975a).

*(b) OctaBDE*

Initial investigations into the toxic potential of commercial OctaBDE suggested that target organs for effects would be liver, kidney and thyroid. Short-term (up to 14 days) and subchronic exposure of rats to dietary concentrations of OctaBDE from 100 to 10 000 mg/kg (equivalent to 7–9 to 1000 mg/kg bw per day) resulted in increased relative liver and thyroid weights and a variety of histopathological changes to the above-described target organs. Liver weight increases and microscopic changes were shown to be persistent in the highest dose group, even following a 12-month withdrawal period. The estimated lowest-observed-adverse-

effect level (LOAEL) from these feeding studies was 100 mg/kg diet or approximately 7–9 mg/kg bw per day. In a preliminary investigation with commercial OctaBDE (45.2% octa-, 47.4% nona- and 5.7% decaBDE; Norris et al., 1975b), bioaccumulation was evident, based on detected increases in the bromine content of both adipose tissue and liver that persisted following a 90-day recovery period. Overall, the database for OctaBDE is limited, with no chronic duration studies (e.g. cancer) available for evaluation. Based on the largely negative results from various mutagenicity/genotoxicity screening assays (bacterial mutagenicity, DNA repair, sister chromatid exchange, chromosomal aberrations), any cancer risk by a genotoxic mode of action is unlikely.

Short-term exposure of weanling rats to the OctaBDE commercial mixture DE-79 resulted in hepatic enzyme induction and decreases in both serum TT4 and TT3 levels, with BMDL estimates (20% decrease) of 5.29 and 11.98 mg/kg bw per day, respectively (Zhou et al., 2001). CYP2B enzyme induction was the most sensitive experimental end-point measured, with a BMDL of 0.40 mg/kg bw per day. This dose is in agreement with longer-duration exposure (90 days), where doses as low as 0.78 µmol/kg bw per day (0.62 mg/kg bw per day) of a commercial OctaBDE mixture (8.5% hexaBDE, 45.1% heptaBDE, 30.7% octaBDE) resulted in increases in activity of *O*-ethyl-*O*-*p*-nitrophenyl phenylphosphonothioate detoxification and *p*-nitroanisole demethylation (Carlson, 1980b). The latter substrates have been shown to be preferentially metabolized by phenobarbital-inducible forms of cytochrome P450s.

Developmental toxicity studies have been conducted in rats and rabbits with commercial OctaBDE mixtures (DE-79 and Saytex 111) at doses ranging from 2.0 to 50 mg/kg bw per day during gestation (Great Lakes, 1986). Significant toxic effects on the developing fetus, including reduced weight gain and decreased live births per litter, were observed at doses greater than 10 mg/kg bw per day, while maternal toxicity (reduced gestational weight gain and increased relative liver weight) was seen at doses of 25 mg/kg bw per day and greater. A $BMDL_5$ of 8.7 mg/kg bw per day has been estimated for the reduced fetal weight gain in rats (VCCEP, 2003).

While no neurotoxicity studies have been conducted with commercial OctaBDE mixtures, BDE-153, one of the main congeners detected following oral exposure of male rats to DE-79 (Huwe et al., 2002), has been tested in a spontaneous activity protocol. A single oral dose of BDE-154 at 0.9 or 9.0 mg/kg bw (1.4 or 14 µmol/kg bw) on PND 10 altered locomotor activity and spatial learning in adult mice (Viberg et al., 2003a). Similar effects were observed, albeit at higher doses, when neonatal mice were exposed to BDE-203 at 16.8 mg/kg bw and to BDE-206 at 18.5 mg/kg bw (Eriksson et al., 2004).

The lowest effective dose of 0.4 mg/kg bw per day for CYP2B induction in neonatal rats (Zhou et al., 2001) would not be considered toxicologically relevant of and by itself. Subchronic exposure to doses approximately 10-fold higher have been associated with relative liver weight increases and histological changes. A single BDE-153 dose of 0.45 mg/kg bw during a critical developmental period did not induce alterations in spontaneous behaviour in mice (Viberg et al., 2003a).

Significant time-dependent bioaccumulation of bromine in adipose and liver has been shown in rats after ingestion of OctaBDE at 0.1 mg/kg bw per day for up to 180 days (Norris et al., 1975b).

*(c) PentaBDE*

Unlike the higher brominated congeners that predominate in commercial DecaBDE and, to a certain extent, OctaBDE mixtures, PentaBDEs are readily bioavailable and persistent (bioaccumulation potential). Initial studies in rats with commercial PentaBDEs have shown that subchronic exposure to doses as low as 0.44 mg/kg bw per day results in hepatic enzyme induction that persists into a 30-day recovery period (Carlson, 1980a). At higher doses (greater than 2 mg/kg bw per day), relative liver weight increases along with hepatocytomegaly have been observed. Perinatal exposure (GD 6 to PND 21) of rats to DE-71 resulted in significant decreases in serum T4 levels in offspring, with $BMDL_{20}$ estimates of 0.94 mg/kg bw per day (Zhou et al., 2002). In a recent study (Stoker et al., 2004a), daily oral exposure of juvenile rats to DE-71 from PND 22 to PND 26 also resulted in decreases in serum TT4, with a $BMDL_5$ of 0.28 mg/kg bw per day. In adult C57BL/6 mice, acute doses of DE-71 as low as 0.8 mg/kg bw have been reported to decrease serum TT4. Gestational exposure of Wistar rats to BDE-99, a major congener found in PentaBDE mixtures, has also been shown to disrupt thyroid hormones in offspring at single doses as low as 60 µg/kg bw (Kuriyama et al., 2004a). In a similar experimental design, exposure of rats to BDE-47 on GD 6 also caused thyroid hormone changes in offspring at a dose of 140 µg/kg bw (Kuriyama et al., 2004b). These latter responses may be species-specific, as perinatal exposure of NMRI mice to multiple BDE-99 doses of 80 µmol/kg bw (45 mg/kg bw) had no effect on thyroid hormones of dams or offspring (Skarman et al., 2005). While thyroid histological changes and thyroid hormone perturbations by Penta-BDEs are a consistent experimental observation, the significance of this end-point to humans is open to interpretation. In rodents, fluctuations in serum T4 are influenced by a number of mechanisms, including enhanced biliary excretion through induction of UDPGT and competition for TTR binding by hydroxylated BDE metabolites. In humans, TBG has the highest binding affinity and carries the majority of T4, while UDPGT is thought to be more easily inducible in rodents (Capen, 1997).

Neurobehavioural alterations in rodents have also been observed following exposure to the two main congeners found in PentaBDE commercial mixtures, BDE-47 and BDE-99. The calculation of BMDs for BDE-99, using doses of 0, 0.4, 0.8, 4.0, 8.0 or 16 mg/kg bw by gavage on PND 10 in mice, revealed lower-bound BMDs of 0.31, 0.85 and 1.2 mg/kg for a 10% change in total activity, locomotion and rearing, respectively (Sand et al., 2004). The authors of the primary study had suggested a NOEL of between 0.4 and 0.8 mg/kg bw (Viberg et al., 2004b).

Compared with rats, mice appear to be more sensitive to these effects, with BMDLs (total activity) for BDE-99 estimated at 0.31 mg/kg bw following a single neonatal exposure (Sand et al., 2004). However, gestational exposure of rats to BDE-47 (140 µg/kg bw) or BDE-99 (60 µg/kg bw) has also produced slightly increased locomotor activity in offspring at puberty. In contrast, perinatal exposure

of rats to DE-71 at doses up to 100 mg/kg bw per day (estimated BDE-99 dose of 50 mg/kg bw per day) had no effect on motor activity or spatial learning in the adult male offspring, but doses of 30 and 100 mg/kg bw per day were able to affect fear conditioning (cue-based performance) (Taylor et al., 2003).

While no reproductive toxicity studies are available for commercial Penta-BDEs or their major congeners, gestational exposure to BDE-99, while not affecting fertility, did cause significant decreases in spermatid numbers and daily sperm production in adult rat offspring. At a single dose of 60 µg/kg bw on GD 6, male offspring had a 31% decrease in daily sperm production (95% CI 25–38%), without associated changes in gonadotrophins (inhibin, LH, testosterone) or testis and seminal vesicle weights (Kuriyama et al., 2005). While not associated with a decline in fertility or follicle numbers, the same low dose of BDE-99 has been shown to induce ultrastructural degenerative changes in ovarian cells in the female offspring (Talsness et al., 2003).

*(d) Benchmark dose calculations for endocrine and neurotoxic effects*

BMDs have been calculated so far only in four studies (Zhou et al., 2001, 2002; Sand et al., 2004; Stoker et al., 2004a). The results are shown in Table 85. BMD values are available only for the technical mixtures DE-71 (mainly penta-BDE) and DE-79 (mainly octaBDE) and the congener BDE-99. Additional calculations may be useful for reduced TT3 and elevated TSH in male rats (Stoker et al., 2004a). Also, gene expression of the AR (Ceccatelli, 2004), decreased thyroid weights and reduced circulating estradiol in male offspring (Lilienthal et al., 2004) appear to be particularly sensitive to BDE-99 after gestational exposure, but in these studies only three dose levels were used.

### *10.1.2 Pivotal data from human clinical/epidemiological studies*

Limited quantitative information is available for evaluation purposes from either clinical or epidemiological studies.

### *10.1.3 Biomarker studies*

A number of detailed reviews have been conducted with various human tissues (serum/plasma, adipose and human milk) that provide evidence for the bioaccumulative potential of PBDEs. In general, lower brominated congeners such as BDE-47, BDE-99 and BDE-153, found in commercial PentaBDE mixtures, predominate. Preliminary analysis of serum and milk samples collected in North America indicated higher concentrations of PBDEs than in similar samples from European countries or Japan (Hites, 2004). Maternal blood samples ($n$ = 12) collected in the United States in 2001 give median concentrations of sum PBDEs of 41 ng/g lipid, with congeners BDE-47 and BDE-99 representing approximately 82% of the total. In a larger survey of human milk collected in 2001 ($n$ = 47; Texas, USA), the median sum PBDE concentration was 34 ng/g lipid, with the same two congeners accounting for 70% of the total. In Canadian human milk samples ($n$ = 98) collected in 2001–2002, median concentrations of sum PBDEs are similar,

*Table 85. BMD estimations for PBDEs*

| Dosing regimen | Species, strain, age | End-point | BMDL (lower bounds) | BMD | Reference |
|---|---|---|---|---|---|
| DE-71, oral, daily for 4 days | Weanling Long-Evans rats | Reduced TT4 | 6.95 mg/kg bw, 20% change | 12.74 mg/kg bw, 20% change | Zhou et al. (2001) |
| | | Reduced TT3 | 8.56 mg/kg bw | 32.94 mg/kg bw | |
| DE-79, oral, daily for 4 days | Weanling Long-Evans rats | Reduced TT4 | 5.29 mg/kg bw | 9.25 mg/kg bw | |
| | | Reduced TT3 | 11.98 mg/kg bw | 53.38 mg/kg bw | |
| DE-71, oral, daily from GD 6 to PND 21 | Developing Long-Evans rats (F1) | Reduced TT4 | 0.94 mg/kg bw, 20% change | 2.36 mg/kg bw, 20% change | Zhou et al. (2002) |
| DE-71, oral, daily from GD 6 to PND 21 | Gravid Long-Evans rats (F0) | Reduced TT4 | 4.03 mg/kg bw | 6.13 mg/kg bw | |
| DE-71, oral, daily from PND 23 to PND 27 | Juvenile male Wistar rats | Reduced TT4 | 1.28 mg/kg bw, 5% change | 1.42 mg/kg bw, 5% change | Stoker et al. (2004a) |
| DE-71, oral, daily from PND 23 to PND 53 | | Reduced TT4 | 0.94 mg/kg bw per day | 0.91 mg/kg bw per day | |
| DE-71, oral, daily from PND 22 to PND 26 | Juvenile female Wistar rats | Reduced TT4 | 0.28 mg/kg bw | 0.37 mg/kg bw | |
| DE-71, oral, daily from PND 22 to PND 41 | | Reduced TT4 | 1.16 mg/kg bw | 1.36 mg/kg bw | |
| BDE-99, oral, on PND 10 | Infant C57BL mice | Altered total activity in adult males | 0.31 mg/kg bw, 10% change | 0.51 mg/kg bw, 10% change | Sand et al. (2004) |

22.1 ng/g lipid, with the highest value being 956 ng/g lipid (Ryan, 2004). As with the other North American samples, BDE-47 and BDE-99 were almost 74% of the total. In comparison, in a limited sample of Swedish maternal blood samples collected in 2000, the sum PBDE concentration was 1.8 ng/g lipid, with BDE-47 and BDE-99 contributing 57% of the total. Similar results were found with human milk samples collected in Sweden in 2000.

## *10.2 General modelling considerations*

### *10.2.1 Selection of data*

A variety of experimental data sets from studies with limited dosing schedules that focused on either changes to thyroid hormones or behavioural alterations have been summarized (Tables 86–91).

Additional toxicological end-points for risk estimation include acute dosing of rats during gestation with BDE-47 and BDE-99 and subsequent effects on locomotor activity and sperm production observed in the adult offspring. Mechanistic data are limited for comparison with possible human relevancy.

### *10.2.2 Measure of exposure*

Because PBDEs have long half-lives and tend to bioaccumulate, their hazard to health can be estimated only after consideration of intake over a period of months. Short-term variations in PBDE concentrations in foods have much less effect on overall intake than might be the case for other food contaminants. The distribution of long-term mean intake in various populations was calculated by the following procedure:

- The distributions of PBDE (total of the following congeners: 28, 47, 99, 100, 153 and 154) concentrations were constructed for various regions and food groups from the available data. The distributions were assumed to be log-normal. Data were available to construct such distributions for three regions only (Far East, North America and Western Europe). Since only summary data were available from most studies, two sets of distributions were derived, one representing lower-bound estimates of the concentrations (derived using data from studies where non-detects were set at zero), the other representing upper-bound estimates (derived using data from studies where non-detects were set at the LOD).
- Data on food consumption from the GEMS/Food regional diets were used to estimate mean consumption of six major food groups in each diet. A log-normal distribution was constructed from these data, with a GSD of 1.3 extrapolated from the results of the food consumption survey in the Netherlands in order to account for interindividual variation in consumption. The average contributions of the six basic food groups to total food consumption were derived for each diet.

***Table 86. Effects of PBDE mixtures on thyroid hormones***

| Dosing regimen | Species, strain, sex, age | End-point | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| DE-71, single oral dose | Adult female C57BL/6J mice | Reduced TT4 | – | 0.8 mg/kg bw; no clear dose–response | Fowles et al. (1994) |
| DE-71, oral, daily for 14 days | | Reduced TT4 and FT4 | – | 18 mg/kg bw | |
| Bromkal 70-5-DE, oral, daily for 14 days | Adult female C57BL/6N mice | Reduced TT4 and FT4 | – | 18 mg/kg bw | Hallgren et al. (2001) |
| | Adult female Sprague-Dawley rats | Reduced TT4 and FT4 | – | 18 mg/kg bw | |
| Bromkal 70-5-DE, oral, every 3rd day from GD 4 to PND 17 (10 doses) | NMRI mice dams | TT4 and FT4 | 80 µmol/kg bw | – | Skarman et al. (2005) |
| | NMRI mice offspring | Reduced TT4 and FT4 on PND 11 | – | 80 µmol/kg bw | |
| DE-71, oral, daily for 4 days | Weanling Long-Evans rats | Reduced TT4 | 10 mg/kg bw; BMDL 6.95 mg/kg bw | 30 mg/kg bw; BMD 12.74 mg/kg bw | Zhou et al. (2001) |
| | | Reduced TT3 | 30 mg/kg bw; BMDL 8.56 mg/kg bw | 100 mg/kg bw; BMD 32.94 mg/kg bw | |
| DE-79, oral, daily for 4 days | Weanling Long-Evans rats | Reduced TT4 | 3 mg/kg bw; BMDL 5.29 mg/kg bw | 10 mg/kg bw; BMD 9.25 mg/kg bw | |
| | | Reduced TT3 | 30 mg/kg bw; BMDL 11.98 mg/kg bw | 60 mg/kg bw; BMD 53.38 mg/kg bw | |
| DE-83R, oral, daily for 4 days | Weanling Long-Evans rats | Reduced TT4 | 100 mg/kg bw | >100 mg/kg bw | |
| | | Reduced TT3 | 100 mg/kg bw | >100 mg/kg bw | |

***Table 86.*** (contd)

| Dosing regimen | Species, strain, sex, age | End-point | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| DE-71, oral, daily from GD 6 to PND 21 | Developing Long-Evans rats (F1) | Reduced TT4 , TT3 unaffected | 1 mg/kg bw; BMDL 0.94 mg/kg bw | 10 mg/kg bw; BMD 2.36 mg/kg bw | Zhou et al. (2002) |
| | Long-Evans rat dams (F0) | Reduced TT4 , TT3 unaffected | 1 mg/kg bw; BMDL 4.03 mg/kg bw | 10 mg/kg bw; BMD 6.13 mg/kg bw | |
| DE-71, oral, daily from PND 23 to PND 27 | Juvenile male Wistar rats | Reduced TT4 | 3 mg/kg bw; BMDL 1.28 mg/kg bw | 30 mg/kg bw; BMD 1.42 mg/kg bw | Stoker et al. (2004a) |
| | | Reduced TT3 | 60 mg/kg bw | >60 mg/kg bw | |
| | | Elevated TSH | 60 mg/kg bw | >60 mg/kg bw | |
| DE-71, oral, daily from PND 23 to PND 53 | Juvenile male Wistar rats | Reduced TT4 | –; BMDL 0.94 mg/kg bw | 3 mg/kg bw; BMD 0.91 mg/kg bw | |
| | | Reduced TT3 | 3 mg/kg bw | 30 mg/kg bw | |
| | | Elevated TSH | 3 mg/kg bw | 30 mg/kg bw | |
| DE-71, oral, daily from PND 22 to PND 26 | Juvenile female Wistar rats | Reduced TT4 | 3 mg/kg bw; BMDL 0.28 mg/kg bw | 30 mg/kg bw; BMD 0.37 mg/kg bw | |
| | | Reduced TT3 | 60 mg/kg bw | >60 mg/kg bw | |
| | | Elevated TSH | 60 mg/kg bw | >60 mg/kg bw | |
| DE-71, oral, daily from PND 22 to PND 41 | Juvenile female Wistar rats | Reduced TT4 | 3 mg/kg bw; BMDL 1.16 mg/kg bw | 30 mg/kg bw; BMD 1.36 mg/kg bw | |
| | | Reduced TT3 | 60 mg/kg bw | >60 mg/kg bw | |
| | | Elevated TSH | 60 mg/kg bw | >60 mg/kg bw | |

*Table 86.* (contd)

| Dosing regimen | Species, strain, sex, age | End-point | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| Dust of technical-grade octaBDE mixture, inhalation, 6 h/day, 5 days/week for 90 days | Adult Charles River rats | Reduced TT4 | 12 mg/m$^3$ | 200 mg/m$^3$ | WIL Research Laboratories (1984); Gill et al. (2004) |
| Technical-grade decaBDE mixture (77% purity), oral, for 30 days | Adult Sprague-Dawley rats | Thyroid hyperplasia | 8 mg/kg bw | 80 mg/kg bw | Norris et al. (1975a) |
| DE-79, oral, for 28 or 90 days | Adult Charles River rats | Thyroid hyperplasia | – | 100 mg/kg diet (at both exposure durations) | IRDC (1976, 1977); Gill et al. (2004) |

*Table 87. Effects of PBDE congeners on thyroid hormones*

| Dosing regimen | Species, strain, sex, age | End-point | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| BDE-47, oral, daily for 14 days | Adult female C57BL/6N mice | Reduced TT4 and FT4 | – | 18 mg/kg bw | Hallgren et al. (2001) |
| BDE-47, oral, daily for 14 days | Adult female Sprague-Dawley rats | Reduced FT4 | 6 mg/kg bw | 18 mg/kg bw | Hallgren & Darnerud (2002) |
| BDE-99, oral, every 3rd day from GD 4 to PND 17 (10 doses) | NMRI mice dams | TT4 and FT4 | 80 µmol/kg bw | – | Skarman et al. (2005) |
| | NMRI mice offspring | TT4 and FT4 | 80 µmol/kg bw | – | |
| BDE-47, oral, daily for 4 days | Juvenile female Long-Evans rats | Reduced TT4 | 3 mg/kg bw | 10 mg/kg bw | Hedge et al. (2004) |
| | | Reduced TT3 | 10 mg/kg bw | 30 mg/kg bw | |
| BDE-99, oral, single dose on GD 6 | Wistar rat offspring | Reduced TT4 in F1 | – | 60 µg/kg bw | Kuriyama et al. (2004a) |
| BDE-47, oral, single dose on GD 6 | Wistar rat dams | Reduced TT4 on PND 1 | 140 µg/kg bw | 700 µg/kg bw | Kuriyama et al. (2004b) |
| | | Reduced TSH on PND 1 | 140 µg/kg bw | 700 µg/kg bw | |
| BDE-47, oral, single dose on GD 6 | Male Wistar rat offspring | Reduced TT3 on PND 1 | 140 µg/kg bw | 700 µg/kg bw | Andrade et al. (2004) |
| | | Reduced TT3 on PND 14 | – | 140 µg/kg bw | |
| | | Reduced TSH on PND 14 | – | 140 µg/kg bw | |
| | | Elevated TT4 on PND 22 | 140 µg/kg bw | 700 µg/kg bw | |
| | | Reduced TSH on PND 22 | – | 140 µg/kg bw | |
| BDE-99, subcutaneous, daily from GD 10 to GD 18 | Long-Evans rat offspring | Decreased thyroid weight | – | 1 mg/kg bw | Lilienthal et al. (2004) |

***Table 88. Effects of PBDE mixtures on steroid hormones and related effects***

| Dosing regimen | Species, strain, sex, age | End-point | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| DE-71, oral, daily for 14 days | Adult female C57BL/6J mice | Elevation of stress-induced corticosterone | – | 18 mg/kg bw | Fowles et al. (1994) |
| DE-71, oral, daily from PND 22 to PND 41 | Juvenile female Wistar rats | Delayed vaginal opening | 30 mg/kg bw | 60 mg/kg bw | Stoker et al. (2004a) |
| DE-71, oral, daily from PND 23 to PND 53 | Juvenile male Wistar rats | Elevated serum prolactin | 30 mg/kg bw | 60 mg/kg bw | |
| | | Delayed preputial separation | 3 mg/kg bw | 30 mg/kg bw | |
| | | Ventral prostate, decreased weight | 30 mg/kg bw | 60 mg/kg bw | |
| | | Seminal vesicle, decreased weight | 30 mg/kg bw | 60 mg/kg bw | |

***Table 89. Effects of PBDE congeners on steroid hormones and related effects***

| Dosing regimen | Species, strain, sex | End-point in F1 animals | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| BDE-47, oral, single dose on GD 6 | Male Wistar rat offspring | Reduced FSH on PND 22 | 140 µg/kg bw | 700 µg/kg bw | Andrade et al. (2004) |
| BDE-99, subcutaneous, daily from GD 10 to GD 18 | Long-Evans rat offspring | Delayed vaginal opening | 1 mg/kg bw | 10 mg/kg bw | Ceccatelli (2004) |
| | | Accelerated preputial separation | – | 1 mg/kg bw | |
| | | Ovary, increased weight | – | 1 mg/kg bw | |
| | | Dorsal prostate, increased weight | – | 1 mg/kg bw | |
| | | Ventral prostate, increased weight | – | Only at 1 mg/kg bw | |
| | | Epididymis, decreased weight | – | 1 mg/kg bw | |
| | | Markedly reduced AR mRNA, ventral prostate | – | 1 mg/kg bw | |
| | | Elevated AR mRNA, dorsal prostate | – | 1 mg/kg bw | |
| | | Reduced ERα and ERβ mRNA, ventral prostate | – | 1 mg/kg bw | |
| | | Elevated ERα mRNA, dorsal prostate | 1 mg/kg bw | 10 mg/kg bw | |
| | | Reduced ERβ mRNA, ventral prostate | – | 1 mg/kg bw | |
| | | Reduced IGF-I mRNA, ventral prostate | – | 1 mg/kg bw | |
| | | Reduced PR mRNA, uterus | – | 1 mg/kg bw | |
| | | ERβ mRNA elevated at low dose, reduced at high dose, uterus | – | 1 mg/kg bw | |

*Table 89.* (contd)

| Dosing regimen | Species, strain, sex | End-point in $F_1$ animals | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| BDE-99, subcutaneous, daily from GD 10 to GD 18 | Long-Evans rat dams | Reduced serum estradiol | 1 mg/kg bw | 10 mg/kg bw | Lilienthal et al. (2004) |
| | | Reduced serum 25-hydroxyvitamin $D_3$ | 1 mg/kg bw | 10 mg/kg bw | |
| | Male Long-Evans rat offspring | Markedly reduced serum estradiol | – | 1 mg/kg bw | |
| | | Reduced serum testosterone | – | 1 mg/kg bw | |
| | | Reduced anogenital distance | 1 mg/kg bw | 10 mg/kg bw | |
| | | Feminization of sexually dimorphic behaviour | 1 mg/kg bw | 10 mg/kg bw | |
| | Female Long-Evans rat offspring | Reduced serum 1,25-dihydroxyvitamin $D_3$ | 1 mg/kg bw | 10 mg/kg bw | |

***Table 90. Effects of PBDE mixtures and congeners on neurobehavioural toxicity in mice***

| Dosing regimen | Species, strain | End-point in F1 animals | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| BDE-47 or BDE-99, oral, on PND 10 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | BDE-47: 0.7 mg/kg bw<br>BDE-99: – | BDE-47: 10.5 mg/kg bw<br>BDE-99: 0.8 mg/kg bw | Eriksson et al. (2001) |
| BDE-99, oral, on PND 3, 10 or 19 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | PND 3: –<br>PND 10: –<br>PND 19: 8 mg/kg bw | PND 3 and PND 10: 8 mg/kg bw<br>PND 19: >8 mg/kg bw | Eriksson et al. (2002) |
| BDE-99, oral, on PND 10 | Infant NMRI mice | Altered locomotor activity in response to cholinergic stimulation with nicotine | – | 8 mg/kg bw | Viberg et al. (2002) |
| BDE-153, oral, on PND 10 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | 0.45 mg/kg bw | 0.9 mg/kg bw | Viberg et al. (2003a) |
| | | Altered density of nicotinic receptors in hippocampus | 0.9 mg/kg bw | 9 mg/kg bw | |
| BDE-209, oral, on PND 3, 10 or 19 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | PND 3: 2.22 mg/kg bw; PND 10 or PND 19: 20.1 mg/kg bw | PND 3: 20.1 mg/kg bw<br>PND 10 and PND 19: >20.1 mg/kg bw | Viberg et al. (2003b) |
| BDE-99, oral, on PND 10 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | 0.4 mg/kg | 12 mg/kg bw | Viberg et al. (2004a) |
| | | Decreased density of nicotinic receptors in hippocampus | (lower dose not studied) | 12 mg/kg bw | |

*Table 90.* (contd)

| Dosing regimen | Species, strain | End-point in F1 animals | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| BDE-99, oral, on PND 10 | Infant C57BL mice | Altered locomotor activity and habituation in adults | 0.4 mg/kg bw in both sexes | 0.8 mg/kg bw in both sexes | Viberg et al. (2004b) |
| BDE-183, oral, on PND 3 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | <15.2 mg/kg bw | 15.2 mg/kg bw | Eriksson et al. (2004) |
| BDE-203, oral, on PND 3 or 10 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | <16.8 mg/kg bw | 16.8 mg/kg bw | |
| BDE-206, oral, on PND 10 | Infant NMRI mice | Altered locomotor activity and habituation in adult males | <18.5 mg/kg bw | 18.5 mg/kg bw | |
| BDE-203, oral, on PND 10 | Infant NMRI mice | Altered learning and memory in adult males | <16.8 mg/kg bw | 16.8 mg/kg bw | |
| BDE-206, oral, on PND 10 | Infant NMRI mice | Altered learning and memory in adult males | <18.5 mg/kg bw | 18.5 mg/kg bw | |
| BDE-99, oral, from GD 6 to PND 21 | CD-1 Swiss mice | Delayed maturation of climbing in preweaning pups | 6 mg/kg bw | 30 mg/kg bw | Branchi et al. (2002) |
| | | Altered locomotor activity in offspring | – | 0.6 mg/kg bw, not at 30 mg/kg bw | |

***Table 91. Effects of PBDE mixtures and congeners on neurobehavioural toxicity in rats***

| Dosing regimen | Species, strain, sex | End-point in F1 animals | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| DE-71, oral, daily from GD 6 to PND 21 | Long-Evans rat offspring | Impaired long-term potentiation in dentate gyrus | 30 mg/kg bw | 100 mg/kg bw | Gilbert et al. (2004) |
| DE-71, oral, daily from GD 6 to PND 21 | Male Long-Evans rat offspring | Impaired cue-conditioned fear | 5 mg/kg bw | 30 mg/kg bw | Taylor et al. (2003) |
| BDE-99, subcutaneous, daily from GD 11 to GD 19 | Female Wistar rat offspring | Increased locomotor activity | – | 30 mg/kg bw | Wiegand et al. (2003) |
| BDE-99, subcutaneous, daily from GD 2 to GD 9 or from GD 11 to GD 19 | Wistar rat offspring | Altered contents of proteins in the glutamate – nitric oxide – cGMP signal transduction system and increased extracellular cGMP after NMDA stimulation | – | 30 mg/kg bw | |
| BDE-99, oral, on PND 10 | Infant Sprague-Dawley rats | Altered locomotor activity and habituation in adult male offspring | 0.8 mg/kg bw | 8 mg/kg bw | Viberg et al. (2004c) |
| BDE-99, oral, on GD 6 | Wistar rat male and female offspring | Increased locomotor activity | – | 60 µg/kg bw | Kuriyama et al. (2004a) |
| BDE-47, oral, on GD 6 | Female Wistar rat offspring | Increased locomotor activity on PND 70 | – | 140 µg/kg bw | Kuriyama et al. (2004c) |
| BDE-99, subcutaneous, daily from GD 10 to GD 18 | Long-Evans rat offspring | Abolition of sexual dimorphism in PR mRNA in hypothalamus | – | 1 mg/kg bw | Lichtensteiger et al. (2004) |
| | Female Long-Evans rat offspring | Markedly reduced mating behaviour | – | 10 mg/kg bw | |

*Table 91.* (contd)

| Dosing regimen | Species, strain, sex | End-point in F1 animals | NOEL | LOEL | Reference |
|---|---|---|---|---|---|
| BDE-99, subcutaneous, daily from GD 10 to GD 18 | Male Long-Evans rat offspring | Altered catalepsy after induction with haloperidol | – | 1 mg/kg bw | Lilienthal et al. (2004) |
| | | Altered reactivity after aversive stimulation | – | 1 mg/kg bw | |
| BDE-99, subcutaneous, daily from GD 10 to GD 18 | Male Long-Evans rat offspring | Impaired LTP in cortex and hippocampus, persistent after decline of fat tissue levels | – | 1 mg/kg bw | Wiegand et al. (2003, 2004) |

- The dietary intake of a particular population was assessed by combining the concentrations in food and food consumption distributions for that population with a Monte Carlo approach. In each Monte Carlo trial, the dietary intake was estimated by multiplying random values for food consumption and concentrations in various food groups. The concentrations were weighted according to the contribution of the food group to total food consumption. The estimates of intake were combined to form a distribution of long-term mean dietary intake for each population studied. The distributions are characterized by median, 80th-percentile and 90th-percentile intake.

The simulated intakes of PBDEs in the GEMS/Food regional diets are presented in Table 49 in section 7.3.2. These intakes are, however, likely to be overestimates, as it was generally not possible to determine whether the data on concentrations were derived from targeted surveys or whether they were truly random samples, and as the GEMS/Food regional diets are based on data on food supply (apparent consumption), which are known to overestimate food consumption by at least 15%.

More reliable estimates of intake, derived from national studies (see Table 47 in section 7.3.1), use national food consumption data rather than data on the food supply (apparent consumption) from the GEMS/Food regional diets.

The calculated contributions of various food categories to the intake of PBDEs showed that the largest fraction (>60%) is from food of animal origin in GEMS/Food regional and national diets.

Information was lacking on both the quality of data and geographical representativeness for some regions. More data are required on the occurrence of PBDEs in food products, particularly from geographical regions other than Europe and North America, so that more representative estimates of intake can be made for all regions.

The regional difference, in terms of exposure to PBDEs, is also apparent when considering intake by nursing infants. Based on a North American median human milk PBDE concentration of 30 ng/g lipid, total intake by a nursing infant can be estimated at 126 ng/kg bw per day (average 3.0% fat content of milk, 800 ml milk/day, 5.0 kg bw during nursing) (see Table 51 in section 7.3.3). For two of the main PBDE congeners detected in human milk, this would be approximately 73 ng/kg bw per day for BDE-47 and 22.5 ng/kg bw per day for BDE-99. In comparison, based on an average total PBDE concentration of 2.3 ng/g lipid found in German milk samples, estimated exposure by a nursing infant would be approximately 10-fold lower.

Limited biomarkers of exposure (internal dosing) are available from the identified experimental data sets. Pharmacokinetic studies indicate that lower brominated congeners such as BDE-47 and BDE-99 are readily bioavailable following oral exposure, whereas higher brominated congeners have limited potential for bioaccumulation. PBDE concentrations (lipid normalized) have been reported (McDonald, 2004) from a study in which rats were exposed by gavage to doses of

1.0 mg/kg bw per day from GD 6 to GD 21 (Taylor et al., 2003). In another study, plasma PBDE concentrations following oral exposure were also reported in relation to observed changes in thyroid hormone levels in rats (Darnerud et al., 2004). A total estimated exposure to BDE-47 of 2.7 mg (14 consecutive doses of 1 mg/kg bw per day; Hallgren & Darnerud, 2002) resulted in a plasma concentration of 28 µg/g lipid and had no effect on hepatic enzyme induction or thyroid hormones (TT4 or FT4). In comparison, exposure of rats to the commercial PentaBDE mixture Bromkal 70-5-DE at an estimated total dose of 48 mg (18 mg/kg bw per day for 14 days) resulted in a total plasma PBDE concentration of 463 µg/g lipid (sum BDE-28, BDE-47, BDE-66, BDE-99, BDE-100, BDE-138, BDE-153, BDE-154) and significant decreases in both FT4 and TT4.

#### *10.2.3 Measure of response*

The indicated data sets have been used to estimate benchmark doses (see Table 85 above).

### *10.3 Potency estimates*

#### *10.3.1 Potency estimates in humans based on epidemiological data*

No studies are available in humans for evaluating either potency estimations or dose–response relationships.

#### *10.3.2 Potency estimates in humans based on biomarkers*

Biomarkers of exposure are available in the form of lipid-normalized serum or human milk values. For the purpose of risk estimations, comparison with any experimental biomarkers assumes that food is the main source of exposure. In a survey of human milk collected across Canada in 2002 ($n$ = 98), the mean concentration of total PBDEs (sum of congeners 28, 47, 99, 100, 154, 154 and 183) was 60.4 ng/g lipid (Ryan, 2004). This represented an approximate 4-fold increase when compared with the previous human milk survey conducted in 1992 (mean = 15 ng/g). Five per cent of the 2002 sample set had a PBDE concentration of equal to or greater than 236 ng/g lipid, similar to a sample from the United States for which the 95% value was 378 ng/g lipid (Schecter et al., 2005).

However, while comparison of PBDE exposures in the United Kingdom suggests that diet is the major source, maximum inhalation exposure (96 ng/person per day) can equal that of average dietary intakes (90–107 ng/person per day) (Harrad et al., 2004).

#### *10.3.3 Potency estimates in test species and basis for extrapolation to humans*

Major congeners detected in foods and human tissue samples more closely resemble commercial PentaBDE and OctaBDE mixtures. Although sum PBDE results for human samples sometimes include highly brominated congeners such

as BDE-183 and BDE-209, they comprise only a minor component (less than 2% of total mass).

Only the DecaBDE commercial mixture has been subject to a chronic toxicity test, and the lowest concentration tested (2.5% in the diet) produced adverse effects. For PBDE commercial mixtures (PentaBDE and OctaBDE) whose congener patterns resemble residues found in food and human samples, there is limited toxicological information. Only short-term feeding studies (up to 13 weeks) have been conducted in rats, with liver, kidney and thyroid identified as target organs. Dose-related increases in relative liver weights and microscopic liver changes (hepatocellular enlargement with vacuolation) were noted in a study with a commercial OctaBDE mixture (DE-79) at 100 mg/kg diet or approximately 8 mg/kg bw per day. Similar effects were seen in a subchronic feeding study with a PentaBDE mixture (DE-71); dose-related increases in liver weights and histological changes (hypertrophy, slight degeneration and necrosis) were noted at the lowest dose level, 2 mg/kg bw per day. The effects were still partially evident in female animals at the lowest dose group after a 24-week recovery period. At higher doses (≥10 mg/kg bw per day), decreases in circulating thyroid hormones (T4) were observed. This latter observation is supported by a developmental toxicity study conducted in rats with the commercial PentaBDE (DE-71), in which decreases in serum T4 were seen in both fetuses and newborn pups at a maternal dose of 10 mg/kg bw per day (GD 6 to PND 21).

A number of additional preliminary studies were reviewed, available as extended abstracts involving acute dosing protocols on a single day during either gestation or lactation using mainly PentaBDE commercial mixtures (DE-71), BDE-47 or BDE-99. A variety of effects in both mice and rats were observed involving neurological development (behaviour, memory and activity), thyroid hormone perturbation and sexual maturation at doses as low as 60 µg/kg bw. Due to a lack of mechanistic information and adequate dose–response relationships, a clear interpretation of the significance to human health could not be made at this time.

Developmental exposure of rats to the PentaBDE commercial mixture, DE-71, results in reductions in thyroid hormones in offspring, with an estimated $BMDL_{20}$ of 0.94 mg/kg bw per day. In comparison, exposure of weanling rats to DE-71 also resulted in thyroid hormone decreases, with a $BMDL_5$ estimate of 0.28 mg/kg bw per day. Differences in the two values are related not only to the exposure protocols but to the level of response for effect modelling (20% former, 5% latter). Based on a single exposure of newborn mice to BDE-99, a $BMDL_{10}$ for total activity changes was estimated at 0.31 mg/kg bw. Exposure during a similar critical developmental stage in humans can be compared based on PBDE concentrations in human milk. Median intake for total PBDEs by North American newborns would be on average 135 ng/kg bw per day, or approximately 2000-fold lower than the BMDL for a 5% decrease in thyroid hormones. Alternatively, the maximum concentration of total PBDEs found in human milk samples in the United States was approximately 420 ng/g, which would result in an estimated intake of 1.9 µg/kg bw per day, or 147-fold less than the thyroid hormone BMDL. Based on results from a Canadian survey of human milk samples collected in 2001–2002, 5% of the sample population ($n$ = 98) had total PBDE values equal to or greater

than 236 ng/g lipid (maximum 956.2 ng/g lipid). Comparison of this 95th percentile value with the estimated BMDL for thyroid hormone changes would give a difference of 226. Similarly, the $BMDL_{10}$ for total activity changes induced by BDE-99 in mice is approximately 940-fold greater than the estimated single-day exposure of 0.3 µg/kg bw by a nursing infant based on a BDE-99 concentration in human milk of 62.8 ng/g lipid (average of 95th percentile values from human milk surveys in the United States and Canada).

## *11. COMMENTS*

### *11.1 Absorption, distribution, metabolism and excretion*

The majority of detailed studies of the absorption, distribution, metabolism and excretion of PBDEs are limited to the individual congeners BDE-47, BDE-99 and BDE-209. The absorption of PBDEs is directly related to the extent of bromination of the parent diphenyl ether; as a general rule, greater substitution with bromine leads to a decrease in bioavailability. Intestinal absorption of deca-BDE is limited, with >90% of an orally administered dose being rapidly excreted in the faeces. For congeners with a lower degree of bromination (tetra- and penta-substituted), >80% of an orally administered dose is absorbed, with patterns of distribution in tissue being largely determined by lipid content. The metabolism of PBDEs consists of hydroxylation and methoxylation reactions and, in the case of congeners with a higher degree of bromination, oxidative debromination. Faecal excretion appears to be the predominant route of elimination; however, some differences exist between species. Urinary excretion of BDE-47 is a minor pathway in rats but is as important as faecal excretion in mice. Limited data were available regarding the half-lives of individual PBDE congeners; however, preliminary values in female rats exposed to a commercial pentaBDE mixture, Bromkal 70-5-DE, ranged from 30 to 90 days for the tetra- to hexa-substituted congeners.

Limited pharmacokinetic data were available for humans. On the basis of the observed increase in concentrations of PBDEs in tissue with time, PBDEs are absorbed and bioaccumulate.

### *11.2 Toxicological data*

In the toxicological studies reviewed, PBDEs were administered by the oral (gavage or diet) route of exposure, unless otherwise stated.

The acute toxicity of mixtures of PBDEs is low in rodents. Generally, even at the highest doses (several grams per kilogram of body weight), there are no observable effects in standard tests for acute toxicity after exposure to decaBDE and octaBDE, although certain effects (increased mortality, behavioural symptoms and changes in gross pathology) are seen after exposure to pentaBDE at similar high doses. Induction of enzymes, changes in levels of hormones and neurobehavioural effects are observed after bolus administration of mixtures of PBDEs (pentaBDE and octaBDE) and of specific congeners at considerably lower doses. In short-term studies of toxicity, the main effects of mixtures of PBDEs were seen in the liver, kidney and thyroid of both sexes. Enlargement of the liver is a common

finding, which may be connected to increased activity of microsomal enzymes in the liver. Histological changes occur in liver (enlargement, "round bodies," vacuolization, necrosis), kidney (hyaline degenerative cytoplasmic changes) and thyroid (hyperplasia). In short-term studies, effects on thyroid hormone, vitamin A homeostasis and microsomal enzymes were observed at doses of 1–10 mg/kg bw per day.

The only long-term study with PBDEs was conducted with the decaBDE mixture. In this NTP study of carcinogenicity (NTP, 1986), decaBDE (purity, 94–99%; brominated dioxins and furans reported not to be detected), given in the diet at high concentrations (2.5% or 5%) for 111–113 weeks, significantly increased the combined incidence of hepatocellular adenomas and carcinomas in male mice, but not in female mice. In spite of an increase in follicular cell hyperplasia, the incidence of thyroid follicular cell adenoma/carcinoma was not significantly increased. In male and female rats, the incidence of liver adenomas, but not hepatocellular carcinomas, was increased. Other effects, such as liver hypertrophy, granulomas, thrombosis and degeneration, thyroid follicular cell hypertrophy and lymphoid hyperplasia, were also noted. The Committee concluded that evidence for the carcinogenicity of decaBDE in experimental animals was limited and noted that no information was available on the carcinogenic potential of the other PBDE mixtures.

The results of the majority of tests for genotoxicity performed in vitro (point mutations, chromosomal aberrations, unscheduled DNA synthesis, sister chromatid exchange) and limited data from tests in vivo (chromosomal aberration) indicated that PBDE mixtures and individual congeners are not genotoxic.

The developmental toxicity of deca-, octa- and pentaBDE mixtures has been studied in rats and rabbits. In rats, preparations of pure decaBDE (purity, 97–98%) had no effects on developmental parameters, while decaBDE of lower purity (decaBDE, 77.4%; nonaBDE, 21.8%; octaBDE, 0.8%) caused fetotoxic effects. Exposure to commercial octaBDE mixtures (Saytex 111 and DE-79) produced developmental toxicity as indicated by increased numbers of late resorptions, reduced fetal weight, severe oedemas, reduced ossification of skull bones and bent rib and limb bones at a dose range of 10–50 mg/kg bw per day; only slight maternal toxicity (decreased body weight) was observed at doses of 25–50 mg/kg bw per day. A pentaBDE mixture (Saytex 115) has been tested in only one study, with no clear adverse effects at a dose of 100 mg/kg bw per day.

In rabbits given a commercial octaBDE mixture (Saytex 111) during gestation, no major fetotoxic effects were observed, but an increase in the incidence of delayed ossification of sternebrae was seen at 15 mg/kg bw per day.

The Committee concluded that the embryo and fetus may be more sensitive to PBDEs than maternal animals and that exposure to octaPBDE mixtures causes an increase in the incidence of developmental abnormalities.

### *11.3 Special studies*

Studies with purified PBDE congeners in vitro have shown lack of activation of the Ah receptor at doses 6 orders of magnitude higher than the half-maximal effective concentration ($EC_{50}$) of TCDD, suggesting that some toxicity data may be confounded by the presence of traces of impurities that are potent agonists of the Ah receptor.

In studies with the commercial PBDE mixtures PentaBDEs (Bromkal 70-5-DE and DE-71), OctaDBE (DE-79) and DecaBDE (DE-83R), various strains and both sexes of adult mice and rats have been used and acute or short-term dosing schedules applied to examine effects on thyroid hormone homeostasis. In the majority of studies, concentrations of TT4 and, in some cases, FT4 in the blood were found to be suppressed, with almost no corresponding alteration in TSH. DE-79 was reported to be more potent than DE-71, while no effects were found after exposure to DE-83R. When pregnant rats were given DE-71 at maternal doses of ≥3 mg/kg bw per day, circulating concentrations of T4 in the offspring were found to be reduced until weaning, with recovery of T4 values within 2 weeks thereafter. In juvenile rats given DE-71, reductions in serum concentrations of T4 were similar in both sexes, but concentrations of TSH were elevated and serum concentrations of T3 were significantly decreased only in males. Plasma concentrations of TT4 and FT4 were decreased in adult female mice and rats given Bromkal 70-5-DE at a dose of 18 mg/kg bw per day for 2 weeks. At doses at which circulating concentrations of T4 were decreased (>1 mg/kg bw per day), the activities of UDPGT and EROD were often found to be increased, suggesting that Ah receptor-dependent effects are most likely to be mediated by contamination of commercial PBDE mixtures with dioxin-like compounds. A similar observation was also made in studies with individual PBDE congeners (BDE-47 and BDE-99).

Of the individual congeners, only BDE-47, BDE-99 and BDE-209 have been studied. With regard to effects on the concentrations and activities of thyroid hormones, the available data indicated that BDE-209 is much less potent than BDE-47 and BDE-99, but lack of data precluded a comparison of the potencies of BDE-47 and BDE-99. In general, the results of studies with individual congeners indicated that their effects on thyroid hormones were similar to those observed with mixtures. The most pronounced effects were reduced concentrations of circulating TT4 and FT4. TSH was not affected in the majority of studies.

Recent studies, available as extended abstracts, showed that the offspring (both males and females) of rats given a single oral dose of BDE-99 (60 µg/kg bw) or BDE-47 (140 µg/kg bw) on day 6 of gestation had altered concentrations of T3 and T4 during the weaning period. Serum concentrations of TSH were also reduced during lactation. These alterations in thyroid hormones recovered during postnatal development. In general, examination of effects on the thyroid after maternal exposure to mixtures of PBDEs or to individual congeners demonstrated that the offspring were more susceptible than the dams.

While competitive inhibition of the binding of T4 to TTR by hydroxylated metabolites of PBDE is thought to be one of the mechanisms responsible for decreases in circulating concentrations of thyroid hormones in rats, the

significance of this for human exposure is questionable. TBG, which is absent in rats, is the main thyroid hormone transport protein in humans. Metabolites of PBDE have been shown to have limited binding affinity to human TBG. A general observation by the Committee was the apparent lack of consistency in the results of a number of experimental studies measuring thyroid hormone changes; significant decreases in serum concentrations of T4 were observed in the absence of corresponding effects on TSH. There was insufficient information about the effects of PBDEs on feedback mechanisms in the hypothalamus and pituitary. In a number of studies in which the effects of PBDE congeners or mixtures on thyroid hormones were measured, induction of hepatic EROD was also observed, which could indicate the presence of dioxin-like contaminants. Alterations in thyroid hormones are also a sensitive response in experimental animals exposed to dioxin-like chemicals. The available data were considered to be insufficient to determine the mechanism for the reported effects on thyroid hormones and the possible role of pure PBDEs in altering delivery of maternal thyroid hormones across the placental barrier to the developing embryo/fetus and into the brain.

Possible effects of PBDEs on steroid hormones and steroid-related end-points have been reported in a limited number of studies (mainly in extended abstracts) with a commercial PentaBDE mixture (DE-71) and two congeners, BDE-47 and BDE-99. In weanling rats treated by oral administration with a commercial PentaBDE mixture (DE-71) for 20 days (female) or 31 days (male), the onset of puberty was delayed in both sexes at doses of 30–60 mg/kg bw per day. After a single oral dose of BDE-47 (700 µg/kg bw) on day 6 of gestation, decreased serum concentrations of FSH were seen in male offspring. With the same exposure protocol, BDE-99 was recently reported to reduce sperm production at a dose of 60 µg/kg bw. Induction of hepatic EROD was observed in all these experiments; therefore, Ah receptor-mediated effects by possible dioxin-like contaminants could not be excluded.

In rats given BDE-99 at doses as low as 1 mg/kg bw per day by subcutaneous administration during days 10–18 of gestation, decreases in the circulating concentrations of sex steroid hormones (estradiol and testosterone) were observed in weanling and adult male offspring. Anogenital distance was reduced in male offspring, and reproductive organ weights were altered in both sexes. The onset of puberty was delayed in females and accelerated in males, while there was a marked reduction in the expression of AR mRNA in the ventral prostate on PND 120. In the same study, exposure to a technical mixture of PCBs (Aroclor 1254), known to possess dioxin-like activity, at a dose of 30 mg/kg bw per day did not affect several of these end-points, indicating that contamination of the BDE-99 with dioxin-like compounds was unlikely to account for these observations.

The majority of investigations examining neurotoxicity in vivo involved oral exposure of mice and rats to individual congeners. In almost all experiments in mice, individual congeners (e.g. BDE-47, BDE-99, BDE-153, BDE-183, BDE-203, BDE-206 and BDE-209) given to neonates as a single oral dose on a specific postnatal day produced changes in activity patterns and habituation, which became more pronounced with ageing. Essentially identical results were observed in the same laboratory with two different strains of mice, in both sexes, and also in

rats. In general, the congeners with a lower degree of bromination appeared to be more potent than the congeners with a higher degree of bromination. Most of the neurotoxicological examinations were performed in rats treated with BDE-99 during gestation. Decreases in LTP in the cortex and hippocampus, as well as influences on sexually dimorphic brain structures, reductions in mating behaviour and feminization of sweet preference behaviour, were reported at doses of ≥1 mg/kg bw per day administered subcutaneously. As some of these end-points were not affected by administration of Aroclor 1254 at higher doses, this would indicate that mechanisms similar to those for dioxins are unlikely to be involved. Impaired hippocampal LTP and conditioned behaviour were also detected in the offspring of female rats treated with the PentaBDE mixture (DE-71) at oral doses of 30–100 mg/kg bw per day from day 6 of gestation to PND 21. Altered locomotor activity was reported in the offspring of female rats given a single oral dose of BDE-47 (140 or 700 µg/kg bw) or BDE-99 (60 or 300 µg/kg bw) on day 6 of gestation. Because of the preliminary nature of these findings, an interpretation of their significance for human health could not be made.

### *11.4 Observations in humans*

No clinical observations have been reported in humans after oral ingestion of PBDEs. Although several studies have been conducted in workers exposed occupationally to PBDEs, these subjects were also exposed to other substances, making it difficult to attribute any observed effects solely to PBDEs. Therefore, the Committee did not consider these studies to be useful for evaluation of the potential health effects of dietary exposure to PBDEs. In a case–control study, elevated concentrations of BDE-47 were found in the adipose tissue of patients with NHL (incident cases), but the etiological significance of this association is uncertain. In a study of adult male consumers of Baltic fish, plasma concentrations of BDE-47 were inversely related to concentrations of TSH and were not related to the concentrations of any of the thyroid hormones measured, suggesting that exposure to BDE-47 via frequent consumption of fish does not impair thyroid function in adult men.

The Committee concluded that the available studies in humans were not adequate to evaluate whether exposure to PBDEs, at the levels studied, is associated with adverse health effects.

In human milk collected in Sweden between 1972 and 1997, the concentrations of PBDEs increased, doubling every 5 years, resulting in current concentrations in the low nanogram per gram of lipid range. Recent investigations with human milk from other European countries showed similar levels of contamination.

Analysis of a limited number of samples of human serum collected between 1985 and 1999 in the United States also showed an increase in concentrations of PBDEs over time.

Analysis of a limited number of recently collected human samples (blood, milk, adipose) from North America has indicated that average concentrations of PBDEs are 10–20 times higher than those in samples collected in European

countries. The reason for the higher values found for North America was not thought to be solely related to dietary intake. The significance of pathways of exposure other than food, such as indoor air and indoor dust, is currently under investigation.

Generally, lipid-based concentrations are similar in different human samples, such as milk, blood and adipose tissue.

The typical pattern of congeners found in humans is normally dominated by BDE-47, followed by BDE-99 and the hexabrominated congener BDE-153. Preliminary results indicated that congener BDE-153 is becoming more prominent in European samples.

### *11.5 Analytical methods*

GC-HRMS using the isotope dilution technique ($^{13}$C-labelled standards) has been found to be the most reliable method for the determination of PBDE congeners in food and environmental samples, as well as in samples of human tissues.

The total number of possible PBDE congeners is 209. For reasons of occurrence in food and human samples and analytical capability, only a limited number of congeners has been measured in recent years. This number ranged between three and nine congeners (BDE-28, BDE-47, BDE-66, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, BDE-209). With increasing analytical power and availability of standards, the number of individual congeners measured in food and human samples could be increased.

The physical and chemical properties of the BDE-209 congener are such that great demands are made of the analytical method, including sample preparation, extraction and cleanup, as well as final chromatographic separation. The problems encountered during the analysis of PBDE congeners of high relative molecular mass are associated with thermal instability and sensitivity to light rather than with their high boiling points.

Typical limits of detection for tetra/pentaBDEs range from 0.005 to 0.05 ng/g, depending on lipid content and sample size.

The Committee noted that as DecaBDE was the only commercial formulation currently marketed in Europe and North America, analytical methods should include the determination of this fully brominated congener.

### *11.6 Effects of processing*

No data were available on the effect of processing on concentrations of PBDEs in foods.

### 11.7 Prevention and control

As with other lipophilic contaminants, control of PBDE residues in animal feed is likely to have an impact on the concentrations of PBDEs found in meat, poultry, farmed fish and other animal-derived products. Additional investigations should also consider the significance of exposure from other non-food sources (indoor air, dust) as a means of control.

### 11.8 Levels and pattern of food contamination

The Committee reviewed data available on concentrations of PBDEs in foods (Table 92). Some of the data were from TDS conducted either at the national level (Finland, Netherlands and Sweden) or at the regional level within a given country (e.g. Vancouver and Whitehorse in Canada, and Catalonia in Spain), while others were from more limited, market basket surveys targeting special foods, e.g. foods of animal origin or fish and seafood, or were from grab samples collected from local markets (Canada, Germany, Japan, United Kingdom, United States). The data from the Canadian TDS and Special Fish and Seafood Survey and the TDS from the Netherlands and Sweden were available in reports published by the respective national agencies, while the data from the other studies were available in published scientific journals or were submitted by local governments. Concentration data were available for individual congeners or their sum. The patterns of congeners detected were not uniform across the various foods tested and were different from those present in any one commercial mixture.

In general, the available data on concentrations of PBDEs in food for the various countries have not covered the entire diets in these countries or are based on a small number of samples. Thus, the currently available data do not allow a comprehensive assessment to be made of contamination in all foods. Differences in concentrations were detected in samples of similar foods collected from various geographical areas.

### 11.9 Dietary intake assessment

Preliminary estimates of mean intake of PBDEs, based on a limited number of samples from Canada, some European countries, Japan and the United States, as reported in published studies and reports, range from 13 to 113 ng/day (Table 92). Fish and shellfish were the main contributors to total intakes of PBDEs in the European countries and Japan, while meats, poultry and products of these foods were the major contributors to the total intakes of PBDEs in Canada and the United States.

Estimates of regional intakes for the European and North American region were made using the GEMS/Food regional diets and concentration data from studies summarized in Table 92. Table 93 summarizes the food consumption data used in this estimation and the estimated mean intakes of total PBDEs for these regions. Although the North American diet is included under the European diet in GEMS/Food, intake estimates for the North American and European regions were

***Table 92. Summary of available data on concentrations of PBDEs and associated national intakes***

| Country | Type of study | Foods | PBDEs measured | Data reported | Concentrations detected (ng/g fresh weight) | Consumption data | Reported mean intake of PBDEs (ng/day) |
|---|---|---|---|---|---|---|---|
| Canada | Food basket survey | Foods of animal origin | NA | NA | NA | National estimates | 44 |
| | TDS (1998) | About 50 foods representing the total diet | Total PBDEs (28, 47, 99, 100, 153, 154, 183) | Level/food sample | Range of means/food group 0.024 (dairy) to 0.333 (egg — 1 sample) | National estimates | 38 |
| | TDS, Vancouver (2002) | About 50 foods representing the total diet | Total PBDEs (28, 47, 99, 100, 153, 154, 183) | Level/food sample | Range of means/food group 0.035 (dairy) to 0.680 (fish) | National estimates | 30 |
| | Special Fish & Seafood Survey (2002) | 70 samples of farmed and wild fish | Total PBDEs (28, 47, 99, 100, 153, 154, 183) | *N*, Mean, SE, SD, Min, Max per species and source | Range of means:<br>0.2–2.2 (farmed)<br>0.1–0.6 (wild) | NA | NA |
| Finland | Market basket survey (1997–1999) | 228 foods grouped in 10 market baskets (about 4000 samples) | Total PBDEs (47, 99, 100, 153, 154) | Level/basket | Range of means/food group 0.009 (other) to 0.85 (fish) | 1997 Dietary Survey of Finnish Adults | 43 |
| | Total diet basket | 228 foods | Total PBDEs (47, 99, 100, 153, 154) | Level in total diet basket | 0.043 | 1997 Dietary Survey of Finnish Adults | 44 |

***Table 92.*** (contd)

| Country | Type of study | Foods | PBDEs measured | Data reported | Concentrations detected (ng/g fresh weight) | Consumption data | Reported mean intake of PBDEs (ng/day) |
|---|---|---|---|---|---|---|---|
| Germany | Samples collected from German markets (2001–2003) | Fish, meats, dairy (607 samples) | Total PBDEs (28, 47, 99, 100, 153, 154) | *N*, Number of detects; Number of non-detects; Mean concentration (positive samples); Range | Range of means/food group 0.030 (dairy) to 1.45 (fish and shellfish) | NA | NA |
| | Fish samples collected from German markets (2004) | 13 fish samples | 17, 28, 47, 66, 77, 99, 100, 153, 154, 183, 209, and total | Data/congener per sample | Mean: 0.66<br>Range: 0.01–2.87 | NA | NA |
| Japan | TDS | 13 food groups (two composites each for fish, meats and eggs, and milk and milk products, one composite for each of the remaining food groups) | 47, 49, 66, 99, 100, 119, 153, 154, 183 | Total PBDE/food group | Range of levels/food group<br>(for detects)<br>0.009 (dairy) to 1.26 (fish) (ND = LOD) | National Nutrition Survey | 113 |

***Table 92.*** (contd)

| Country | Type of study | Foods | PBDEs measured | Data reported | Concentrations detected (ng/g fresh weight) | Consumption data | Reported mean intake of PBDEs (ng/day) |
|---|---|---|---|---|---|---|---|
| Japan (contd) | Duplicate-diet study | Duplicate meals collected from six subjects for 2–3 days | 47, 49, 66, 99, 100, 119, 153, 154, 183 | Data/congener per person | Mean: 0.29<br>Range: 0.003–0.081 | Total diet of six subjects for 2–3 days | 68 |
| | Market basket survey | Fish, shellfish, meats & vegetables (26 samples) | 28, 47, 99, 100, 153, 154 | Total PBDE per sample | Range of means/food group 0.030 (meats & poultry) to 0.91 (fish and shellfish) | NA | NA |
| Netherlands | TDS (2001–2002) | 84 samples (dairy, eggs, meats, animal fats, fish, oil) | 28, 47, 99, 100, 153, 154, 71, 77, 190, 209 | Data per congener per sample | Range of means/food group ND (eggs) to 6.82 (fish and shellfish) | Data from 6250 individuals in Dutch National Food Consumption Survey | 13 |
| Spain | Market basket, in Catalonia (2000) | Fish, meats, dairy, vegetables, cereals, fats and oils ($n$ = 54) | Tetra-, penta-, hexa-, hepta-, octaBDE | Total PBDE per food group and congener level/entire diet | Range of means/food group 0.001 (other foods) to 0.46 (fats and oils) | Consumption data for Catalonia | 82 |
| Sweden | TDS | Fish, meats, dairy, fats and oils ($n$ = 20 composite samples) | 47, 99, 100, 153, 154 | Total PBDE level per sample | Range of means/food group: 0.04 (eggs) to 1.884 (fish and shellfish)<br>(ND = LOD/2) | National Consumption Survey<br>(1997–98) | Adults aged 17–74 years<br>Females: 41<br>Males: 47<br>(ND = LOD/2) |

*Table 92.* (contd)

| Country | Type of study | Foods | PBDEs measured | Data reported | Concentrations detected (ng/g fresh weight) | Consumption data | Reported mean intake of PBDEs (ng/day) |
|---|---|---|---|---|---|---|---|
| Sweden (contd) | Market basket | Fish, meat, dairy products, eggs, fats/oils, pastry | Sum of congeners 47, 99, 100, 153, 154 | NA | NA | Based on production | 51<br>(ND = LOD/2) |
| UK | Targeted study | Fish (18 samples) | Total PBDEs | Range per fish type and location | Range<br>12–53 (control location)<br>59–288 (target location) | Standard portion sizes | Maximum intakes<br>Control: 9 ng/kg bw per day<br>Target: 56 ng/kg bw per day |
| | Duplicate-diet study | Total diet of 10 individuals | Sum of 47, 99, 100, 153, 154 | NA | NA | 10 individuals | 90 |
| USA | Market basket survey (2003) | 32 food samples (fish, meats, dairy) | 17, 28, 47, 66, 77, 85, 99, 100, 138, 153, 154, 183, 209 | Total PBDEs per sample | Range 0.0009 (fats and oils), 1.487 (fish and shellfish) | USDA 1994–1996 Continuing Survey of Food Intakes by Individuals | Females: 1.4 ng/kg bw per day<br>Males: 2.0 ng/kg bw per day |
| | Grab samples from local supermarkets (Texas) | 15 meat samples | 17, 28, 47, 66, 85, 99, 100, 138, 153, 154, 183, 209 | Individual congeners and total PBDEs per sample | Mean: 0.58<br>Range: ND–2.86 | NA | NA |

***Table 92.*** (contd)

| Country | Type of study | Foods | PBDEs measured | Data reported | Concentrations detected (ng/g fresh weight) | Consumption data | Reported mean intake of PBDEs (ng/day) |
|---|---|---|---|---|---|---|---|
| USA (contd) | Grab samples from local supermarkets (Texas) | 11 dairy samples | 17, 28, 47, 66, 85, 99, 100, 138, 153, 154, 183, 209 | Individual congeners and total PBDEs per sample | Mean: 0.17<br>Range: 0.03–0.66 | NA | NA |
| | Samples from supermarkets in nine cities | 48 bacon and meat trimmings | 28/33, 47, 85, 99, 100, 153, 154, 183, 209 | Mean and range for each congener and total PBDEs per food type | Mean: 0.20 (bacon), 1.07 (meat trimmings) | NA | NA |
| | Samples from local markets (California) | Nine meat samples | 26 congeners | Individual congeners and total PBDEs per sample | Mean: 0.60<br>Range: 0.16–2.52 | NA | NA |
| United States and EU | Review paper | Various fish species | 47, 99, 100, 153, 154 | *N* for each study, Mean concentration for each congener and total PBDEs | Range of means (ng/g lipid):<br>European studies: 6.31–515<br>USA studies: 12.1–7200 | NA | NA |

Max, maximum; Min, minimum; *N*, number of samples; NA, not available or analysis not conducted; ND, not detected and counted as zero unless otherwise stated; SD, standard deviation; SE, standard error; USDA, United States Department of Agriculture

derived separately in light of the potential differences between concentrations of PBDEs detected in foods in Europe and North America. The estimated mean intakes of PBDEs for the European and North American regions were 2.2 and 3.6 ng/kg bw per day, respectively. Consumption of fish contributed most to European intake estimates, while meats and poultry contributed most to the North American intake estimates. No data on concentrations of PBDEs were available for countries in the following GEMS/Food regions: Africa, the Middle East or Latin America, and limited data were available for the Far East. The Committee derived estimates of international intake for these regions using the GEMS/Food regional diets and assuming that concentrations of PBDEs in food in these regions were equal to the average levels of contamination derived from European and North American data.[1] Estimated intakes for Africa, the Middle East, Latin America and the Far East were 1.5, 1.3, 2.1 and 1.2 ng/kg bw per day, respectively. Fish and shellfish contributed most to estimated intakes in the African, Latin American and Far Eastern regions, while fats and oils contributed most to the estimates for the Middle East. It should be noted that these estimates were only rough approximations since they were based on concentration data from other regions.

***Table 93. Estimated intakes of total PBDEs in GEMS/Food regional diets***

| Food group | Consumption (g/day) | Estimated intake of PBDEs (ng/day)[a] | |
|---|---|---|---|
| | | European diet[b] | North American diet[c] |
| Dairy and products | 336 | 10 | 24 |
| Eggs | 38 | 2 | 8 |
| Fats and oils | 49 | 13 | 47 |
| Fish and shellfish | 47 | 84 | 40 |
| Meat and poultry | 217 | 17 | 66 |
| Other foods | 826 | 6 | 29[d] |
| Total (ng/day) | | 131 | 213 |
| Total (ng/kg bw per day)[e] | | 2.2 | 3.6 |

[a] Non-detects set at zero.

[b] Concentration data from Finland, Germany, Netherlands, Spain and Sweden were used in the estimation.

[c] United States and Canada.

[d] Limited data were available for this region; therefore, the combined data from the other regions were used instead.

[e] Based on a body weight of 60 kg.

[1] For the Far Eastern region, limited data were available for some food groups and were used in combination with data from the North American and European regions for the remaining food groups.

A regional difference was apparent when considering intake by breastfeeding infants. Based on a median concentration of PBDEs of approximately 23 ng/g of lipid in human milk ($n$ = 145), intake by a breastfeeding infant in North America was estimated at 120 ng/kg bw per day (average fat content of milk, 3.0%; 750 ml of milk per day; 5.0 kg bw during nursing). In comparison, based on a median concentration of PDBEs of 1.8 ng/g of lipid in samples of human milk, estimated intake for a breastfeeding infant in Germany would be approximately 10 ng/kg bw per day.

The Committee recognized the preliminary nature of the data on concentrations of PBDEs in food and human milk, which adds considerable uncertainty to the intake estimates.

### *11.10 Dose–response analysis*

Only the commercial DecaBDE mixture has been tested in a long-term study of toxicity; the lowest concentration tested (2.5% in the diet) produced adverse effects. Limited toxicological information was available for commercial PBDE mixtures (PentaBDE and OctaBDE) whose congener patterns resemble those of residues found in food and human tissues. Only short-term feeding studies (up to 13 weeks) have been conducted in rats, with liver, kidney and thyroid being identified as target organs. Dose-related increases in relative liver weights and microscopic liver changes (hepatocellular enlargement with vacuolation) were noted in a study with a commercial OctaBDE mixture (DE-79) at a concentration of 100 mg/kg of diet (approximately 8 mg/kg bw per day). Similar effects were seen in a short-term feeding study with a commercial PentaBDE mixture (DE-71); dose-related increases in liver weights and histological changes (hypertrophy, slight degeneration and necrosis) were noted at the lowest dose, 2 mg/kg bw per day. The effects were still partially evident in females at the lowest dose after a 24-week recovery period. At higher doses (≥10 mg/kg bw per day), decreases in concentrations of circulating thyroid hormones (T4) were observed. The latter observation was supported by the results of a study of developmental toxicity in rats given the commercial PentaBDE mixture (DE-71); decreases in serum concentrations of T4 were seen in both fetuses and newborn pups at a maternal dose of 10 mg/kg bw per day administered on day 6 of gestation to PND 21.

The Committee also reviewed a number of preliminary studies of acute toxicity involving dosing with mainly commercial PentaBDE mixtures, BDE-47 or BDE-99 on a single day during gestation or lactation. In mice and rats, there were a variety of effects involving neurological development (behaviour, memory and activity), thyroid hormone perturbation and sexual maturation at doses as low as 60 µg/kg bw. Owing to a lack of mechanistic information and adequate data on dose–response relationships, a clear interpretation of the significance to human health could not be made at the present time.

## *12. EVALUATION*

For non-genotoxic substances, the Committee would normally allocate a provisional maximum tolerable daily intake (PMTDI) or provisional tolerable weekly intake (PTWI) based on the NOEL for the most sensitive adverse effect; however, the available data on PBDEs were not adequate for such an approach because:

- PBDEs represent a complex group of related chemicals, and the pattern of PDBE congeners in food is not clearly defined by a single commercial mixture.
- 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, alternatively, as the basis for establishing toxic equivalence 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.
- Several of the reported effects are biological outcomes for which the toxicological significance remains unclear.
- Studies with purified PBDE congeners in vitro have shown a lack of activation of the Ah receptor; 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 agonists of the Ah receptor.

DecaBDE was the only brominated diphenyl ether for which a long-term study of toxicity was available. A complete hazard characterization for this PBDE will become increasingly important, as at the time of the present evaluation it was the primary commercial mixture in use worldwide.

The limited toxicity data suggested that for the more toxic PBDE congeners, adverse effects would be unlikely to occur in rodents at doses of less than approximately 100 µg/kg bw per day. The current estimates of dietary intake were approximately 0.004 µg/kg bw per day, while intake by breastfeeding infants could be up to 0.1 µg/kg bw per day for the sum of all measured PBDE congeners, including the less toxic ones. In consequence, there appeared to be a large margin of exposure (MOE) for a non-genotoxic compound, which, despite the inadequacy of the data on toxicity and intake, gave reassurance that intakes of PBDEs are not likely to be a significant health concern. The Committee noted that, as with related bioaccumulative persistent contaminants (PCBs, dioxins), a more appropriate dose metric for interspecies comparison of risk would be a measure of the internal dose. For the majority of PBDEs studied, however, the data from experimental animals or on concentrations in human tissue were insufficient to allow a comparison with external dose.

### 12.1 Recommendations

Although no specific recommendations for PBDEs were made by the Committee, it was noted that as DecaBDE was the only commercial formulation currently marketed in Europe and North America, analytical methods should include the determination of this fully brominated congener.

The Committee also 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.

## 13. REFERENCES

Akutsu, K., Kitagawa, M., Nakazawa, H., Makino, T., Iwazaki, K., Oda, H. & Hori, S. (2003) Time-trend (1973–2000) of polybrominated diphenyl ethers in Japanese mother's milk. *Chemosphere*, **53** (6), 645–654.

Alaee, M. & Wenning, R.J. (2002) The significance of brominated flame retardants in the environment: current understanding, issues and challenges. *Chemosphere*, **46** (5), 579–582.

Alaee, M., Sergeant, D.B., Ikonomou, M.G. & Luross, J.M. (2001) A gas chromatography/ high-resolution mass spectrometry (GC/HRMS) method for determination of polybrominated diphenyl ethers in fish. *Chemosphere*, **44** (6),1489–1495.

Alaee, M., Arias, P., Sjodin, A. & Bergman, A. (2003) An overview of commercially used brominated flame retardants, their applications, their use patterns in different countries/ regions and possible modes of release. *Environ. Int.*, **29** (6), 683–689.

Andersson, Ö. & Blomkvist, G. (1981) Polybrominated aromatic pollutants found in fish in Sweden. *Chemosphere*, **10**, 1051–1060.

Andrade, A.J.M., Kuriyama, S.N., Akkoc, Z., Talsness, C. & Chahoud, I. (2004) Effects of low dose PBDE 47 exposure on thyroid hormone status and serum concentrations of FSH and inhibin B in male rats. *Organohalogen Compd.*, **66**, 3907–3912.

Ashizuka, Y., Nakagawa, R., Hori, T., Tobiishi, K. & Iida, T. (2004) Levels of polybrominated diphenyl ethers and polybrominated dioxins in fish, total diet study food groups and Japanese meals. *Organohalogen Compd.*, **66**, 2553–2559.

Asplund, L., Athanasiadou, M., Sjödin, A., Bergman, A. & Börjeson, H. (1999) Organohalogen substances in muscle, egg and blood from healthy Baltic salmon (*Salmo salar*) and Baltic salmon that produce offspring with the M74 syndrome. *Ambio*, **28**, 67–76.

ATSDR (2004) *Toxicological Profile for Polybrominated Biphenyls and Polybrominated Diphenyl Ethers.* Atlanta, Georgia: United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

Bahn, A.K., Mills, J.L., Snyder, P.J., Gann, P.H., Houten, L., Bialik, O., Hollmann, L. & Utiger, R.D. (1980) Hypothyroidism in workers exposed to polybrominated biphenyls. *N. Engl. J. Med.*, **302** (1), 31–33.

Ballschmitter, K.H. & Zell, M. (1980) Analysis of polychlorinated biphenyls (PCBs) by glass capillary chromatography. *Fresenius Z. Anal. Chem.*, **302**, 20–31.

Baumann, B., Hijman, W., van Beuzekom, S., Hoogerbrugge, R., Houweling, D. & Zeilmaker, M. (2003) PBDEs in human milk from the Dutch 1998 monitoring programme. *Organohalogen Compd.*, **61**, 187–190.

Behnisch, P.A., Hosoe, K. & Sakai, S.I. (2003) Brominated dioxin-like compounds: in vitro assessment in comparison to classical dioxin-like compounds and other polyaromatic compounds. *Environ. Int.*, **29**, 861–877.

BFRIP (1990) *Brominated Flame Retardants. A Review of Recent Research.* Arlington, Virginia: Brominated Flame Retardant Industry Panel (Unpublished Report No. III/4143//90). As cited in IPCS (1994).

BIBRA (1977) *BIBRA Report.* Surrey: British Industrial Biological Research Association (Project No. 193/1/77).

Björklund, J., Tollbäck, P. & Österman, C. (2003) Evaluation of the gas chromatographic column system for the determination of polybrominated diphenyl ethers. *Organohalogen Compd.*, **63**, 361–364.

Bocio, A., Llobet, J.M., Domingo, J.L., Corbella, J., Teixido, A. & Casas, C. (2003) Polybrominated diphenyl ethers (PBDEs) in foodstuffs: human exposure through the diet. *J. Agric. Food Chem.*, **51** (10), 3191–3195.

Boon, J.P., Lewis, W.E., Tjoen-A-Choy, M.R., Allchin, C.R., Law, R.J., de Boer, J., Ten Hallers-Tjabbes, C.C. & Zegers, B.N. (2002) Levels of polybrominated diphenyl ether (PBDE) flame retardants in animals representing different trophic levels of the North Sea food web. *Environ. Sci. Technol.*, **36** (19), 4025–4032.

Branchi, I., Alleva, E. & Costa, L.G. (2002) Effects of perinatal exposure to a polybrominated diphenyl ether (PBDE 99) on mouse neurobehavioural development. *Neurotoxicology*, **23**, 375–384.

Breslin, W.J., Kirk, H.D. & Zimmer, M.A. (1989) Teratogenic evaluation of a polybromodiphenyl oxide mixture in New Zealand white rabbits following oral exposure. *Fundam. Appl. Toxicol.*, **12** (1), 151–157.

BSEF (2003) *Major Brominated Flame Retardants Volume Estimates.* Bromine Science and Environmental Forum (http://www.bsef-site.com).

Buitenhuis, C., Cenijn, P.C., van Velzen, M., Lilienthal, H., Malmberg, T., Bergman, Å., Gutleb, A.C., Legler, J. & Brouwer, A. (2004) Effects of prenatal exposure to hydroxylated PCB metabolites and some brominated flame retardants on the development of rats. *Organohalogen Compd.*, **66**, 3586–3592.

Burreau, S., Broman, D. & Zebuhr, Y. (1999) *Biomagnification Quantification of PBDEs in Fish Using Stable Nitrogen Isotope.* Poster presentation at the 19th International Symposium on Halogenated Environmental Organic Pollutants and POPs, 12–17 September 1999, Venice.

CAC (2003) *Report of the Thirty-fifth Session of the Codex Committee on Food Additives and Contaminants, Arusha, Tanzania, 17–21 March 2003.* Rome: Food and Agriculture Organization of the United Nations, Codex Alimentarius Commission (ALINORM 03/12A; http://www.codexalimentarius.net/web/archives.jsp?year=03).

Capen, C.C. (1997) Mechanistic data and risk assessment of selected toxic end points of the thyroid gland. *Toxicol. Pathol.*, **25** (1), 39–48.

Carlson, G.P. (1980a) Induction of xenobiotic metabolism in rats by brominated diphenyl ethers administered for 90 days. *Toxicol. Lett.*, **6**, 207–212.

Carlson, G.P. (1980b) Induction of xenobiotic metabolism in rats by short-term administration of brominated diphenyl ethers. *Toxicol. Lett.*, **5**, 19–25.

Ceccatelli, S. (2004) *Effects of Polybrominated Diphenyl Ether (PBDE) and PCB on the Development of Reproductive Organs and Estrogen-Regulated Gene Expression in the Rat* [Ph.D. thesis]. Zurich: University of Zurich.

Cheek, A.O., Kow, K., Chen, J. & McLachlan, J.A. (1999) Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor transthyretin and thyroid-binding globulin. *Environ. Health Perspect.*, **107**, 273–278.

Chen, G. & Bunce, N.J. (2003) Polybrominated diphenylethers as Ah receptor agonists and antagonists. *Toxicol. Sci.*, **76**, 310–320.

Chen, G., Konstantinov, A.D., Chittim, B.G., Joyce, E.M., Bols, N.C. & Bunce, N.J. (2001) Synthesis of polybrominated diphenylethers and their capacity to induce CYP1A1 by the Ah receptor mediated pathway. *Environ. Sci. Technol.*, **35**, 3749–3756.

Choi, J.W., Fujimaki, S., Kitamura, K., Hashimoto, S., Ito, H., Suzuki, N., Sakai, S.I. & Morita, M. (2002) Polybrominated dibenzo-*p*-dioxins (PBDDs), dibenzofurans (PBDFs) and diphenylethers (PBDEs) in Japanese human adipose tissue. *Organohalogen Compd.*, **58**, 169–171.

Christensen, J.H., Glasius, M., Pecseli, M., Platz, J. & Pritzl, G. (2002) Polybrominated diphenyl ethers (PBDEs) in marine fish and blue mussels from southern Greenland. *Chemosphere*, **47** (6), 631–638.

Chui, Y.C., Hansell, M.M., Addison, F. & Law, F.C.P. (1985) Effects of chlorinated diphenyl ethers on the mixed-function oxidases and ultrastructure of rat and trout liver. *Toxicol. Appl. Pharmacol.*, **81**, 287–294.

CMA (1996) *Chromosome Aberrations in Human Peripheral Blood Lymphocytes*. Rockville, Maryland: Microbiological Associates Inc. (Study No. G96A063.342; Chemical Manufacturers Association).

Covaci, A. & Schepens, P. (2001) Simplified method for determination of organochlorine pollutants in human serum by solid-phase disk extraction and gas chromatography. *Chemosphere*, **43** (4–7), 439–447.

Covaci, A., de Boer, J., Ryan, J.J., Voorspoels, S. & Schepens, P. (2002a) Distribution of organobrominated and organochlorinated contaminants in Belgian human adipose tissue. *Environ. Res.*, **88** (3), 210–218.

Covaci, A., de Boer, J., Ryan, J.J., Voorspoels, S. & Schepens, P. (2002b) Determination of polybrominated diphenyl ethers and polychlorinated biphenyls in human adipose tissue by large-volume injection-narrow-bore capillary gas chromatography/electron impact low-resolution mass spectrometry. *Anal. Chem.*, **74** (4), 790–798.

Crhova, S., Cerna, M., Grabic, R., Tomsey, T. & Ocelka, T. (2002) Polybrominated flame retardants in human adipose tissue in Czech Republic inhabitants. The pilot study. *Organohalogen Compd.*, **58**, 241–244.

Crofton, K.M., Taylor, M.M., Hedge, J.M., Gilbert, M.E. & DeVito, M.J. (2003) Developmental exposure to polybrominated diphenyl ethers; disruption of thyroid homeostasis, hepatic metabolism and neurobehavioral development. In: *9th Meeting of the International Neurotoxicology Association, Dresden*, Abstract 65, p. 65 (http://www.neurotoxicology.org).

CVUA (2001) *Annual Report (2001)*. Chemisches und Veterinaruntersuchungsamt Freiburg.

Darnerud, P.O. & Risberg, S. (2005) Tissue localization of tetra- and pentabromodiphenyl ether congeners (BDE-47, -85 and -100) in perinatal and adult C57BL mice. *Chemosphere* (in press).

Darnerud, P.O., Atuma, S., Aune, M., Cnattingius, S., Wernroth, M.L. & Wicklund-Glynn, A. (1998a) Polybrominated diphenyl ethers (PBDEs) in breast milk from primiparous women in Uppsala County, Sweden. *Organohalogen Compd.*, **35**, 411–414.

Darnerud, P.O., Eriksen, G., Johannesson, T., Larsen, P. & Viluksela, M. (1998b) *Polybrominated Diphenyl Ethers: Food Contamination and Potential Risks.* Copenhagen: Nordic Council of Ministers (Thema Nord 503).

Darnerud, P.O., Atuma, S., Aune, M., Becker, W., Wicklund-Glynn, A. & Petersson-Grewe, K. (2000) New Swedish estimate on dietary intake of PBDE (a brominated flame retardant), dioxins, PCBs and DDT derived from market basket data. *Toxicol. Lett.*, **116** (Suppl.), 28 (abstract).

Darnerud, P.O., Eriksen, G., Johannesson, T., Larsen, P. & Viluksela, M. (2001) Polybrominated diphenyl ethers: occurrence, dietary exposure, and toxicology. *Environ. Health Perspect.*, **109** (Suppl. 1), 49–68.

Darnerud, P.O., Aune, M., Larsson, L. & Hallgren, S. (2004) Serum PBDE levels in exposed rats in relation to effects on thyroxine homeostasis. *Organohalogen Compd.*, **66**, 3977–3981.

Dead Sea Bromide Works (1984) *Penta-bromo-diphenyl-ether. Assessment of Its Mutagenic Potential in Histidine Auxotrophs of* Salmonella typhimurium. Life Sciences Research Ltd. (Unpublished Report No. 84/DSB006/064). As cited in EU (2001).

de Boer, J. & Denneman, M. (1998) Polychlorinated diphenylethers: origin, analysis, distribution, and toxicity in the marine environment. *Rev. Environ. Contam. Toxicol.*, **157**, 131–144.

de Boer, J., van der Zande, T.E., Pieters, H., Ariese, F., Schipper, C.A., van Brummelen, T. & Vethaak, A.D. (2001) Organic contaminants and trace metals in flounder liver and sediment from the Amsterdam and Rotterdam harbours and off the Dutch coast. *J. Environ. Monit.*, **3** (4), 386–393.

De Felip, E., Päpke, O., Herrmann, T., Cardelli, M., Ingelido, A.M., Porpora, M.G. & di Domenico, A. (2003) PBDE levels in Italian nulliparous women of reproductive age. *Organohalogen Compd.*, **61**, 287–290.

de Winter-Sorkina, R., Bakker, M.I., van Donkersgoed, G. & van Klaveren, J.D. (2003) *Dietary Intake of Brominated Flame Retardants by the Dutch Population.* Bilthoven: National Institute for Public Health and the Environment (RIVM Report 310305001/2003).

de Wit, C.A. (2002) An overview of brominated flame retardants in the environment. *Chemosphere*, **46**, 583–624.

Dodder, N.G., Strandberg, B. & Hites, R.A. (2002) Concentrations and spatial variations of polybrominated diphenyl ethers and several organochlorine compounds in fishes from the northeastern United States. *Environ. Sci. Technol.*, **36** (2), 146–151.

el Dareer, S.M., Kalin, J.R. & Tillery, K.F. (1987) Disposition of decabromobiphenyl ether in rats dosed intravenously or by feeding. *J. Toxicol. Environ. Health*, **22**, 405–415.

Eriksson, P. & Talts, U. (2000) Neonatal exposure to neurotoxic pesticides increases adult susceptibility: a review of current findings. *Neurotoxicology*, **21** (1–2), 37–47.

Eriksson, P., Jakobsson, E. & Fredriksson, A. (2001) Brominated flame retardants: A novel class of developmental neurotoxicants in our environment? *Environ. Health Perspect.*, **109**, 903–908.

Eriksson, P., Viberg, H., Jakobsson, E., Örn, U. & Fredriksson, A. (2002) A brominated flame retardant, 2,2'4,4',5-pentabromodiphenyl ether: uptake, retention, and induction of neurobehavioral alterations in mice during a critical phase of neonatal brain development. *Toxicol. Sci.*, **67**, 98–103.

Eriksson, P., Johansson, N., Viberg, H., Fischer, C. & Fredriksson, A. (2004) Comparative developmental neurotoxicity of flame retardants, polybrominated flame retardants and organophosphorous compounds, in mice. *Organohalogen Compd.*, **66**, 3163–3165.

Ethyl Corporation (1985) *Embryo/Fetal Toxicity and Teratogenic Potential of Saytex 115 Administered Orally Via Gavage to Sprague-Dawley Rats, Presumed Pregnant Rats.* Horsham, Pennsylvania: Argus Research Laboratories Inc. (Protocol No. 305-002).

EU (2001) *European Union Risk Assessment Report: Pentabromophenyl (Diphenyl Ether, Pentabromo Derivative; CAS No. 32534-81-9.* Brussels: European Union.

EU (2003) *European Union Risk Assessment Report: Diphenyl Ether, Octabromo Derivative. CAS No: 32536-52-0, EINECS No: 251-087-9.* Brussels: European Union.

EU (2004) *European Union Risk Assessment Report: Update of the Risk Assessment Addendum of Bis(pentabromophenyl)ether.* Brussels: European Union.

Evandri, M.G., Mastrangelo, S., Costa, L.G. & Bolle, P. (2003) In vitro assessment of mutagenicity and clastogenicity of BDE-99, a pentabrominated diphenyl ether flame retardant. *Environ. Mol. Mutagen.*, **42** (2), 85–90.

Fängström, B., Strid, A., Athanassiadis, I., Grandjean, P., Weihe, P. & Bergman, Å. (2004a) A retrospective study of PBDEs in human milk from the Faroe Islands. In: *The Third International Workshop on Brominated Flame Retardants.* BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 33–36 (http://www.bfr2004.com).

Fängström, B., Strid, A., Athanassiadis, I., Grandjean, P., Weihe, P. & Bergman, Å. (2004b) A retrospective time trend study of PBDEs and PCBs in human milk from the Faroe Islands. *Organohalogen Compd.*, **66**, 2829–2833.

Fattore, E., Filipsson, A., Hanberg, A., Bergendorff, A. & Håkansson, H. (2001) Toxicity of a technical mixture of polybrominated diphenyl ethers following 28 days of oral exposure in male and female rats. *Organohalogen Compd.*, **53**, 357–360.

Fernlof, G., Gadhasson, I., Podra, K., Darnerud, P.O. & Thuvander, A. (1997) Lack of effects of some individual polybrominated diphenyl ether (PBDE) and polychlorinated biphenyl (PCB) congeners on human lymphocyte functions in vitro. *Toxicol. Lett.*, **90** (2–3), 189–197.

Food Standards Australia New Zealand (2004) Submission to JECFA: *Individual Dietary Records Approach: PBDEs.* Australian National Nutrition Survey (Information Sheet 4).

Fowles, J.R., Fairbrother, A., Baecher-Steppan, L. & Kerkvliet, N. (1994) Immunologic and endocrine effects of the flame-retardant pentobromodiphenyl ether (DE-71) in C57BL/6J mice. *Toxicology*, **86**, 49–61.

Fürst, P. (2001) Organochlorine pesticides, dioxins, PCBs and polybrominated biphenyl ethers in human milk from Germany in the course of time. *Organohalogen Compd.*, **52**, 185–188.

Garner, C.E. & Matthews, H.B. (1998) The effect of chlorine substitution on the dermal absorption of polychlorinated biphenyls. *Toxicol. Appl. Pharmacol.*, **149** (2), 150–158.

Gilbert, M.E., Sui, I. & Crofton, K.M. (2004) Developmental exposure to polybrominated diphenyl ethers impairs synaptic transmission and LTP in hippocampus. *Toxicologist*, **78** (1-S), 1915.

Gill, U., Chu, I., Ryan, J.J. & Feeley, M. (2004) Polybrominated diphenyl ethers: human tissue levels and toxicology. *Rev. Environ. Contam. Toxicol.*, **182**, 55–96.

Gillner, M. & Jakobsson, E. (1996) Structure–affinity relationships for thyroid and dioxin receptor binding of halogenated naphthalenes and diphenylethers. *Organohalogen Compd.*, **29**, 220–221.

Gold, L.S., Slone, T.H., Stern, B.R., Manley, N.B. & Ames, B.N. (1992) Rodent carcinogens: setting priorities. *Science*, **258**, 261–265.

Great Lakes (1974) *Toxicity Data on DBDPO (DE-83). Acute Oral Toxicity in the Albino Rat.* Prepared by International Research and Development Corporation for Great Lakes Chemical Corporation.

Great Lakes (1975) *Acute Toxicity Studies of Pentabromodiphenyl Ether, 345-76A in Rats and Rabbits.* Prepared by International Research and Development Corporation for Great Lakes Chemical Corporation (Report No. 2764-025).

Great Lakes (1986) *Toxicity Data of Octabromo-diphenyloxide (DE-79). A Range Finding Teratology Study in Rats with DE-79. Final Report.* Hazelton Laboratories, prepared for Great Lakes Chemical Corporation. As cited in EU (2003).

Great Lakes (1987) *Toxicity Data of Octabromo-diphenyloxide (DE-79).* West Lafayette, Indiana: Great Lakes Chemical Corporation. As cited in IPCS (1994).

Great Lakes (1990) *Great Lakes DE-79. Product Information.* West Lafayette, Indiana: Great Lakes Chemical Corporation. As cited in IPCS (1994).

Great Lakes (1999) *Toxicity Data of Octabromo-diphenyloxide (DE-79). In Vitro Mammalian Chromosome Aberration Test. Final Report.* Prepared by BioReliance for Great Lakes Chemical Corporation. As cited in EU (2003).

Haglund, P.S., Zook, D.R., Buser, H.-R. & Hu, J. (1997) Identification and quantification of polybrominated diphenyl ethers and methoxy-polybrominated diphenyl ethers in Baltic biota. *Environ. Sci. Technol.*, **31** (11), 3281–3287.

Hagmar, L., Sjödin, A., Höglund, P., Thuresson, K., Rylander, L. & Bergman, Å. (2000) Biological half-lives of polybrominated diphenylethers and tetrabromobisphenol A in exposed workers. *Organohalogen Compd.*, **47**, 198–201.

Hagmar, L., Bjork, J., Sjodin, A., Bergman, A. & Erfurth, E.M. (2001) Plasma levels of persistent organohalogens and hormone levels in adult male humans. *Arch. Environ. Health*, **56** (2), 138–143.

Hakk, H. & Letcher, R.J. (2003) Metabolism in the toxicokinetics and fate of brominated flame retardants — a review. *Environ. Int.*, **29** (6), 801–828.

Hakk, H., Huwe, J.K. & Lorentzsen, M. (2001) A mass balance study of a commercial pentabromodiphenyl ether mixture in male Sprague-Dawley rats. *Organohalogen Compd.*, **52**, 5–8.

Hakk, H., Larsen, G.L. & Klasson-Wehler, E. (2002) Tissue disposition, excretion, and metabolism of 2,2',4,4',5-pentabromodiphenyl ether (BDE-99) in male Sprague-Dawley rats. *Xenobiotica*, **32**, 369–382.

Hale, R.C., La Guardia, M.J., Harvey, E.P., Gaylor, M.O., Mainor, T.M. & Duff, W.H. (2001) Flame retardants. Persistent pollutants in land-applied sludges. *Nature*, **412** (6843), 140–141.

Hallgren, S. & Darnerud, P.O. (1998) Effects of polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) on thyroid hormone levels and enzyme activities in rats. *Organohalogen Compd.*, **35**, 391–394.

Hallgren, S. & Darnerud, P.O. (2002) Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats — testing interactions and mechanisms for thyroid hormone effects. *Toxicology*, **177** (2–3), 227–243.

Hallgren, S., Sinjari, T., Hakansson, H. & Darnerud, P.O. (2001) Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. *Arch. Toxicol.*, **75**, 200–208.

Hanberg, A., Ståhlberg, M., Georgellis, A., de Wit, C. & Ahlborg, U. (1991) Swedish dioxin survey: evaluation of the H-4IIE bioassay for screening environmental samples for dioxin-like enzyme induction. *Pharmacol. Toxicol.*, **69**, 442–449.

Hardell, L., Lindström, G., van Bavel, B., Wingfors, H., Sundelin, E. & Liljegren, G. (1998) Concentrations of the flame retardant 2,2',4,4'-tetrabrominated diphenyl ether in human adipose tissue in Swedish persons and the risk for non-Hodgkin's lymphoma. *Oncol. Res.*, **10**, 429–432.

Hardell, L., Eriksson, M., Lindström, G., van Bavel, B., Lind, A., Carlberg, M. & Liljegren, G. (2001) Case–control study on concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens in the etiology of non-Hodgkin lymphoma. *Leuk. Lymphoma*, **42**, 619–629.

Harden, F., Toms, L.M., Ryan, J.J. & Müller, J. (2004) Determination of the levels of polybrominated diphenylethers (PBDEs) in pooled blood sera obtained from Australians aged 31–45 years. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 59–62 (http://www.bfr2004.com).

Hardy, M.L., Schroeder, R., Biesemeier, J. & Manor, O. (2002) Prenatal oral (gavage) developmental toxicity study of decabromodiphenyl oxide in rats. *Int. J. Toxicol.*, **21**, 83–91.

Harrad, S., Wijesekera, R., Hunter, S., Halliwell, C. & Baker, R. (2004) Preliminary assessment of U.K. human dietary and inhalation exposure to polybrominated diphenyl ethers. *Environ. Sci. Technol.*, **38**, 2345–2350.

Health Canada (2004a) *Concentrations (ppt, based on wet wt.) of Polybrominated Biphenyl Ethers (PBDEs) from Total Diet Study in Whitehorse, 1998.* Ottawa, Ontario: Health Canada, Food Program (http://www.hc-sc.gc.ca/food-aliment/cs-ipc/fr-ra/e_pbde_conc_whitehorse98.html).

Health Canada (2004b) *Concentrations (ppt, based on wet wt.) of Polybrominated Biphenyl Ethers (PBDEs) from Total Diet Study in Vancouver, 2002.* Ottawa, Ontario: Health Canada, Food Program (http://www.hc-sc.gc.ca/food-aliment/cs-ipc/fr-ra/e_pbde_conc_vancouver2002.html).

Health Canada (2004c) *Fish and Seafood Survey — 2002.* Ottawa, Ontario: Health Canada, Food Program (http://www.hc-sc.gc.ca/food-aliment/cs-ipc/fr-ra/e_seafood_survey.html).

Health Canada (2004d) *Dietary Intakes of Polybrominated Diphenyl Ethers (PBDEs) for All Ages Canadians from Total Diet Study in Whitehorse, 1998.* Ottawa, Ontario: Health Canada, Food Program (http://www.hc-sc.gc.ca/food-aliment/cs-ipc/fr-ra/e_pbde_intake_whitehorse98.html).

Health Canada (2004e) *Dietary Intakes of Polybrominated Diphenyl Ethers (PBDEs ) for All Ages Canadians from Total Diet Study in Vancouver, 2002.* Ottawa, Ontario: Health Canada, Food Program (http://www.hc-sc.gc.ca/food-aliment/cs-ipc/fr-ra/e_pbde_intake_vancouver2002.html).

Health Canada (2004f) *Screening Assessment Report. Polybrominated Diphenyl Ethers (PBDEs) (Tetra-, Penta-, Hexa-, Hepta-, Octa-, Nona- and Deca-Congeners) (CAS Nos. 40088-47-9, 32534-81-9, 36483-60-0, 68928-80-3,32536-52-0, 63936-56-1, 1163-19-5).* Ottawa, Ontario: Health Canada, Existing Substances Division (http://www.ec.gc.ca/CEPARegistry/documents/subs_list/HC_PBDEs_f.pdf).

Hedge, J.M., Crofton, K.M., Laws, S.C., DeVito, M.J., Ross, D.G. & Das, P.C. (2004) 2,2'4,4'-Tetrabromodiphenyl ether (PBDE-47) alters thyroid function in rats. *Toxicologist*, **78** (1-S), 1909.

Helleday, T., Tuominen, K.L., Bergman, A. & Jenssen, D. (1999) Brominated flame retardants induce intragenic recombination in mammalian cells. *Mutat. Res.*, **439** (2), 137–147.

Herrmann, T., Schilling, B. & Päpke, O. (2003) Photolysis of PBDEs in solvents by exposure to daylight in routine laboratory procedure. *Organohalogen Compd.*, **63**, 361–364.

Herzke, D., Kallenborn, R., Nygard, T. & Sandanger, T. (2001) Species dependent distribution of polybrominated biphenyls and diphenylethers in eggs of Norwegian birds of prey. In: *The Second International Workshop on Brominated Flame Retardants.* BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, pp. 321–324.

Hirai, T., Fujimine, Y., Watanabe, S., Hata, J. & Watanabe, S. (2003) Concentration of polybrominated diphenyl ethers (PBDEs) in human samples in Japan. *Organohalogen Compd.*, **61**, 51–154.

Hites, R. (2004) Polybrominated diphenyl ethers in the environment and in people: a meta-analysis of concentrations. *Environ. Sci. Technol.*, **38** (4), 945–956.

Hites, R., Foran, J., Schwager, S., Knuth, B., Hamilton, C. & Carpenter, D. (2004) Global assessment of polybrominated diphenyl ethers in farmed and wild salmon. *Environ. Sci. Technol.*, **38** (19), 4945–4949.

Holden, A., She, J., Tanner, M., Lunder, S., Sharp, R. & Hooper, K. (2003) PBDEs in San Francisco Bay area: measurements in fish. *Organohalogen Compd.*, **61**, 255–258.

Howie, L., Dickerson, R., Davis, D. & Safe, S. (1990) Immunosuppressive and monooxygenase induction activities of polychlorinated diphenyl ether congeners in C57BL/6N mice: quantitative structure–activity relationships. *Toxicol. Appl. Pharmacol.*, **105**, 254–263.

Huwe, J. (2004) Polybrominated diphenyl ethers in meat samples collected from supermarkets across the US. In: *The Third International Workshop on Brominated Flame Retardants.* BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 41–44 (http://www.bfr2004.com).

Huwe, J.K., Hakk, H. & Lorentzsen, M. (2002) A mass balance feeding study of a commercial octabromodiphenyl ether mixture in rats. *Organohalogen Compd.*, **58**, 229–232.

IARC (1990) Decabromodiphenyl oxide. In: *Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry.* Lyon: International Agency for Research on Cancer, pp. 73–84 (IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Vol. 48).

Ikonomou, M.G., Rayne, S., Fischer, M., Fernandez, M.P. & Cretney, W. (2002) Occurrence and congener profiles of polybrominated diphenyl ethers (PBDEs) in environmental samples from coastal British Columbia, Canada. *Chemosphere*, **46** (5), 649–663.

Ingelido, A.M., Di Domenico, A., Ballard, T., De Felip, E., Dellatte, E., Ferri, F., Fulgenzi, A.R., Herrmann, T., Iacovella, N., Minero, R., Päpke, O. & Porpora, M. (2004) Levels of polybrominated diphenyl-ethers in milk from Italian women living in Rome and Venice. *Organohalogen Compd.*, **66**, 2722–2728.

IPCS (1994) *Brominated Diphenyl Ethers.* Geneva: World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 162).

IPCS (1997) *Flame Retardants: A General Introduction.* Geneva: World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 192).

IRDC (1976) *Decabromodiphenyl Ether and Octabromodiphenyl Ether. A 28-Day Toxicity Study in Rats.* Submitted by the International Research and Development Corporation to the United States Environmental Protection Agency under TSCA Section 8D (OTS0523322).

IRDC (1977) *Octabromodiphenyl Ether. Thirteen Week Feeding Study in Rats.* Submitted by the International Research and Development Corporation to the United States Environmental Protection Agency under TSCA Section 8D (OTS0522297).

ISCCL (1977) *Tardex 50 Ames Test.* Unpublished report, Consultox Laboratories Inc. I.S.C. Chemicals Limited (Project No. CL 77:178). As cited in EU (2001).

Jackson, J.A., Diliberto, J.J. & Birnbaum, L.S. (1993) Estimation of octanol–water partition coefficients and correlation with dermal absorption for several polyhalogenated aromatic hydrocarbons. *Fundam. Appl. Toxicol.*, **21**, 334–344.

Jacobs, M., Covaci, A. & Schepens, P. (2002) Investigation of selected persistent organic pollutants in farmed Atlantic salmon (*Salmo salar*), salmon aquaculture feed, and fish oil compartments of feed. *Environ. Sci. Technol.*, **36**, 2797–2805.

Jansson, B., Anderson, R., Asplund, L., Bergman, A., Litzen, K., Reutergardh, L., Sellstrom, U., Uvemo, U.-B., Wahlberg, C. & Wideqvist, U. (1991) Multiresidue method for the gas-chromatographic analysis of some polychlorinated and polybrominated pollutants in biological samples. *Fresenius Z. Anal. Chem.*, **340**, 439–445.

Johansson, F., Allkvist, A., Erixon, K., Malmvarn, A., Nilsson, R., Bergman, A., Helleday, T. & Jenssen, D. (2004) Screening for genotoxicity using the DRAG assay: investigation of halogenated environmental contaminants. *Mutat. Res.*, **563** (1), 35–47.

Johnson, A. & Olson, N. (2001) Analysis and occurrence of polybrominated diphenyl ethers in Washington state freshwater fish. *Arch. Environ. Contam. Toxicol.*, **41** (3), 339–344.

Jones-Otazo, H.A., Clarke, J.P., Diamond, M.L., Archbold, J.A., Ferguson, G., Harner, T., Richardson, G.M., Ryan, J.J. & Wilford, B. (2005) Is house dust the missing exposure pathway for PBDEs? An analysis of the urban fate and human exposure to PBDEs. *Environ. Sci. Technol.*, **39** (14), 5121–5130.

Kalantzi, O.I., Martin, F.L., Thomas, G.O., Alcock, R.E., Tang, H.R., Drury, S.C., Carmichael, P.L., Nicholson, J.K. & Jones, K.C. (2004) Different levels of polybrominated diphenyl ethers (PBDEs) and chlorinated compounds in breast milk from two U.K. regions. *Environ. Health Perspect.*, **112** (10), 1085–1091.

Kalk (1978) *Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of Bromkal 70-5 DE.* Unpublished report, Huntington Research Centre. Chemische Fabrik Kalk GmbH (Report No. 86-9000004000). As cited in EU (2001).

Kalk (1982) *CFK Bromkal® Branschutz Ausrustungen.* Chemische Fabrik Kalk GmbH (Information Sheet No. 3000-7/82). As cited in IPCS (1994).

Kato, Y., Ikushiro, S., Haraguchi, K., Yamazaki, T., Ito, Y., Suzuki, H., Kimura, R., Yamada, S., Inoue, T. & Degawa, M. (2004) A possible mechanism for decrease in serum thyroxine level by polychlorinated biphenyls in Wistar and Gunn rats. *Toxicol. Sci.*, **81**, 309–315.

Khera, K.S. (1984) Maternal toxicity — a possible factor in fetal malformations in mice. *Teratology*, **29** (3), 411–416.

Kiviranta, H., Ovaskainen, M.L. & Vartiainen, T. (2004) Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. *Environ. Int.*, **30**, 923–932.

Klasson-Wehler, E., Mörck, A. & Hakk, H. (2001) Metabolism of polybrominated diphenyl ethers in the rat. In: *The Second International Workshop on Brominated Flame Retardants.* BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, pp. 93–97.

Knoth, W., Mann, W., Meyer, R. & Nebhut, J. (2002) Polybrominated diphenyl ethers in house dust. *Organohalogen Compd.*, **58**, 213–216.

Knoth, W., Mann, W., Meyer, R. & Nebhut, J. (2003) Polybrominated diphenyl ethers in indoor dust. *Organohalogen Compd.*, **61**, 207–210.

Kociba, R.J., Frauson, L.O., Humiston, C.G., Norris, J.M., Wade, C.E., Lisowe, R.W., Quast, J.F., Jersey, G.C. & Jewett, G.L. (1975) Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. *J. Combust. Toxicol.*, **2**, 267–285.

Kodavanti, P.R.S. & Derr-Yellin, E.C. (2002) Differential effects of polybrominated diphenyl ethers and polychlorinated biphenyls on [$^3$H]arachidonic acid release in rat cerebellar granule neurons. *Toxicol. Sci.*, **68**, 451–457.

Koistinen, J., Sanderson, J.T., Giesy, J.P., Nevalainen, T. & Paasivirta, J. (1996) Ethoxyresorufin-*O*-deethylase induction potency of polychlorinated diphenyl ethers in H4IIE rat hepatoma cells. *Environ. Toxicol. Chem.*, **15**, 2028–2034.

Körner, W. & Hagenmaier, H. (1990) PCDD/PCDF formation in smoked, fried and broiled meat and fish. *Organohalogen Compd.*, **4**, 243–248.

Kuriyama, S.N., Talsness, C., Wittfohr, W. & Chahoud, I. (2004a) Exposure to an environmentally relevant dose of PBDE 99 disrupts thyroid hormone homeostasis and causes neurobehavior disturbances in rat offspring. *Toxicologist*, **78** (1-S), 1908.

Kuriyama, S.N., Fidalgo-Nieto, A.A., Grande, S.W., Akkoc, Z., de Souza, C.A.M. & Chahoud, I. (2004b) Thyroid hormone levels and hepatic enzyme activity in lactating dams after gestational exposure to low dose PBDE 47. *Organohalogen Compd.*, **66**, 3901–3906.

Kuriyama, S.N., Talsness, C. & Chahoud, I. (2004c) Sex-dependent behavioral changes in rat offspring after in utero administration of a single low dose PBDE 47. *Organohalogen Compd.*, **66**, 3893–3900.

Kuriyama, S.N., Talsness, C.E., Grote, K. & Chahoud, I. (2005) Developmental exposure to low dose PBDE 99: 1. Effects on male fertility and neurobehavior in rat offspring. *Environ. Health Perspect.*, **113** (2),149–154.

Lee, S.-J., Kim, B., Kim, H. & Chang, Y.-S. (2002) Human blood levels of polybrominated diphenylethers in Korea. *Organohalogen Compd.*, **58**, 205–208.

Leonards, P., Santillo, D., Bridgen, K., van der Veen, I., Heselingen, J., de Boer, J. & Johnston, P. (2001) Brominated flame retardants in office dust samples. In: *The Second International Workshop on Brominated Flame Retardants.* BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, pp. 299–302.

Lepom, P., Karasyova, T. & Sawal, G. (2002) Occurrence of PBDEs in freshwater fish from Germany. *Organohalogen Compd.*, **58**, 209–212.

Leung, H.-W. & Paustenbach, D.J. (1994) Techniques for estimating the percutaneous absorption of chemicals due to occupational and environmental exposure. *Appl. Occup. Environ. Hyg.*, **9**, 187–197.

Lichtensteiger, W., Ceccatelli, R., Faass, O., Fleischmann, I. & Schlumpf, M. (2003) Effects of PBDE and PCB on neuroendocrine ontogeny and sex hormone target gene expression. In: *9th Meeting of the International Neurotoxicology Association, Dresden*, p. 143 (abstract) (http://www.neurotoxicology.org).

Lichtensteiger, W., Faass, O., Ceccatelli, R. & Schlumpf, M. (2004) Developmental exposure to PBDE 99 and PCB affects estrogen sensitivity of target genes in rat brain regions and female sexual behavior. *Organohalogen Compd.*, **66**, 3965–3970.

Lilienthal, H., Hack, A., Roth-Härer, A., Altmann, L., Winneke, G. & Wiegand, H. (2004) Developmental neurotoxicity of polybrominated diphenyl ethers (PBDE): Steroid-dependent behavior, sexual development and circulating steroids. *Toxicologist*, **78** (1-S), 1905.

Lind, Y., Atuma, S., Aune, M., Bjerselius, R., Darnerud, P.O., Cnattingius, S. & Glynn, A. (2001) Polybrominated diphenyl ethers (PBDEs) in breast milk from Uppsala women — extension and updating of data. In: *The Second International Workshop on Brominated*

*Flame Retardants*. BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, p. 222.

Lind, Y., Aune, M., Atuma, S., Besker, W., Gjerselius, R., Glynn, A. & Darnerud, P.O. (2002) Food intake of the brominated flame retardants PBDEs and HBCD in Sweden. *Organohalogen Compd.*, **58**, 181–184.

Lind, Y., Darnerud, P.O., Atuma, S., Aune, M., Becker, W., Bjerselius, R., Cnattingius, S. & Glynn, A. (2003) Polybrominated diphenyl ethers in breast milk from Uppsala County, Sweden. *Environ. Res.*, **93** (2), 186–194.

Lopez, D., Athanasiadou, M., Athanssiadis, I., Estrada, L. & Bergmann, A. (2004) A preliminary study on PBDEs and HBCDD in blood and milk from Mexican women. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 483–487 (http://www.bfr2004.com).

Luksemburg, W., Wenning, R., Patterson, A. & Meier M. (2004) Levels of polybrominated diphenyl ethers (PBDEs) in fish, beef and fowl purchased in food markets in northern California, USA. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 479–482 (http://www.bfr2004.com).

Lunder, S. & Sharp, R. (2003) *Mothers' Milk: Record Levels of Toxic Fire Retardants Found in American Mothers' Breast Milk*. Washington, D.C.: Environmental Working Group (http://www.ewg.org/reports_content/mothersmilk/pdf/mothersmilk_final.pdf).

Luross, J.M., Alaee, M., Sergeant, D.B., Cannon, C.M., Whittle, D.M., Solomon, K.R. & Muir, D.C. (2002) Spatial distribution of polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Laurentian Great Lakes. *Chemosphere*, **46** (5), 665–672.

Madina, F., Giordano, G., Fattori, V., Vitalone, A., Branchi, I., Capone, F. & Costa, L.G. (2004) Differential in vitro neurotoxicity of the flame retardant PBDE-99 and of the PCB Aroclor 1254 in human astrocytoma cells. *Toxicol. Lett.*, **154**, 11–21.

Manchester-Neesvig, J.B., Valters, K. & Sonzogni, W.C. (2001) Comparison of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in Lake Michigan salmonids. *Environ. Sci. Technol.*, **35** (6), 1072–1077.

Mariussen, E. & Fonnum, F. (2003) The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. *Neurochem. Int.*, **43**, 533–542.

Marsh, G., Bergman, A., Bladh, L.G., Gillner, M. & Jakobsson, E. (1998) Synthesis of *p*-hydrobromodiphenyl ethers and binding to the thyroid receptor. *Organohalogen Compd.*, **37**, 305–308.

Mayer, R. (1998) Polychlorinated dibenzo-*p*-dioxins and dibenzofurans in smoked meat products. *Organohalogen Compd.*, **38**, 139–142.

Mayer, R. & Jahr, D. (1998) *Lebensmittelchemie*, **52**, 100–104.

McDonald, T.A. (2004) Distribution of PBDE levels among U.S. women: estimates of daily intake and risk of developmental effects. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 443–446 (http://www.bfr2004.com).

McGregor, D.B. (1992) Chemicals classified by IARC: their potency in tests for carcinogenicity in rodents and their genotoxicity and acute toxicity. In: Vainio, H., Magee, P., McGregor, D.B. & McMichael, A.J., eds., *Mechanisms of Carcinogenesis in Risk Identification*. Lyon, International Agency for Research on Cancer, pp. 323–352 (IARC Scientific Publications No. 116).

Meerts, I.A.T.M., Luijks, E.A.C., Marsh, G., Jakobsson, E., Bergman, Å. & Brouwer, A. (1998) Polybrominated diphenylethers (PBDEs) as Ah-receptor agonists and antagonists. *Organohalogen Compd.*, **37**, 147–150.

Meerts, I.A.T.M., van Zanden, J.J., Luijks, E.A.C., van Leeuwen-Bol, I., Marsh, G., Jakobson, E., Berman, A. & Brouwer, A. (2000) Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin in vitro. *Toxicol. Sci.*, **56**, 95–104.

Meerts, I.A.T.M., Letcher, R.J., Hoving, S., Marsh, G., Bergman, A., Lemmen, J.G., van der Burg, B. & Brouwer, A. (2001) In vitro estrogenicity of polybrominated diphenyl ethers, hydroxylated PBDEs, and polybrominated bisphenol A compounds. *Environ. Health Perspect.*, **109**, 399–407.

Meironyté Guvenius, D. & Norén, K. (2001) Polybrominated diphenyl ethers in Swedish human milk. The follow-up study. In: *The Second International Workshop on Brominated Flame Retardants.* BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, pp. 303–305.

Meironyté Guvenius, D., Bergman, A. & Norén, K. (1998) Analysis of polybrominated diphenyl ethers in human milk. *Organohalogen Compd.*, **35**, 387–390.

Meironyté Guvenius, D., Norén, K. & Bergman, A. (1999) Analysis of polybrominated diphenyl ethers in Swedish human milk. A time-related study, 1972–1997. *J. Toxicol. Environ. Health*, **A58**, 329–341.

Meironyté Guvenius, D., Bergman, A. & Norén, K. (2001) Polybrominated diphenylethers in Swedish human liver and adipose tissue. *Arch. Environ. Contam. Toxicol.*, **40**, 564–570.

Meironyté Guvenius, D., Aronsson, A., Ekman-Ordeberg, G., Bergman, A. & Noren, K. (2003) Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobiphenylols, and pentachlorophenol. *Environ. Health Perspect.*, **111** (9), 1235–1241.

Meneses, M., Wingfors, H., Schuhmacher, J.L., Lindstrom, G. & Bavel, B. (1999) Polybrominated diphenyl ethers detected in human adipose tissue from Spain. *Chemosphere*, **39**, 2271–2273.

Mörck, A. & Klasson-Wehler, E. (2001) Metabolism of decabromodiphenyl ether (BDE-209) in the rat. *Organohalogen Compd.*, **52**, 9–12.

Mörck, A., Hakk, H., Örn, U. & Klasson-Wehler, E. (2003) Decabromodiphenyl ether in the rat — absorption, distribution, metabolism and excretion. *Drug Metab. Dispos.*, **31** (7), 900–907.

Mundy, W.R., Freudenreich, T.M., Crofton, K.M. & De Vito, M.J. (2004) Accumulation of PBDE-47 in primary cultures of rat neocortical cells. *Toxicol. Sci.*, **82**, 164–169.

NAS (2000) *Toxicological Risks of Selected Brominated Flame Retardant Chemicals. Decabromodiphenyl Oxide.* Washington, D.C.: National Academy of Sciences, National Academy Press.

Norén, K. & Meironyté Guvenius, D. (1998) Contaminants in Swedish human milk. Decreasing levels of organochlorine and increasing levels of organobromine compounds. *Organohalogen Compd.*, **358**, 1–4.

Norén, K. & Meironyté Guvenius, D. (2000) Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20–30 years. *Chemosphere*, **40** (9–11), 1111–1123.

Norris, J.M., Ehrmantraut, J.W., Gibbons, C.L., Kociba, R.J., Schwetz, B.A., Rose, J.Q., Humistone, C.G., Jewett, G.L., Crummett, W.B. & Gehring, P.J. (1973) Toxicological

and environmental factors involved in the selection of decabromodiphenyl oxide as a fire retardant chemical. *Appl. Polym. Symp.*, **22**, 195–219.

Norris, J.M., Ehrmantraut, J.W., Kociba, R.J., Schwetz, B.A., Rose, J.Q., Humistone, C.G., Jewett, G.L., Crummet, W.B., Gehring, P.J. & Tirsell, J.B. (1975a) Evaluation of decabromodiphenyl oxide as a flame-retardant chemical. *Chem. Hum. Health Environ.*, **1**, 100–116.

Norris, J.M., Kociba, R.J., Schwetz, B.A., Rose, J.Q., Humiston, C.G., Jewett, G.L., Gehring, P.J. & Mailhes, J.B. (1975b) Toxicology of octabromodiphenyl and decabromodiphenyl oxide. *Environ. Health Perspect.*, **11**, 153–161.

Norstrom, R.J., Simon, M., Moisey, J., Wakeford, B. & Weseloh, D.V. (2002) Geographical distribution (2000) and temporal trends (1981–2000) of brominated diphenyl ethers in Great Lakes herring gull eggs. *Environ. Sci. Technol.*, **36** (22), 4783–4789.

Northwest Environment Watch (2004) *Flame Retardants in Puget Sound Residents. First Round of Results from a Study on Toxic Body Burdens*. Seattle, Washington: Northwest Environment Watch, February (http://www.northwestwatch.org/pollution/WA_PBDEs.pdf).

NTP (1986) *Toxicology and Carcinogenesis Studies of Decabromodiphenyl Oxide (CAS No 1163-19-5) in F344/N Rats and B6C3F1 Mice (Feed Studies)*. Research Triangle Park, North Carolina: United States Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program (NTP Technical Report Series No. 309).

Nylund, K., Kierkegaard, A., Eriksson, U., Asplund, L., Bignert, A. & Olsson, M. (2001) Spatial distribution of some polybrominated diphenyl ethers and hexabromocyclododecane in herring along the Swedish coast. In: *The Second International Workshop on Brominated Flame Retardants*. BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, pp. 349–352.

Öberg, K., Warman, K. & Öberg, T. (2002) Distribution and levels of brominated flame retardants in sewage sludge. *Chemosphere*, **48** (8), 805–809.

Ohta, S., Ishizuka, D., Nishimura, H., Nakao, T., Aozasa, O., Shimidzu, Y., Ochiai, F., Kida, T., Nishi, M. & Miyata, H. (2002) Comparison of polybrominated diphenyl ethers in fish, vegetables, and meats and levels in human milk of nursing women in Japan. *Chemosphere*, **46**, 689–696.

Örn, U. (1997) *Synthesis of Polybrominated Diphenyl Ethers and Metabolism of 2,2',4,4'-Tetrabromo[$^{14}$C]diphenyl Ether* [Licentiate Thesis]. Stockholm: Stockholm University.

Örn, U. & Klasson-Wehler, E. (1998) Metabolism of 2,2',4,4'-tetrabromodiphenyl ether in rat and mouse. *Xenobiotica*, **28**, 199–211.

PAI (1984) *Initial Submission: Acute Oral Toxicity in Rats (14 Days) of Saytex 115 (Pentabromodiphenyloxide)*. Submitted to the United States Environmental Protection Agency under TSCA Section FYI. OTS0000972. Pharmakon Associates, Inc. As cited in ATSDR (2004).

Päpke, O., Bathe, L., Bergman, Å., Fürst, P., Meironyté Guvenius, D., Herrmann, T. & Norén, K. (2001) Determination of PBDEs in human milk from the United States, comparison of results from three laboratories. *Organohalogen Compd.*, **52**, 197–200.

Päpke, O., Fürst, P. & Herrmann, T. (2004) Determination of polybrominated diphenyl ethers (PBDEs) in biological tissues with special emphasis on QC/QA measures. *Talanta*, **63**, 1203–1211.

Pereg, D., Ryan, J.J., Ayotte, P., Muckle, G., Patry, B. & Dewailly, E. (2003) Temporal and spatial changes of brominated diphenyl ethers (BDEs) and other POPs in human milk from Nunavik (Arctic) and southern Quebec. *Organohalogen Compd.*, **61**, 127–130.

Peters, A.K., Van Londen, K., Bergman, A., Bohonowych, J., Denison, M.S., Van den Berg, M. & Sanderson, T.S. (2004) Effects of polybrominated diphenyl ethers (PBDEs) on basal and TCDD-induced ethoxyresorufin (EROD) activity and cytochrome P450 1A1 expression in MCF7, HepG2 and H4IIE cells. *Toxicol. Sci.*, **82** (2), 488–496.

Petreas, M., She, J., Brown, F.R., Winkler, J., Visita, P., Li, C., Chand, D., Dhaliwal, J., Rogers, E., Zhao, G. & Charles, M. (2002) High PBDE concentrations in Californian human and wildlife populations. *Organohalogen Compd.*, **58**, 177–180.

Petroske, E., Zaylskie, R.G. & Feil, V.J. (1997) The effect of cooking on dioxin and furan concentrations in beef. *Organohalogen Compd.*, **33**, 436–439.

Petroske, E., Zaylskie, R.G. & Feil, V.J. (1998) Reduction in polychlorinated dibenzodioxin and dibenzofuran residues in hamburger meat during cooking. *J. Agric. Food Chem.*, **46**, 3280–3284.

Pirard, C., de Pauw, E. & Focant, J.F. (2003) Levels of selected PBDE and PCBs in Belgian human milk. *Organohalogen Compd.*, **61**, 263–266.

Polder, A., Thomsen, C., Bescher, G., Skaare, J., Löken, K. & Eggesbö, M. (2004) The Norwegian Human Milk Study HUMIS: Variation in levels of chlorinated pesticides, PCBs and PBDEs in Norwegian breast milk. *Organohalogen Compd.*, **66**, 2476–2482.

Prevedouros, K., Jones, K.C. & Sweetman, A.J. (2004) Estimation of the production, consumption, and atmospheric emissions of pentabrominated diphenyl ether in Europe between 1970 and 2000. *Environ. Sci. Technol.*, **38** (12), 3224–3231.

Rahman, F., Langford, K.H., Scrimshaw, M.D. & Lester, J.N. (2001) Polybrominated diphenyl ether (PBDE) flame retardants. *Sci. Total Environ.*, **275**, 1–17.

Rayne, S., Ikonomou, M.G. & Antcliffe, B. (2003) Rapidly increasing polybrominated diphenyl ether concentrations in the Columbia River system from 1992 to 2000. *Environ. Sci. Technol.*, **37** (13), 2847–2854.

Rice, C.P., Chernyak, S.M., Begnoche, L., Quintal, R. & Hickey, J. (2002) Comparisons of PBDE composition and concentration in fish collected from the Detroit River, MI and Des Plaines River, IL. *Chemosphere*, **49** (7), 731–737.

Richards, R.G., DiAugustine, R.P., Petrusz, P., Clark, G.C. & Sebastian, J. (1996) Estradiol stimulates tyrosine phosphorylation of the insulin-like growth factor-1 receptor and insulin receptor substrate-1 in the uterus. *Proc. Natl. Acad. Sci. U.S.A.*, **93** (21), 12002–12007.

Rowsell, P., Yagminas, A., Chu, I. & Arnold, D.L. (2004) 28 day gavage study with a technical mixture of lower polybrominated diphenyl ethers in Sprague-Dawley rats. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 419–423 (http://www.bfr2004.com).

Rozman, K.K. (1991) Letter to the Editor. *Toxicol. Appl. Pharmacol.*, **108**, 568–569.

Ryan, J.J. (2004) Polybrominated diphenyl ethers (PBDEs) in human milk; occurrence worldwide. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 17–22 (http://www.bfr2004.com).

Ryan, J.J. & Patry, B. (2000) Determination of brominated diphenyl ethers (BDEs) and levels in Canadian milks. *Organohalogen Compd.*, **47**, 57–60.

Ryan, J.J. & Patry, B. (2001) Body burdens and food exposure in Canada for polybrominated diphenylethers (BDEs). *Organohalogen Compd.*, **51**, 226–229.

Ryan, J.J. & van Oostdam, J. (2004) Polybrominated diphenyl ethers (PBDEs) in maternal and cord blood plasma of several northern Canadian populations. *Organohalogen Compd.*, **66**, 2579–2585.

Ryan, J.J., Patry, B., Mills, P. & Beaudoin, N. (2002) Recent trends in levels of brominated diphenyl ethers in human milk from Canada. *Organohalogen Compd.*, **58**, 173–176.

Safe, S. (1990) Polychlorinated biphenyls (PCBs), dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). *Crit. Rev. Toxicol.*, **21**, 51–88.

Sand, S., von Rosen, D., Eriksson, P., Frederiksson, A., Viberg, H., Victorin, K. & Falk Felipsson, A. (2004) Dose–response modeling and benchmark calculations from spontaneous behavior data on mice neonatally exposed to 2,2',4,4',5-pentabromodiphenyl ether. *Toxicol. Sci.*, **81**, 491–501.

Sandholm, A. (2003) *Metabolism of Some Polychlorinated Biphenyl and Polybrominated Diphenyl Ether Congeners in the Rat* [Doctoral dissertation]. Stockholm: Stockholm University, Department of Environmental Chemistry.

Sandholm, A., Emanuelsson, B.-M. & Klasson-Wehler, E. (2003) Bioavailability and half-life of decabromodiphenyl ether (BDE-209) in the rat. *Xenobiotica*, **33** (11), 1149–1158.

Schecter, A.J., Päpke, O., Dellarco, M. & Olson, J.R. (1996) A comparison of dioxins and dibenzofurans in cooked and uncooked food. *Organohalogen Compd.*, **28**, 166–170.

Schecter, A., Päpke, O. & Dellarco, M. (1997) Dioxin, dibenzofuran, and PCB congeners in cooked and uncooked foods. *Organohalogen Compd.*, **33**, 462–466.

Schecter, A., Dellarco, M., Päpke, O. & Olson, J. (1998) A comparison of dioxins, dibenzofurans and coplanar PCBs in uncooked and broiled ground beef, catfish and bacon. *Chemosphere*, **37**, 1723–1730.

Schecter, A., Pavuk, M., Päpke, O., Ryan, J.J., Birnbaum, L. & Rosen, R. (2003) Congener specific measurements of polybrominated diphenyl ethers in 47 individual milk samples from nursing mothers in the USA. *Organohalogen Compd.*, **61**, 13–16.

Schecter, A., Päpke, O., Tung, K.C., Staskal, D. & Birnbaum, L. (2004a) Polybrominated diphenyl ethers contamination of United States food. *Environ. Sci. Technol.*, **38** (20), 5306–5311.

Schecter, A., Päpke, O., Staskal, D., Tung, K.C., Ryan, J.J., Rosen, R. & Birnbaum, L. (2004b) PBDE contamination of U.S. food and human milk; and PBDE, PCDD/F, PCB, and [*sic*] levels in U.S. human blood (1973 and 2003). In: *The Third International Workshop on Brominated Flame Retardants.* BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 27–32 (http://www.bfr2004.com).

Schecter, A., Pavuk, M., Päpke, O., Ryan, J.J., Birnbaum, L. & Rosen, R. (2004c) Polybrominated diphenyl ethers (PBDEs) in US mothers' milk. *Environ. Health Perspect.*, **111** (14), 1723–1729.

Schecter, A., Päpke, O., Tung, K.C., Joseph, J., Dahlgren, J. & Harris, T.R. (2005) Polybrominated diphenylether (PBDE) flame retardants in the US population: current levels, temporal trends, and comparison with dioxins, dibenzofurans and polychlorinated biphenyls. *J. Occup. Environ. Med.*, **47** (3), 199–211.

Schlabach, M., Fjeld, E. & Brevik, E. (2001) PBDEs and other persistent organic pollutants in Norwegian freshwater fish. In: *The Second International Workshop on Brominated Flame Retardants.* BFR 2001, 14–16 May 2001, Stockholm University, Stockholm, pp. 371–374.

Schröter-Kermani, C., Helm, D., Herrmann, T. & Päpke, O. (2000) The German environmental specimen bank — application in trend monitoring of polybrominated diphenyl ethers in human blood. *Organohalogen Compd.*, **47**, 49–52.

Schumacher, M., Kiviranta, H., Varitainen, T. & Domingo, L.L. (2004) Concentrations of PCBs and PBDEs in breast milk of women from Catalonia, Spain. *Organohalogen Compd.*, **66**, 2560–2566.

Sellström, U. (1996) *PBDEs in the Swedish environment* [Licentiate Thesis]. Stockholm: Stockholm University, Institute of Applied Research (ITM Report, 1996:45).

Sellström, U., Jansson, B., Kierkegaard, A., de Wit, C., Odsjo, T. & Olsson, M. (1993) Polybrominated diphenyl ethers (PBDE) in biological samples from the Swedish environment. *Chemosphere*, **26** (9), 1703–1718.

Sellström, U., Söderström, G. & Tysklind, M. (1998) Photolytic debromination of decabromodiphenyl ether (DeBDE). *Organohalogen Compd.*, **35**, 447–450.

She, J., Winkler, J., Visita, P., McKinney, M. & Petreas, M. (2000) Analysis of PBDEs in seal blubber and human breast adipose samples. *Organohalogen Compd.*, **47**, 53–56.

She, J., Holden, A., Sharp, M., Tanner, M., Williams-Derry, C. & Hooper, K. (2004) Unusual pattern of polybrominated diphenyl ethers (PBDEs) in US breast milk. *Organohalogen Compd.*, **66**, 3945–3950.

Sjödin, A. (2000) *Occupational and Dietary Exposure to Organohalogen Substances with Special Emphasis on Polybrominated Diphenyl Ethers* [Thesis]. Stockholm: Stockholm University.

Sjödin, A., Jakobsson, E., Kierkegaard, A., Marsh, G. & Sellström, U. (1998) Gas chromatographic identification and quantification of polybrominated diphenyl ethers in a commercial product, Bromkal 70-5DE. *J. Chromatgraph. A*, **822** (1), 83–89.

Sjödin, A., Hagmar, L., Klasson-Wehler, E., Kronholm-Diab, K., Jakobsson, E. & Bergman, A. (1999) Flame retardant exposure: polybrominated diphenyl ethers in blood from Swedish workers. *Environ. Health Perspect.*, **107** (8), 643–648.

Sjödin, A., Patterson, D.G., Jr., & Bergman, Å. (2003) A review on human exposure to brominated flame retardants — particularly polybrominated diphenyl ethers. *Environ. Int.*, **29**, 829–839.

Sjödin, A., Jones, R., Focant, J.-F., Lapeza, C., Wang, R., Needham, L. & Patterson, D. (2004a) Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. *Environ. Health Perspect.*, **112**, 654–658.

Sjödin, A., Päpke, O., McGahee, E., Jones, R., Focant, J.F., Pless-Mulloli, T., Tooms, L.M., Wang, R., Needham, L.L., Herrmann, T. & Patterson, D. (2004b) Concentration of polybrominated diphenyl ethers (PBDEs) in household dust from various countries — inhalation a potential route of human exposure. *Organohalogen Compd.*, **66**, 3817–3822.

Skarman, E., Darnerud, P.O., Öhrvik, H. & Oskarsson, A. (2005) Reduced thyroxine levels in mice perinatally exposed to polybrominated diphenyl ethers. *Environ. Toxicol. Pharmacol.*, **19**, 273–281.

Stanley, J., Cramer, P., Thornburg, K., Remmers, J., Breen, J.J. & Schwemberger, J. (1991) Mass spectral confirmation of chlorinated and brominated diphenylethers in human adipose tissues. *Chemosphere*, **23**, 1185–1195.

Stapelton, H., Dodder, N., Schantz, M. & Wise, S. (2004) Measurement of the flame retardants polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD) in house dust. *Organohalogen Compd.*, **66**, 3740–3744.

Staskal, D.H., Diliberto, J.J., DeVito, M.J. & Birnbaum, L.S. (2005) Toxicokinetics of BDE 47 in female mice: effect of dose, route of exposure, and time. *Toxicol. Sci.*, **83**, 215–223.

Stoker, T.E., Laws, S.C., Crofton, K.M., Hedge, J.M., Ferrell, J.M. & Cooper, R.L. (2004a) Assessment of DE-71, a commercial polybrominated diphenyl ether (PBDE) mixture, in the EDSP male and female pubertal protocols. *Toxicol. Sci.*, **78**, 144–155.

Stoker, T.E., Cooper, R.L., Lambright, C.S., Wilson, V.S. & Gray, L.E. (2004b) In vivo and in vitro anti-androgenic effects of DE-71, a commercial polybrominated diphenyl ether (PBDE) mixture. *Toxicologist*, **78** (1-S), 573.

Strandman, T., Koistinen, J., Kiviranta, H., Vuorinen, P., Tuomisto, J. & Vartiainen, T. (1999) Levels of some polybrominated diphenyl ethers in fish and human adipose tissue in Finland. *Organohalogen Compd.*, **40**, 355–357.

Strandman, T., Koistinen, J. & Vartiainen, T. (2000) Polybrominated diphenyl ethers (PBDEs) in placenta and human milk. *Organohalogen Compd.*, **47**, 61–64.

Takasuga, T., Tsuji, H. & Nagayama, J. (2002) Gender specific dynamics of PCDD/Fs, PCBs, PBDEs and organochlorines in blood of Japanese families over two-year study period. *Organohalogen Compd.*, **58**, 297–300.

Talsness, C.E., Shakibaei, M., Kuriyama, S., de Souza, C. & Chahoud, I. (2003) Ultra-structural changes in the ovaries of adult offspring following a single maternal exposure to low dose 2,2',4,4',5-pentabromodiphenyl ether. *Organohalogen Compd.*, **61**, 88–91.

Taylor, M.M., Hedge, J.M., Gilbert, M.E., DeVito, M.J. & Crofton, K.M. (2003) Perinatal exposure to a polybrominated diphenyl ether mixture (DE-71): Disruption of thyroid homeostasis and neurobehavioral development. *Toxicologist*, **77** (1-S), 602.

Thomsen, C., Lundanes, E. & Becher, G. (2001) A time trend study on brominated flame retardants in serum samples from the general population in Norway. *Organohalogen Compd.*, **52**, 206–209.

Thomsen, C., Frøshaug, M., Leknes, H. & Becher, G. (2003) Brominated flame retardants in breast milk from Norway. *Organohalogen Compd.*, **64**, 33–36.

Thomsen, C., Frøshaug, M., Becher, G., Kvalem, H.E., Knutsen, H., Alexander, J., Bergsten, C. & Meltzer, H.M. (2004) PBDEs in serum from persons with varying consumption of fish and game. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 37–40 (http://www.bfr2004.com).

Thuvander, A. & Darnerud, P.O. (1999) Effects of polybrominated diphenyl ether (PBDE) and polychlorinated biphenyl (PCB) on some immunological parameters after oral exposure in rats and mice. *Toxicol. Environ. Chem.*, **70**, 229–242.

Tollbäck, P., Björklund, J. & Östman, C. (2003) Evaluation of gas chromatographic injection techniques for PBDE. *Organohalogen Compd.*, **61**, 49–52.

Tritscher, A., Stadler, R., Scanlan, F., Collingro, C. & Päpke O. (2003) Determination of poly-chlorinated diphenylethers in samples of raw cow's milk, fish and egg. *Organohalogen Compd.*, **61**, 131–134.

UK COT (2004) *COT Statement on Brominated Flame Retardants in Fish from the Skerne-Tees Rivers System.* United Kingdom Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment.

US EPA (1986) *Brominated Diphenyl Ethers. Chemical Hazard Information Profile.* Washington, D.C.: United States Environmental Protection Agency. As cited in IPCS (1994).

US EPA (1990a) *Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of MUSTER 13 with Cover Letter Dated 031290.* Unpublished laboratory report,

Huntingdon Research Centre. Office of Toxic Substances, United States Environmental Protection Agency (Document No. 86-9000004040).

US EPA (1990b) EPA/OTS. *Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of MUSTER 82 with Cover Letter Dated 031290.* Unpublished laboratory report, Huntingdon Research Centre. Office of Toxic Substances, United States Environmental Protection Agency (Document No. 86-900000403).

US EPA (1990c) *Ames Metabolic Activation Test to Assess the Potential Mutagenic Effect of MUSTER 84 with Cover Letter Dated 031290.* Unpublished laboratory report, Huntingdon Research Centre. Office of Toxic Substances, United States Environmental Protection Agency (Document No. 86-900000402.

US EPA (2003) *EPA Method 1614, Brominated Diphenyl Ethers in Water, Soil, Sediment and Tissue by HRGC/HRMS* (draft). Washington, D.C.: United States Environmental Protection Agency.

van Bavel, B., Hughes, J., Davis, S., Wingfors, H. & Lindström, G. (1999) Fast screening for PCBs, pesticides, and brominated flame retardants in biological samples by SFE-LC in combination with GC-TOF. *Organohalogen Compd.*, **40**, 293–296.

van Bavel, B., Hardell, L., Kitti, A., Lijedahl, M., Karlsson, M., Petterson, A., Tysklind, M. & Lindström, G. (2002) High levels of PBDEs in 5 % of 220 blood samples from the Swedish population. *Organohalogen Compd.*, **58**, 161–164.

Van den Berg, M., Birnbaum, L., Bosveld, A.T., Brunstrom, B., Cook, P., Feeley, M., Giesy, J.P., Hanberg, A., Hasegawa, R., Kennedy, S.W., Kubiak, T., Larsen, J.C., van Leeuwen, F.X., Liem, A.K., Nolt, C., Peterson, R.E., Poellinger, L., Safe, S., Schrenk, D., Tillitt, D., Tysklind, M., Younes, M., Waern, F. & Zacharewski, T. (1998) Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ. Health Perspect.*, **106** (12), 775–792.

VCCEP (2003) *Voluntary Children's Chemical Evaluation Program Pilot Tier 1: Assessment of the Potential Health Risks to Children Associated with Exposure to the Commercial Octabromodiphenyl Ether Product. CAS No. 32536-52-0* (http://www.tera.org/peer/VCCEP/OctaPenta/Octabromodiphenyl%20Ether%20VCCEP%20Tier%201_Main%20Report%20(04-21-03).pdf).

Viberg, H. (2004) *Neonatal Developmental Neurotoxicity of Brominated Flame Retardants, the Polybrominated Diphenyl Ethers (PBDEs).* Acta Universitatis Upsaliensis: Comprehensive summaries of Uppsala dissertations from the Faculty of Science and Technology. 62 pp. (ISBN 91-554-6053-4).

Viberg, H., Fredriksson, A. & Eriksson, P. (2002) Neonatal exposure to the brominated flame retardant 2,2'4,4',5-pentabromodiphenyl ether causes altered susceptibility in the cholinergic transmitter system in the adult mouse. *Toxicol. Sci.*, **67**, 104–107.

Viberg, H., Fredriksson, A. & Eriksson, P. (2003a) Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. *Toxicol. Appl. Pharmacol.*, **192**, 95–106.

Viberg, H., Fredriksson, A., Jakobsson, E., Örn, U. & Eriksson, P. (2003b) Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. *Toxicol. Sci.*, **76**: 112–120.

Viberg, H., Fredriksson, A. & Eriksson, P. (2004a) Neonatal exposure to the brominated flame retardant, 2,2'4,4',5-pentabromodiphenyl ether, decreases cholinergic nicotinic receptors in the hippocampus and affects spontaneous behavior in the adult mouse. *Environ. Toxicol. Pharmacol.*, **17**, 61–65.

Viberg, H., Fredriksson, A. & Eriksson, P. (2004b) Investigations of strain and/or gender differences in developmental neurotoxic effects of polybrominated diphenyl ethers in mice. *Toxicol. Sci.*, **81**, 344–353.

Viberg, H., Fredriksson, A. & Eriksson, P. (2004c) Comparative developmental neurotoxicity of PBDE 99 in two different mouse strains and rat. *Toxicologist*, **78** (1-S), 1907.

Vieth, B., Herrmann, T., Mielke, H., Ostermann, B., Päpke, O. & Rüdiger, T. (2004) PBDE levels in human milk: the situation in Germany and potential influencing factors — a controlled study. *Organohalogen Compd.*, **66**, 2643–2648.

Vijverberg, H. & van den Berg, M. (2004) Letter to the editor. *Toxicol. Sci.*, **79** (1), 205–206.

von Meyerinck, L., Hufnagel, B., Schmoldt, A. & Benthe, H.F. (1990) Induction of rat liver microsomal cytochrome P-450 by the pentabromo diphenyl ether Bromkal 70 and half-lives of its components in the adipose tissue. *Toxicology*, **61**, 259–274.

Weber, H. & Heseker, H. (2004) Analysis of polybrominated diphenyl ethers in breast milk of German mothers — results of a pilot study. *Fresenius Environ. Bull.*, **13** (4), 356–360.

Weiss, J., Meijer, L., Sauer, P., Linderholm, L., Athanasiadis, I. & Bergman, A. (2004a) PBDE and HBCDD levels in blood from Dutch mothers and infants. In: *The Third International Workshop on Brominated Flame Retardants*. BFR 2004, Toronto, Ontario, 6–9 June 2004, pp. 71–74 (http://www.bfr2004.com).

Weiss, J., Meijer, L., Sauer, P., Linderholm, L., Athanasiadis, I. & Bergman, A. (2004b) PBDE and HBCDD levels in blood from Dutch mothers and infants — analysis of a Dutch Groningen infant cohort. *Organohalogen Compd.*, **66**, 2677–2682.

WHO (1998) *GEMS/Food Regional Diets (Regional Per Capita Consumption of Raw and Semi-processed Agricultural Commodities)*. Geneva: World Health Organization, Global Environment Monitoring System Food Contamination Monitoring and Assessment Programme (WHO/FSF/FOS/98.3; http://www.who.int/foodsafety/publications/chem/regional_diets/en/).

WHO (2000) *Methodology for Exposure Assessment of Contaminants and Toxins in Food*. Report of a Joint FAO/WHO Workshop, 7–8 June 2000. Geneva: World Health Organization (WHO/SDE/PHE/FOS/00.5).

Wicklund-Glynn, A., Darnerud, P.O., Andersson, Ö., Atuma, S., Johansson, H., Linder, C.E. & Becker, W. (1996) *Revised Fish Consumption Advisory Regarding PCBs and Dioxins*. Uppsala: National Food Administration (Report 4/96).

Wiegand, H., Costa, L.G., Eriksson, P., Felipo, V., Lichtensteiger, W., Alleva, E., Altmann, L., Branchi, I., Canales, J.J., Ceccatelli, R., Bordi, F., Erceg, S., Faass, O., Fleischmann, I., Frederiksson, A., Lilienthal, H., Llansola, M., Montoliu, C., Pettersson, A., Saez, R., Santucci, D., Schlumpf, M., Silvestrini, B., Smolnikar, K. & Viberg, H. (2003) *Developmental Neurotoxicity of Polybrominated Diphenyl Ethers (PBDE): Mechanisms and Effects. Final Report*. Brussels: European Commission (EU Project QLK4-CT-1999-1562).

Wiegand, H., Altmann, L. & Lilienthal, H. (2004) Developmental neurotoxicity of PBDEs: impairment of synaptic plasticity in rat cortex and hippocampus. *Toxicologist*, **78** (1-S), 1906.

Wijesekera, R., Halliwell, C., Hunter, S. & Harrad, S. (2002) A preliminary assessment of UK human exposure to polybrominated diphenyl ethers (PBDEs). *Organohalogen Compd.*, **55**, 239–242.

Wilford, B.H., Harner, T., Zhu, J.P., Shoeib, M. & Jones, K.C. (2004) Passive sampling survey of polybrominated diphenyl ether flame retardants in indoor and outdoor air in

Ottawa, Canada: Implications for sources and exposure. *Environ. Sci. Technol.*, **38** (20), 5312–5318.

Wilford, B.H., Shoeib, M., Harner, T., Zhu, J.P. & Jones, K.C. (2005) Polybrominated diphenyl ethers in indoor dust in Ottawa, Canada: Implications for sources and exposure. *Environ. Sci. Technol.*, **39** (18), 7027–7035.

WIL Research Laboratories (1984) *90-Day Dietary Study in Rats with Pentabromo Diphenyl Oxide Including Recovery Periods of 6, 12 and 24 Weeks. Final Report.* Ashland, Ohio: WIL Research Laboratories (Project 12042).

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. & Speck, W. (1987) *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ. Mutagen.*, **9** (Suppl. 9), 1–11.

Zennegg, M., Kohker, M., Gerecke, A.C. & Schmid, P. (2003) Polybrominated diphenyl ethers in whitefish from Swiss lakes and farmed rainbow trout. *Chemosphere*, **51** (7), 545–553.

Zhou, T., Ross, D.G., DeVito, M.J. & Crofton, K.M. (2001) Effects of short-term in vivo exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats. *Toxicol. Sci.*, **61**, 76–82.

Zhou, T., Taylor, M.M., DeVito, M.J. & Crofton, K.M. (2002) Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. *Toxicol. Sci.*, **66**, 105–116.

## APPENDIX 1: LIST OF COMMON BROMINATED DIPHENYL ETHER (BDE) CONGENERS

| Congener number | Bromine substitution pattern |
|---|---|
| BDE-0 | diphenyl ether |
| BDE-1 | 2-monobromodiphenyl ether |
| BDE-2 | 3-monobromodiphenyl ether |
| BDE-3 | 4-monobromodiphenyl ether |
| BDE-7 | 2,4-dibromodiphenyl ether |
| BDE-8 | 2,4'-dibromodiphenyl ether |
| BDE-10 | 2,6-dibromodiphenyl ether |
| BDE-11 | 3,3'-dibromodiphenyl ether |
| BDE-12 | 3,4-dibromodiphenyl ether |
| BDE-13 | 3,4'-dibromodiphenyl ether |
| BDE-15 | 4,4'-dibromodiphenyl ether |
| BDE-17 | 2,2',4-tribromodiphenvl ether |
| BDE-25 | 2,3',4-tribromodiphenvl ether |
| BDE-28 | 2,4,4'-tribromodiphenvl ether |
| BDE-30 | 2,4,6-tribromodiphenyl ether |
| BDE-32 | 2,4',6-tribromodiphenyl ether |
| BDE-33 | 2',3,4-tribromodiphenyl ether |
| BDE-35 | 3,3',4-tribromodiphenyl ether |
| BDE-37 | 3,4,4'-tribromodiphenyl ether |
| BDE-39 | 3,4',5-tribromodiphenyl ether |
| BDE-47 | 2,2',4,4'-tetrabromodiphenyl ether |
| BDE-51 | 2,2',4,6'-tetrabromodiphenyl ether |
| BDE-66 | 2,3',4,4'-tetrabromodiphenyl ether |
| BDE-71 | 2,3',4',6-tetrabromodiphenyl ether |
| BDE-75 | 2,4,4',6-tetrabromodiphenyl ether |
| BDE-77 | 3,3',4,4'-tetrabromodiphenyl ether |
| BDE-85 | 2,2',3,4,4'-pentabromodiphenyl ether |
| BDE-99 | 2,2',4,4',5-pentabromodiphenyl ether |
| BDE-100 | 2,2',4,4',6-pentabromodiphenyl ether |
| BDE-101 | 2,2',4,5,5'-pentabromodiphenyl ether |
| BDE-105 | 2,3,3',4,4'-pentabromodiphenyl ether |

***Appendix 1*** (contd)

| Congener number | Bromine substitution pattern |
|---|---|
| BDE-116 | 2,3,4,5,6-pentabromodiphenyl ether |
| BDE-119 | 2,3',4,4',6-pentabromodiphenyl ether |
| BDE-126 | 3,3',4,4',5-pentabromodiphenyl ether |
| BDE-128 | 2,2',3,3',4,4'-hexabromodiphenyl ether |
| BDE-138 | 2,2',3,4,4',5'-hexabromodiphenyl ether |
| BDE-140 | 2,2',3,4,4',6'-hexabromodiphenyl ether |
| BDE-151 | 2,2',3,5,5',6-hexabromodiphenyl ether |
| BDE-153 | 2,2',4,4',5,5'-hexabromodiphenyl ether |
| BDE-154 | 2,2',4,4,5,6'-hexabromodiphenyl ether |
| BDE-155 | 2,2',4,4',6,6'-hexabromodiphenyl ether |
| BDE-166 | 2,3,4,4',5,6-hexabromodiphenyl ether |
| BDE-172 | 2,2',3,3',4,5,5'-heptabromodiphenyl ether |
| BDE-176 | 2,2',3,3',4,6,6'-heptabromodiphenyl ether |
| BDE-181 | 2,2',3,4,4',5,6'-heptabromodiphenyl ether |
| BDE-183 | 2,2',3,4,4',5',6-heptabromodiphenyl ether |
| BDE-185 | 2,2',3,4,4',5',6-heptabromodiphenyl ether |
| BDE-189 | 2,3,3',4,4',5,5'-heptabromodiphenyl ether |
| BDE-190 | 2,3,3',4,4',5,6-heptabromodiphenyl ether |
| BDE-192 | 2,3,3',4,5,5',6-heptabromodiphenyl ether |
| BDE-197 | 2,2',3,3',4,4',6,6'-octabromodiphenyl ether |
| BDE-203 | 2,2',3,4,4',5,5',6-octabromodiphenyl ether |
| BDE-206 | 2,2',3,3',4,4',5,5',6-nonabromodiphenyl ether |
| BDE-209 | 2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether |