

Polybrominated Diphenyl Ethers: Occurrence, Dietary Exposure, and Toxicology

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Polybrominated diphenyl ethers (PBDEs) are used as flame retardants in plastics (concentration, 5–30%) and in textile coatings. Commercial products consist predominantly of penta-, octa-, and decabromodiphenyl ether mixtures, and global PBDE production is about 40,000 tons per year. PBDEs are bioaccumulated and biomagnified in the environment, and comparatively high levels are often found in aquatic biotopes from different parts of the world. During the mid-1970–1980s there was a substantial increase in the PBDE levels with time in both sediments and aquatic biota, whereas the latest Swedish data (pike and guillemot egg) may indicate that levels are at steady state or are decreasing. However, exponentially increasing PBDE levels have been observed in mother's milk during 1972–1997. Based on levels in food from 1999, the dietary intake of PBDE in Sweden has been estimated to be 0.05 µg per day. Characteristic end points of animal toxicity are hepatotoxicity, embryotoxicity, and thyroid effects as well as maternal toxicity during gestation. Recently, behavioral effects have been observed in mice on administration of PBDEs during a critical period after birth. Based on the critical effects reported in available studies, we consider the lowest-observed-adverse-effect level (LOAEL) value of the PBDE group to be 1 mg/kg/day (primarily based on effects of pentaPBDEs). In conclusion, with the scientific knowledge of today and based on Nordic intake data, the possible consumer health risk from PBDEs appears limited, as a factor of over 10⁶ separates the estimated present mean dietary intake from the suggested LOAEL value. However, the presence of many and important data gaps, including those in carcinogenicity, reproduction, and developmental toxicity, as well as additional routes of exposure, make this conclusion only preliminary. Moreover, the time trend of PBDEs in human breast milk is alarming for the future. **Key words:** brominated, diet, environmental levels, exposure, flame retardant, human, organohalogen compounds, toxicity. — *Environ Health Perspect* 109(suppl 1):49–68 (2001). <http://ehpnet1.niehs.nih.gov/docs/2001/suppl-1/49-68darnerud/abstract.html>

The presence of persistent man-made chemicals in our environment is not a new problem. However, it was not until the beginning of the 1960s that environmental pollutants aroused debate and concern. Since then, a large number of chemicals have been identified in environmental samples, and the time trends of their concentrations have been the subject of continuous interest. Apart from the heavy metals, the group of chlorinated hydrocarbons includes many pollutants regarded as major environmental problems, e.g., the well-known polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs), the two latter groups generally called dioxins. The PCBs and dioxins and their harmful effects on nature and man have been extensively reviewed. Today the effects of these substances are quite well known, although their mechanism(s) of action remains largely unsolved. The toxicity of these chemicals and their presence in certain food items, mostly of animal origin, have resulted in introduction of dietary restrictions and recommendations by food administrations in different countries. Continuous monitoring of the environmental levels of these chemicals has shown a decreasing trend in their occurrence over the last 10 years or more in many Western countries.

There are significant amounts of other chemicals in our environment that we know less about, and one such group is the brominated flame retardants. Even today, limited amounts of data are available on these compounds, with regard to their presence and levels in various products, environmental levels, transformation products, disposition, and toxic effects. Earlier overviews have compiled the present knowledge about brominated flame retardants (1–7).

Polybrominated diphenyl ethers (PBDEs) constitute an important group of brominated flame retardants. The compounds are mostly found in ready-made plastic products. PBDEs are used in large quantities worldwide and are persistent in the environment, possibly because the compounds are in the technosphere and will be released into the environment for years to come. Over the last 10–15 years, there have been indications of increased environmental and human levels of these compounds, although the levels are still lower than those for PCBs and DDT. Therefore, it is important to summarize the present state of knowledge about the environmental occurrence, human exposure, and toxicity of PBDEs to assess health consequences from the present and future use of this group of brominated compounds. This article

reviews risks from PBDEs, with special emphasis on dietary risks.

Chemical and Physical Properties of PBDEs

The general chemical formula of a PBDE is C₁₂H_(9–0)Br_(1–10)O, with the sum of H and Br atoms always equal to 10. Structure formulas are given in Figure 1.

The theoretical number of possible congeners is 209 and is divided into 10 congener groups (mono- to decabromodiphenyl ethers). However, compounds with less than four bromine atoms are generally not found in commercial PBDE products. The number of PBDE congeners used in commercial products, and thus found in environmental samples, is quite small compared to the number of PCB congeners commonly found. PBDE congeners are often numbered according to the International Union of Pure and Applied Chemistry (IUPAC) system originally designed for PCBs (8). Commercial PBDEs are quite resistant to physical, chemical, and biologic degradation. The boiling point of PBDEs is between 310 and 425°C and their vapor pressure is low at room temperature. PBDEs are lipophilic, and their solubility in water is low, especially for the higher brominated compounds. The *n*-octanol–water partition coefficient, log P_{ow}, ranges between 4.3 and 9.9. Physical properties are summarized in Table 1.

Analytical Methods

Extraction methods normally used for environmental (biologic and sediment) samples are batch or Soxhlet extraction. Different methods of cleanup are used depending the nature of other compounds analyzed and the type of analytic method. Among these procedures are sulfuric acid cleanup and different types of column separations (e.g., silica gel, aluminum oxide, and gel permeation chromatography). Recently supercritical fluid extraction also has been described (9). Gas

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chromatography (GC) analysis is normally done on capillary columns with methyl or methyl plus 5% phenyl packing substrates. Detection is made on an electron capture detector (mass spectrometry–electron impact ionization or mass spectrometry–electron capture negative ionization). The high-brominated diphenyl ethers with longer retention times are analyzed using a shorter GC column. More details on PBDE analysis are given in International Programme on Chemical Safety (IPCS) (2) and by Sellström (10,11). See also Örn (12), Haglund et al. (13), and Sellström et al. (14) for further details.

Pure PBDE congeners are needed to unequivocally identify a PBDE congener. Örn et al. (15,16) have described the synthesis and characterization of tetra-, penta-, and hexa-bromodiphenyl ethers. Recovery experiments on tetraBDE (DE-47) and pentaBDEs (DE-99 and DE-100) show that acceptable recoveries are made in fish (111–114%) and in sediment (106–140%) (14).

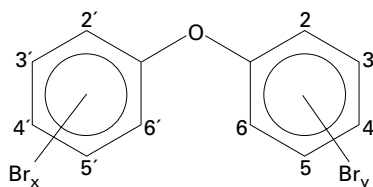


Figure 1. General structural formula of PBDEs.

Table 1. Physical properties for some PBDE congener groups.^a

	TetraBDE	PentaBDE	OctaBDE	DecaBDE
Chemical formula	C ₁₂ H ₆ OBr ₄	C ₁₂ H ₅ OBr ₅	C ₁₂ H ₂ OBr ₈	C ₁₂ OBr ₁₀
Molecular mass	485.8	564.8	801.5	959.2
Vapor pressure (Pa)	2.7–3.3 × 10 ⁻⁴ (20°C)	2.9–7.3 × 10 ⁻⁵ (20°C)	1.2–2.7 × 10 ⁻⁷ (20°C)	< 1 × 10 ⁻⁴ (25°C) 670 (306°C)
Melting point (°C)	79–82 (BDE-47)	92 (BDE-99) 97–98 (BDE-100)	~ 200	290–306
Boiling point (°C)	—	> 300°C (decomposition)	—	(Decomposition)
Water solubility (µg/L)	—	0.0009 (20°C)	—	(20–30 ?)
Log K _{ow}	5.9–6.2	6.5–7.0	8.4–8.9	10

—, no information given; ?, unreliable value.

^aData from IPCS (2), Sellström (10,11), and OECD (20).

Table 2. Composition of commercial PBDEs.^a

Congener group	Commercial product			
	TetraBDE ^b (%)	PentaBDE (%)	OctaBDE (%)	DecaBDE (%)
Unknown	7.6			
TriBDE		0–1		
TetraBDE ^c	41–41.7	24–38		
PentaBDE ^d	44.4–45	50–62		
HexaBDE ^e	6–7	4–8	10–12	
HeptaBDE ^f			43–44	
OctaBDE			31–35	
NonaBDE			9–11	0.3–3
DecaBDE ^g			0–1	97–98

^aData from IPCS (2). ^bNo longer commercially produced. ^cIncluding 2,2',4,4'-tetrabromodiphenyl ether (BDE-47). ^dIncluding 2,2',3,3',4-pentabromodiphenyl ether (BDE-82), 2,2',3,4,4'-pentabromodiphenyl ether (BDE-85), 2,2',4,4',5-pentabromodiphenyl ether (BDE-99), and 2,2',4,4',6-pentabromodiphenyl ether (BDE-100). ^eIncluding 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153) and 2,2',4,4',5,6'-hexabromodiphenyl ether (BDE-154). ^fIncluding 2,2',3,4,4',5,6-heptabromodiphenyl ether (BDE-183). ^gIncluding 2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether (BDE-209).

In experimental studies, it is also beneficial to use synthesized PBDE congeners of high purity to circumvent impurity problems. In commercial PBDEs the presence of contaminants might otherwise affect the results of studies. Consequently, it is important to know the impurity profiles of the PBDE preparations being studied. Up to now, such data are often missing. One type of contaminants that could be found are the PBDDs and PBDFs. These compounds could be formed during heating of PBDE mixtures, but the toxic 2,3,7,8-substituted compounds seem to be produced in minute amounts (17,18).

Production and Use of PBDEs

Commercial PBDEs are synthesized by bromination of diphenyl ethers under conditions resulting in mixtures of brominated diphenyl ethers. The commercial products predominantly consist of penta-, hepta-, octa-, and decabromodiphenyl ethers. Chemically, the pentabromo product is a mixture primarily of tetra and penta congeners, and the octabromo product consists mainly of hepta and octa congeners (Table 2). Consequently, almost no data are available on mono-, di-, tri-, hexa-, and nona-diphenyl ethers. The number of different congeners found in each commercial product is relatively small. The composition of commercial brominated diphenyl ethers is given in Table 2.

PBDEs are used only for flame retardant purposes. The rationale for using brominated compounds as flame retardants is based on the ability of halogen atoms, generated from the thermal decomposition of the bromo-organic compound, to chemically reduce and retard the development of fire. Factors favoring the use of PBDEs are therefore the high bromine content (which means good flame-retardant properties), thermal stability, and relatively low cost. They are used as additive flame retardants at concentrations of 5–30% in many different polymers, resins and substrates, and common plastics, including acrylonitrile butadiene styrene and high impact polystyrene (19). Additive flame retardants leach and escape from the finished polymer product more easily than reactive flame retardants. Examples of products containing flame retardants, and especially PBDEs, include many components of electronic devices, e.g., cabinets for and circuit boards in personal computers and television (TV) sets and various other products (electrical cables, switches and capacitors), building materials, and textiles (Figure 2). The technical decaBDEs have the widest industrial use. More details about the use of PBDEs in various resins or polymers and the applications of these PBDE-containing resins are given in Tables 4 and 5 in IPCS (2).

The annual world production of flame retardants is roughly 600,000 metric tons, of which about 60,000 tons are chlorinated and 150,000 are brominated compounds. Of the brominated products, about one-third contain tetrabromobisphenol A (TBBP-A) and derivatives, another third contain various bromines, including polybrominated biphenyls (PBBs), and the last third contain PBDEs (20).

In 1990, global production of PBDE was 40,000 tons per year, of which approximately 10% was commercial penta-, 15% octa-, and 75% decaBDEs (21). The global production figures have stayed at approximately the same levels for more than 10 years, but there has been a shift in use toward the higher brominated preparations. Consequently, the use of

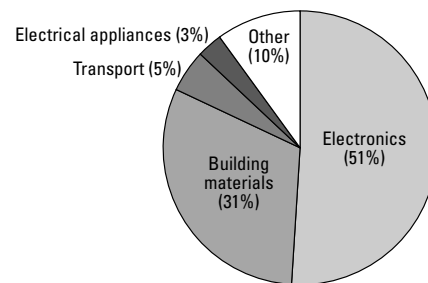


Figure 2. The relative amounts of flame retardants (all types) used in different sectors. Data from Pijnenburg et al. (7).

decaBDE today is even more prevalent. According to IPCS (2), eight manufacturers of PBDEs are located in the Netherlands, France, Great Britain, Israel, Japan, and the United States. In the European Union (EU), the total import and production of PBDEs was approximately 11,000 tons in 1989, of which roughly 4,000 tons were produced (12). No pentaBDEs are produced in the EU. In the United States the commercial production or import of PBDEs (penta-, octa-, and decaBDEs) was greater than 1,500 tons per year during the 1990s (1).

It is difficult to assess the quantities of PBDEs used and consumed in different countries, as the compounds are imported primarily as additives in manufactured products. For example, in Sweden the Chemicals Inspectorate has estimated that in 1993 the import of pure PBDE chemicals to Sweden was 17 tons. However, an additional 20 tons were imported in semimanufactured products. At least 150 tons were supposedly imported in TV sets and at least the same amount in personal computers (6). Consequently, the total import of PBDEs to Sweden was approximately 400 tons per year, or about 1% of world production.

PBDEs: International and National Legislation and Restrictions

The need for restrictions on certain PBDEs in different types of plastics and textiles is currently being discussed within the EU. Consequently, the use of certain brominated flame retardants [PBB and tris(2,3-dibromopropyl) phosphate] in textiles has already been banned. Within the EU Existing Substances Programme, documents are currently being produced that separately assess penta-, octa-, and decaBDEs.

An Organisation for Economic Co-operation and Development (OECD) document proposes precautions for each type of PBDEs. These include recommendations to stop the use of certain compounds (mainly tetra- and pentaBDEs), as well as to limit occupational exposure (20). Also the Paris Commission for the Prevention of Marine Pollution is working toward restricting and phasing out PBDEs and PBBs.

An example of a national restriction is the Swedish government's intention to ban PBDEs and PBBs in products sold on the Swedish market (22).

PBDEs in the Environment

Sources of PBDEs in the Environment

PBDEs are used as flame retardants in a wide range of products, and waste from these products is probably the main source of PBDEs in the environment. The waste is either incinerated as municipal waste or

deposited in landfills. Although specific data are missing, incineration is thought to be an important route of release of PBDEs into the environment. No study on leaching of PBDEs from landfills is available, but PBDE-containing products are widespread, and leaching may be an important long-term pathway of contamination. PBDEs are discharged into the environment through sewage, as indicated by analysis of sewage sludge from various countries. Volatilization of PBDEs into the surrounding air from electrical components and other products during their lifetime can also be significant.

Apart from anthropogenic sources, PBDE-related brominated compounds also appear to be formed by nature and have been detected in certain marine sponges (23,24). These compounds structurally resemble hypothetical phenolic metabolites of PBDE congeners.

Environmental Levels

PBDEs have been detected in environmental samples from aquatic environments and organisms. On a congener basis, the levels of PBDEs in these samples (such as fatty fishes) could be similar to those of PCBs, but the levels of total PBDEs are lower because fewer congeners of PBDEs are present in technical mixtures and in the environment. Only a limited number of PBDE analyses have been conducted on terrestrial environments.

Little data are available about the environmental levels of nona-, hepta-, and hexaBDEs. These compounds probably exist in the environment at lower concentrations than other PBDEs, since nona-, hepta-, and hexaBDEs are impurities of commercial deca-, octa-, and/or pentaBDE preparations. The formation of these compounds as a result of degradation of higher BDs is also possible.

The following review of environmental levels of PBDEs is a selection of important observations and is not intended to be a definitive listing of all studies performed. For recent reviews of environmental levels of PBDEs and other organobrominated compounds, see de Boer et al. (25) and de Wit (26).

Abiotic samples. Air. In air samples from the vicinity of recycling plants in Japan and Taiwan various tri-, tetra-, penta-, and hexaBDEs were detected in the range of 23–53 pg/m³ (Taiwan) and 7.1–21 pg/m³ (Japan) (27). In Swedish air samples from remote sites with no known local source of contamination, the total PBDE levels were approximately 1–8 pg/m³. Whereas the tetraBDE level was higher in the gas phase, the pentaBDE level was higher in the particle fraction, in agreement with the respective vapor pressures of the two PBDE homologs (28).

Sewage sludge. PBDEs with 3–7 bromine atoms were identified in German sewage sludge samples (29). Pooled samples of

sewage sludge from a Swedish sewage treatment plant (Gothenburg) in 1988 were found to contain 15 and 19 ng of 2,2',4,4'-tetraBDE (BDE-47) and 2,2',4,4',5-pentaBDE (BDE-99) per g ignition loss, respectively (ignition loss: the carbon content in sample, measured as the loss in sample weight after incineration) (30). The sum of the levels of BDE-47 and BDE-99 were considerably higher, i.e., 100–190 ng/g dry weight, in recent sludge samples from three Swedish sewage treatment plants (31). The Swedish sludge data in Nylund et al. (30) found a BDE-47+99 level of 21 ng/g, calculated on dry weight basis. Sellström and co-workers (31) found that levels of BDE-209 were even higher—160–260 ng/g dry weight.

Water and sediments. DecaBDE, octaBDE, or hexaBDE were not found in water samples taken from more than 200 river, estuarine, and marine waters collected in Japan in 1977 and 1987–1989 (limit of detection 0.04–2.5 µg/L) (32). This is probably due to the very low water solubility of PBDEs. However, decaBDE, octaBDE, hexaBDE, pentaBDE, and tetraBDE were found in samples of river, estuarine, and marine sediments. DecaBDE was found at concentrations of < 25–11,600 µg/kg dry weight, while the range for the other compounds was from below the limit of detection up to 70 µg/kg sediment dry weight. The highest concentrations were found in contaminated rivers.

PBDE levels in sediment layers from the Baltic Sea (Bornholm Deep) decreased with increasing depth (10,30). At 5 mm deep, the levels of BDE-47 and BDE-99 were 1.6 and 1.1 µg/kg ignition loss, respectively. Below 40 mm, almost no pentaBDE was detected, whereas the concentration of tetraBDE was 0.1 µg/kg. In one situation, river samples collected upstream and downstream pinpointed the PBDE effluent source, a factory manufacturing flameproof textiles (14). For the sum of the three congeners BDE-47, BDE-99, and 2,2',4,4',6-pentaBDE (BDE-100), the concentration in sediment varied from below detection to 120 ng/g ignition loss, whereas BDE-209 (the full-brominated congener) had a peak concentration of 12,000 ng/g. In addition, the peak concentration of another brominated flame retardant, hexabromocyclododecane (HBCD), was 7,000 ng/g ignition loss. All three analyzed compounds or compound groups had the highest levels at the same sampling location.

Analysis of sediments from a number of European estuaries revealed high concentrations of BDE-209 in some rivers in the United Kingdom (e.g., River Mersey, 1,700 ng/g dry weight) and Belgium (River Schelde, 200 ng/g dry weight), whereas most samples showed levels below 20 ng/g dry weight (31).

BDE-47+99 levels were always considerably lower than those of BDE-209.

Biota. Aquatic organisms. In 1981, fish from the Swedish River Viskan were analyzed for PBDEs (33). The maximum levels in pike were 27 mg/kg lipid in muscle and 110 mg/kg lipid in liver. The water system was at that time receiving effluent water from nearby textile factories. Later analysis of PBDEs and HBCD in fish from the River Viskan indicated lower PBDE levels (maximum PBDE levels 4.6 mg/kg lipid; sum of BDE-47, BDE-99, and BDE-100) (14). Concomitant analysis of sediment samples showed that tetra- to pentaBDEs and HBCD are much more bioavailable than the full-brominated BDE-209.

A number of species from Swedish fauna were analyzed for the presence of PBDEs (sum of BDE-47, BDE-99, and BDE-100) from 1979 to 1988 [(34–36); Table 3]. The highest levels were found in fish from waters with known or suspected local sources of contamination. However, fish from other sampling spots also contained measurable levels. It is evident that animals (herring and seal) from the Baltic Sea contain higher levels of PBDEs than the same or similar species from other waters.

Herring collected during 1985 from three North Sea regions and from the Straits of Dover (between Holland and United Kingdom) contained an average of 8.4–100 µg BDE-47/kg lipid. Eels from Dutch rivers and lakes (10 locations) contained from < 20 to 1,700 µg BDE-47/kg lipid (37). Freshwater fish of various species from the waters of North-Rhine Westfalia contained

18–983 µg PBDE/kg lipid, and Baltic and North Sea fish 12–57 and 1–120 µg/kg lipid, respectively, quantified with Bromkal 70-5DE as a reference (38). In fish and shellfish samples from Osaka Bay, Japan, measurable levels of PBDEs were occasionally found (32). Concentrations ranging from 0.1–14.6 µg/kg wet weight were observed for tetra-, penta-, hexa-, and decaBDE, respectively. PBDEs were detected in bottlenose dolphins at levels up to 8 mg/kg lipid (39). PBDEs have also been found in the blubber of pilot whales caught off the coast of the Faroe Islands from 1994 to 1996 (40). Nineteen tetra- to hexaBDEs were identified in the pilot whales at mean total levels of about 1–3 mg/kg lipid, depending on sex and age. BDE-47 and BDE-99 accounted for about 70% of total PBDEs.

Haglund and co-workers (13) reported PBDE levels in fish and seals caught in the Baltic Sea. In herring (different age groups) and in salmon muscle, the BDE-47 levels were 3.2–27 and 167 µg/kg lipid weight, respectively. These BDE values in herring are lower than those earlier analyzed by Jansson and Sellström and their co-workers (35,36). PBDEs and other organohalogen compounds were found in sea-run Baltic salmon from the River Dalälven (total PBDE levels about 300 µg/kg lipid) (41). The presence of methylated and phenolic PBDE derivatives at levels similar to those of the major PBDE congeners was also reported (13,41). Strandman and co-workers (42) showed that the total PBDE (BDE-47, BDE-99, BDE-153) levels in Baltic herring were 13–24 µg/kg lipid weight and in

sprat 22–149 µg/kg lipid weight. In this study, analysis of different age groups of Baltic fish suggests an age-related accumulation of PBDEs in the body fat (Figure 3). PBDE concentrations (sum of BDE-47, BDE-99, and BDE-153) showed an age-related increase in 1- to 3-year-old Baltic herring, as well as in 3- to 13-year-old sprat (42). In sprat, the accumulation seemed to level off at 8 years of age. Also, Haglund et al. (13) found an age-related PBDE uptake (Figure 3).

Recent studies from the American continent have shown relatively high levels of PBDEs in certain samples from the aquatic environment. Canadian samples of crab, fish, and marine mammals all contained PBDEs, and the highest levels were found in porpoise from British Columbia waters (peak value, 1,400 µg BDE-47/kg lipid) (43). PBDE levels in fish from the Great Lakes were analyzed in two studies. One study (44) found total PBDE levels of 135–545 µg/kg lipid in Great Lakes lake trout, and the other (45) found about 3,000 µg PBDE/kg lipid in Lake Michigan steelhead trout. On a wet weight basis, the Lake Michigan fish contained almost 6 times more PBDE (41 µg/kg wet weight) than the Baltic salmon (7 µg/kg fresh weight).

Terrestrial/avian organisms. The osprey (*Pandion haliaetus*), a bird that feeds exclusively on fish, is the only nonaquatic species listed in Table 3 that has relatively high PBDE levels (36). In addition, eggs from the fish-eating guillemot contain relatively high levels of PBDEs. Apart from these species, samples from all other nonaquatic avian or terrestrial wild-living species (e.g., moose, reindeer) showed low or nondetectable PBDE levels.

Table 3. Swedish PBDE levels in sediment and biota, 1979–1988.^a

Sample	No. of samples ^b	2,2',4,4'-tetraBDE ^c	2,2',4,4',5-pentaBDE ^b	Unknown pentaBDE ^b	Sampling year
Aquatic organisms^d					
Whitefish, freshwater	35	15	7.2	3.9	1986
Arctic char, Lake Vättern	15	400	64	51	1987
Herring, Skagerrack	100	59	9.8	4.7	1987 (April)
Herring, Baltic proper	60	450	46	32	1987 (June)
Herring, Baltic proper	10 (in)	38	17	6	1987 (Sept)
Herring, Bothnian Sea	100	82	27	14	1986 (Nov)
Bream, River Viskan ^c	2 (in)	250, 750	2.3, 2.4	11, 37	1987
Perch, River Viskan ^c	2 (in)	2,200	380	230	1987
	24 000	9,400	3500		
Pike, River Viskan ^c	2 (in)	2,000	78,	170	1987
	6 500	1,100	640		
Pike, Dalsland Canal	9 (2 x p)	94–98	60–74	25–36	1988
Trout, Dalsland Canal	22 (in, p)	120–460	64–590	37–150	1988
Grey seal, Baltic Sea	8 (p)	650	40	38	1979–1985
Ringed seal, Svalbard	7 (p)	47	1.7	2.3	1981
Terrestrial/avian organisms^d					
Rabbit	15 (p)	< 1.8	< 0.3	< 0.2	1986
Moose	13 (p)	0.8	0.6	0.2	1985–1986
Reindeer	31 (p)	0.2	0.3	< 0.1	1986
Starling, young	4 (in)	2.7–7.8	2.3–4.2	0.6–1.1	1988
Osprey	35 (p)	1,800	140	200	1982–1986

Abbreviations: p, pooled sample; in, individual sample.

^aData from Jansson et al. (34,35) and Sellström (36). ^bConcentrations in µg/kg lipid weight (sediment: µg/kg ignition loss). ^cEffluents from industry using flame retardants reach the Viskan-Häggån river systems. ^dMuscle samples taken for analysis, except for reindeer (suet) and seal (blubber).

Trend Studies

Time trend. A retrospective time trend of PBDE levels was constructed (10,46) through laminated sediment cores collected in the Bornholm Deep (southern part of the Baltic Proper). In contrast to other environmental pollutants such as PCBs and DDT, PBDEs

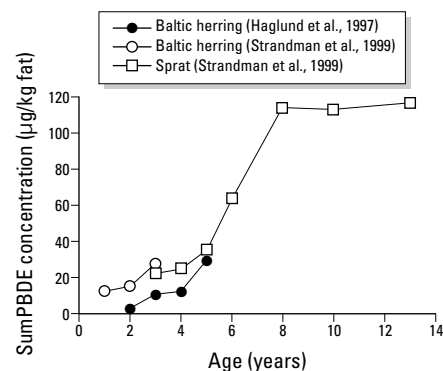


Figure 3. Age-related accumulation of PBDEs (sum of BDE-47, -99 and -153) in Baltic herring and sprat. Data from pooled sample analyses in Haglund et al. (13) and Strandman et al. (42).

were detected quite late in the cores, but from the late 1970s on, the levels increased exponentially (Figure 4). This strong increase in PBDE levels has continued to the most recent part of the study (1988–1989). This is in contrast to other environmental contaminants, the levels of which have decreased or remained unaltered in newly formed sediment layers (47).

The total concentrations of BDE-47, BDE-99, and an unidentified PBDE in guillemot eggs (from Stora Karlsö in the Baltic Sea) increased from 158 µg/kg lipid in 1970 to 1,211 µg/kg lipid in 1989 (36,48). However, subsequent egg analyses suggest a somewhat decreasing trend from 1990 and later (11). The trend analysis is hampered by large annual variations in PBDE concentrations, which may be explained in part by the small number of eggs ($n = 10$) collected per year (10). Concentrations of another brominated flame retardant, HBCD, increased significantly in the eggs over the entire time period (1968–1997) (49).

Studies using sample-bank specimens of pike muscle from fish in Lake Bolmen in southern Sweden showed increasing concentrations of PBDEs from 1974 to 1991 (from about 10 to 100 ng BDE-47/g lipid) (10). Since 1991, the trend in PBDE levels in pike is more difficult to interpret but seems stagnant (49). Levels of the methoxylated derivative of BDE-47 (MeO-BDE-47) decreased in pike during the time period (49).

Eel samples from the Rhine and Meuse Rivers revealed decreasing PBDE time trends levels during 1983–1993, whereas PBDE levels increased in the River Roer eel during the same time period (37,50).

Thus, time trend studies during the 1970s and 1980s show that PBDE levels in biota generally differ from those of most other organohalogenated environmental chemicals: PBDE levels increase or remain constant, whereas levels of most other persistent compounds decrease. Time trends in recent years are often difficult to follow because of small amount of samples and/or lack of data.

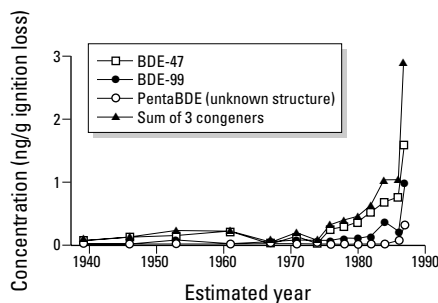


Figure 4. Time trend study of a laminated sediment core from the Baltic Sea (Bornholm Deep). Data from Nylund et al. (30).

In addition to environmental samples, mothers' milk has shown a strong increase in PBDE levels during 1972–1996 (51) (Figure 5) (see "Human Exposure to PBDEs").

Spatial trend. Few studies have been designed to study spatial or regional trends in environmental occurrence of PBDEs. However, de Boer (52) studied levels of BDE-47 in livers of cod caught from various locations in the North Sea. A distinct spatial trend was observed, with decreasing levels from the southern to the northern part of the North Sea (southern NS; 170 µg/kg, central NS; 54 µg/kg; northern NS, 26 µg/kg; mean values, all on wet weight basis). Other organohalogenated compounds such as sumDDT, exhibited the same type of spatial patterns. In the same study, the levels of BDE-47, the PBDE congener found at highest concentrations, remained at a relatively constant level during the period of sample collection. This trend was different from those of several organochlorine compounds that, with the exception of DDT, showed decreasing time trends in the same samples.

Bioaccumulation and Biomagnification

Although limited data are available, existing information strongly suggests that PBDEs are globally transported and distributed in the environment in a manner similar to PCBs. Consequently, they are probably of minor importance in terrestrial systems but may reach levels of concern in aquatic environments. In addition, PBDEs are persistent and have very low water solubility, high binding affinity to particles, and tendencies to accumulate in sediments. The presence of PBDEs in biota is likely to be because of their high lipophilicity and resistance to degradation.

Available data indicate that the higher brominated compounds (heptaBDEs and above) do not bioaccumulate to a significant degree, possibly because of a low uptake in organisms. However, in experimental studies the observation time may have been too short to detect a slow uptake. The uptake of the

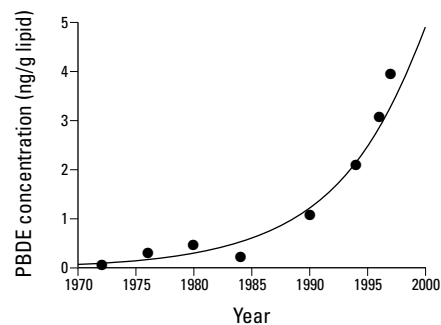


Figure 5. Time trend of the sum concentrations of 8 PBDE congeners in pooled mother's milk samples from Swedish mothers living in the Stockholm region. Data from Norén and Meironyté (51).

lower brominated PBDEs in the biota is more significant.

Increasing levels of the full-brominated BDE-209 were observed in rainbow trout during dietary exposure to this congener (53). Exposure of rainbow trout under static conditions to BDE-209 in water, however, did not result in measurable concentrations in muscle, skin, or viscera after 48 hr (54). The very low solubility of BDE-209 in water makes the latter study of questionable relevance. Bioconcentration factors of < 4 for BDE-209, < 2 for octaBDE, < 4 for heptaBDE, and < 4 for hexaBDE were determined in a bioaccumulation study in carps exposed to a mixture of hexa-, hepta-, nona-, and decaBDE for 8 weeks (probably present in the water) (55). In contrast, a bioconcentration factor of $> 10,000$ was found in a study with carp exposed to 10 or 100 µg pentaBDE/L for 8 weeks (probably a commercial mixture, i.e., a mixture of a tetraBDE and two pentaBDE congeners) (55). Also, components of commercial "tetraBDE" (41% BDE-47; 45% BDE-99, 7% hexa- and 7–8% unknown PBDEs) are considered accumulative (6). An inverse relation was shown between the uptake efficiency and number of bromine atoms in pike when tetra (BDE-47), penta (BDE-99), and hexa (BDE-153) congeners were studied (56). The uptake efficiency of BDE-47 was over 90% and thus the highest of all the studied organohalogenes.

Comparison of PBDE concentrations at different trophic levels of aquatic ecosystem suggests that PBDEs have a biomagnification potential in the food chain. PBDE levels in Baltic herring, salmon, and seals (13), and those in guillemot eggs and osprey (36) are highly indicative of biomagnification in the Baltic ecosystem (Figure 6). In a recent study, Burreau et al. (57) calculated biomagnification potentials for a number of PBDE congeners on the basis of sprat, herring, and salmon

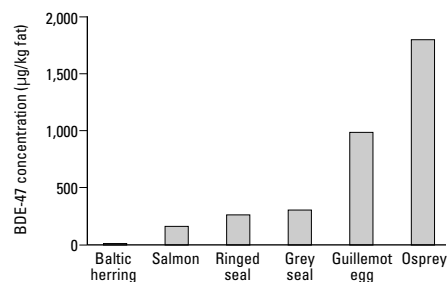


Figure 6. Concentration of the most abundant PBDE congener, BDE-47, at different trophic levels of the Baltic food chain: Baltic herring (muscle), salmon (muscle), ringed seal (blubber) and grey seal (blubber) (13), as well as guillemot (egg) and osprey (muscle) (36). Samples were collected between 1981 and 1991 along the Swedish coastline of the Baltic. The value for guillemot eggs represents the mean of six different analyses from 1982 to 1989.

data. All PBDE congeners analyzed were biomagnified. The tetra- and pentaBDEs were biomagnified to approximately the same degree, the triBDEs slightly less and the hexaBDEs considerably less. Preliminary data indicate that the tri-, tetra- and pentaBDEs are biomagnified more efficiently than any PCB congener.

It can be concluded, therefore, that PBDEs bioaccumulate in biota and that the extent of accumulation is inversely related to the degree of bromination. Available data indicate biomagnification of PBDEs in the food chain.

Environmental Transformation

Small amounts of data are available on transformation of PBDEs in the environment. Most studies have been done with decaBDE and mono/diBDEs.

Incineration. Incineration of waste containing PBDEs may result in formation of PBDDs and PBDFs (17,18). These compounds are structurally similar to the corresponding chlorinated compounds, more toxic than PBDEs, and very persistent in the environment. Formation of these compounds depends largely on combustion conditions. In a modern waste incinerator with well-controlled burning conditions, emission of brominated dioxins and furans is very low. In a Swedish study (58) on incinerator plants with well-controlled combustion conditions and efficient flue gas cleaning, no unacceptable environmental risk was found to be associated with combustion of PBDE-containing materials. On the other hand, uncontrolled fires at waste disposal sites may lead to formation and release of PBDDs and PBDFs into the environment (2).

Photodegradation. Watanabe and Satsukawa (59) showed that debromination of decaBDE, dissolved in organic solvents, occurs in ultraviolet (UV) light and sunlight, leading to formation of lower brominated BDEs and various PBDFs with 1–6 bromine atoms. Formation of PBDFs seems to occur only from low-brominated diphenyl ethers, but not directly from decaBDE. Photodegradation of decaBDE dissolved in water was also shown to occur, but no lower-brominated diphenyl ethers were detected among the degradation products (54,60). Sellström and co-workers (61) studied the photodegradation of decaBDE in various matrices (toluene, silica gel, sand, soil, and sediment). They showed that the time course for decaBDE debromination and formation/debromination of lower-brominated diphenyl ethers was rapid in toluene, whereas the degradation process in other matrices was considerably slower (half-life of decaBDE exposed to UV light in toluene and sand was 15 min and 12 hr, respectively).

Microbiologic degradation. No biotransformation products of BDE-209 were detected in sediment samples after incubation for 4 months (6). For other flame-retardant PBDEs, no data are available. On the other hand, low-brominated diphenyl ethers, not used as flame retardants, are more likely to be biodegradable. Microbiologic degradation of mono- and diBDEs has been demonstrated, but these congeners were not used as a carbon source for the bacteria (62–64). Even though BDEs with less than four bromine atoms are not used as flame retardants, they have been detected in the environment, possibly a result of degradation of higher-brominated diphenyl ethers (DEs). Thus, on the basis of limited data, microbial degradation of PBDEs seems to depend on the degree of bromination, and the full-brominated congener seems to be resistant to microbial degradation.

PBDEs in the Environment: Summary and Conclusions

PBDEs have been detected in air samples, even from remote areas. Analyses of organisms from terrestrial ecosystems indicate low levels of PBDEs but considerably higher levels are found in aquatic environments. In sediments the higher-brominated compounds are prevalent, but in biota these congeners are normally below the limit of detection. This indicates that the bioaccumulation of highly brominated PBDEs (especially decaBDE) is low. Microbial degradation of decaPBDE is negligible, whereas photodegradation of decaBDE may generate lower-brominated PBDEs. Thus, the lower brominated PBDEs, tetraBDEs, and pentaBDEs predominate and accumulate in biota. The uptake efficiency of BDE-47 in fish is very high, but an increase in PBDE bromination will gradually decrease uptake. Accumulation of PBDEs in fish appears to be age-related. The highest concentrations are found in top predators of aquatic ecosystems, suggesting the biomagnification potential of these compounds. Tetra- to hexaBDEs are probably the principal congeners to which humans are exposed via food. On a congener basis, the levels of PBDEs in these samples could be similar to those of the more frequent PCB congeners, but because fewer congeners are present, total PBDE levels are lower than total PCB levels. Observed spatial differences in environmental PBDE levels may reflect emissions from regional or point sources. Series of samples from sediments, guillemot eggs from the Baltic, and banked samples of pike from a Swedish lake have been used for time-trend analyses of PBDE levels. Until the late 1980s, PBDE levels in both sediment and biota generally showed an increasing trend. However, the most recent biologic samples (1990 and onward) indicate somewhat lower PBDE levels, although the variation is large.

Thus, continuation of the time trend studies is important.

Human Exposure to PBDEs

As pointed out previously, the environmental fate of PBDEs appears similar to the fate of other persistent environmental pollutants, PCBs, for example. On the basis of several years of PCB monitoring, it has been established that the main route of human exposure to PCBs is via food. Food of animal origin with high fat content, e.g., fatty fish, meat, and dairy products are major contributors to dietary exposure. Because of the similarity between PCBs and PBDEs in their environmental distribution, attention also should be focused on these food items when assessing exposure to PBDEs. For another persistent organic pollutant, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), as much as 98% of human exposure is suspected to occur through consumption of foods of animal origin (65). However, until recently very few estimates of human dietary PBDE intake have been made. In addition, little is known of other routes of human exposure and their importance in total human exposure to PBDEs.

PBDE Levels in Food

Fish. Several fish species consumed by man have been analyzed for PBDEs. Large variations in PBDE levels observed in freshwater fish may result from widely varying degrees of contamination. PBDE levels in fish sampled in Swedish lakes and rivers (pike, perch, bream, and trout) varied from 26 to 36,900 µg/kg lipid (14,33,36). In German freshwater fish, the levels varied between 18 and 983 µg/kg fat (2,38), and in eel from Dutch waters the variation in BDE-47 levels was < 20–1,700 µg/kg lipid (52). Herring (North Sea, Baltic Sea), salmon (Baltic Sea), and cod liver (North Sea) have been analyzed in studies of marine and brackish-water fish (13,36,37,41,52). Baltic herring contained 24–528 µg/kg lipid, whereas Swedish west coast herring contained 17–74 µg/kg lipid (Swedish herring analyses: sum of three congeners) and the North Sea herring 9–100 µg BDE-47/kg lipid (36,37). Levels in Baltic herring are generally higher than those in Atlantic herring. A similar difference was shown earlier for PCBs (66), which reflects, among other things, the limited water exchange between this inland sea and the ocean.

Dairy products. PBDE levels of 2.5–4.5 µg/kg milk fat, determined to be Bromkal 70-5DE, have been reported in cows' milk in Germany (38). Levels in mixed dairy products from 1999 Swedish market basket samples (sum of levels of BDE-47, -99, -100, -153, and -154), however, are considerably lower, with a mean value of 0.36 µg/kg milk fat (67).

Mothers' milk. PBDE levels in mothers' milk have been studied in a survey of 25

German mothers (38). Levels varied between 0.6–11 µg/kg (i.e., 600–1,100 ng/kg) milk fat.

Darnerud and co-workers (68) studied 39 primiparous women from Uppsala county, Sweden, and analyzed the five most frequently found PBDE congeners in their milk (BDE-47, -99, -100, -153, and -154). The mean value was 4.4 µg/kg lipid and the range 1.1–28.2 µg/kg. Milk PBDE levels correlated positively and significantly with mothers' smoking habits and body mass index. However, no correlation was seen between PBDE and mothers' ages, consumption of fish, places of residence during childhood or adulthood, birth weights, or frequency of using computers.

In another Swedish study, a time trend was created using stored samples of breast milk collected from 1972 to 1997 (51). The mean PBDE level (sum of eight different congeners; predominantly BDE-47) in milk from 1997 was 4 µg/kg, quite similar to the above report by Darnerud et al. (68). Concentrations of PBDEs in milk showed a strong time-dependent increase, with a doubling in levels within 5 years (Figure 4). In contrast, tissue levels of most halogenated aromatic hydrocarbons of concern (e.g., PCB, DDT) were declining. Thus, future levels of PBDE in milk may eclipse those of PCB if trends continue.

PBDE levels detected in mothers' milk are, on a lipid basis, generally within the same range as those observed in human adipose tissue samples from the United States and human serum samples from Sweden (see "PBDE Levels in Humans").

PBDEs from other food groups. Except for the low levels of PBDEs found in samples from animals living in the wild (36) (Table 3), little data are available on PBDE levels in meat and eggs. However, preliminary data from mixed meat products from Sweden (market-basket samples) revealed a mean level of 0.36 µg/kg fat (67). The mean level in Swedish eggs (from the same study) was 0.42 µg/kg fat.

Estimation of PBDE Exposure

From food. Darnerud et al. (69), using primarily Nordic data, estimated the exposure of PBDEs from food in a report to the Nordic Council of Ministers (69). Their estimates were based on the upper range of total PBDE levels in herring caught in the Baltic Sea (36), i.e., 528 µg/kg lipid (of which 450 µg/kg was BDE-47 and the remainder two pentaBDEs). The total PBDE intake can be estimated by assuming a similar relative intake from different dietary sources, as described earlier in a Swedish estimation for PCBs (66). Consequently, according to this very approximate calculation, the total PBDE intake for the Nordic consumer would be 0.2–0.7 µg/day.

A Swedish intake estimate was made recently (67) on the basis of PBDE levels

(BDE-47, -99, -100, -153, and -154) in market basket samples from 1999. Provisions from eight grocers in four major Swedish cities were received and divided into selected groups. Within these groups, each food item was added in an amount determined from per capita consumption statistics. Analyses of the homogenates were performed and sumPBDE levels were obtained by addition of congener levels, assuming that levels below the limit of quantification (LOQ) were equal to one-half of this limit. The total PBDE intake was obtained by adding intake from the fish, meat, dairy products, eggs, fats/oils, and pastry food groups (i.e., the product groups assumed to contribute most to total intake). Using this method, total PBDE intake in Sweden was estimated to be 51 ng/day. Almost half total intake originated from fish products; meat, dairy products, and fat/oils contributed approximately 15% each. Total PBDE intake was 4–14 times below estimates performed earlier but should be a more accurate description of the intake, as it is based of a more complete set of occurrence-level data. However, this estimate should be supplemented by studies from other countries and by using other methods of estimating intake to obtain a more complete picture of the intake of PBDEs from food.

From mothers' milk. The most recent human milk data come from two Swedish surveys (51,68). The mean PBDE levels in these two studies are almost identical, giving a total mean value of 4.2 µg/kg milk fat. To estimate the PBDE intake in infants, consumption data from Ahlborg and co-workers (70) were used. The calculated PBDE intake using these predictions (3.7% fat in milk; consumption of 0.7 L milk daily for 6 months) is 0.11 µg/day from mothers' milk, or 20 µg in 6 months.

Other possible routes of exposure. It appears obvious that sources other than food significantly influence total PBDE intake in humans. There is, however, almost a complete lack of data on these other sources of human exposure. Emission of PBDEs from electronic apparatuses like computers and TV sets, especially from warm devices after prolonged use, are suspected. In an experiment with a TV set, Ball et al. (71) detected PBDEs in air drawn from a warm TV. In Darnerud's previously cited study (68) on PBDE milk levels from primiparous women, however, no correlation was found between frequency of computer usage and PBDE milk levels. Because of these conflicting results, the use of computers and TV sets as sources for human exposure should be further investigated.

Sjödin et al. (72), in a recent publication, monitored the occupational exposure to PBDEs. Subjects working at a Swedish dismantling plant had significantly higher serum

levels of all studied PBDE congeners compared to both hospital cleaners and office clerks using computers (see "PBDE Levels in Humans"). It was concluded that exposure from daily computer work in an office does not appear to increase serum PBDE levels.

PBDE Levels in Humans

PBDEs were detected (up to 5 µg/kg dry weight) in 2 of 40 hair samples from American citizens living in an area where PBDEs are manufactured, according to DeCarlo (73).

In two studies from the United States (74,75), PBDEs were detected in human adipose tissue samples collected in 1987. The presence of PBDEs was demonstrated in all samples (48 composite samples from 865 individuals). These studies also showed a large variation in PBDE levels between individuals (hexaBDE, not detected–1 µg/kg lipid; heptaBDE, 3 ng–2 µg/kg lipid; octaBDE, not detected–8 µg/kg fat; no congener specification was presented).

PBDE levels in adipose tissue were reported in three Swedish studies. In a male Swede 74 years of age, a level of 8.8 µg BDE-47/kg lipid was reported (13). In the second study (76), adipose tissue from 77 individuals of both sexes, 28–85 years of age, some of whom were cancer patients, were analyzed. In persons without malignancies, the mean BDE-47 level was 5.1 µg/kg lipid, but in patients with non-Hodgkin lymphoma (NHL) it was 13 µg/kg lipid. (According to the authors a connection between PBDEs and NHL cannot be excluded.) In the third Swedish study, levels of several PBDEs in adipose and hepatic tissue from two male subjects (66 and 78 years of age) were reported (77). The mean levels of BDE-47 in these two types of tissue were 2 and 2–5 µg/kg lipid, respectively. In a Finnish study (42), the PBDE levels (sum of BDE-74, -99, and -153) in adipose tissue from randomly selected individuals (36–84 years of age) ranged from 6.2 to 22 µg/kg lipid.

Studies on human blood have demonstrated that 2,2',4,4'-tetraBDE is the major PBDE congener (of six congeners analyzed) in serum samples from Swedish blood donors ($n = 40$; sampling year 1996) (78). The mean serum level of sumPBDE was 2.1 ± 1.4 µg/kg lipid, which is approximately two orders of magnitude lower than that of sumPCBs.

Results from analysis of PBDEs in Swedish breast milk are presented above ("PBDE Levels in Food") (51,68). PBDE levels in lipids are in the same range as those for adipose tissue and blood from Swedish individuals.

In a study on Swedish dismantling plant workers, levels of five PBDE congeners [BDE-47, BDE-153, BDE-154, BDE-183 (2,2',3,4,4',5',6-heptaBDE), and BDE-209] were measured in serum (72). Among the dismantling workers heptaBDE congener

BDE-183 was the most abundant at the mean concentration of 8 µg/kg lipid, and also the mean concentration of BDE-209 was as high as 5 µg/kg lipid. The sumPBDE levels in groups of hospital cleaners, computer clerks, and electronics dismantlers were 3, 4, and 26 µg/kg lipid weight, respectively. Therefore, occupational exposure in dismantling plants may contribute significantly to human exposure to PBDEs. Nevertheless, PBDE levels of the dismantling workers are still rather low compared to PCB serum levels (26 µg sumPBDE and 270 µg PCB-153 per kg lipid, respectively).

Human Exposure to PBDEs: Summary and Conclusions

Sufficient data are available on PBDE levels in fish, whereas less is known about PBDE levels in other major food groups or about possible differences in food levels between countries or regions.

A recent intake study based on a complete set of Swedish occurrence (market basket) data from 1999 found PBDE intake from food to be 51 ng/day. The intake from mothers' milk during lactation, using data from Swedish studies, was estimated to be 110 ng/day. These estimates should be supplemented by studies from other countries and by using other methods to estimate intake to obtain a more complete picture of the intake of PBDEs from food.

Analytic data on human blood, adipose tissue, and milk have confirmed that PBDEs are also present in the human body. The major route of human exposure appears to be via food, although other routes of exposure cannot be excluded. Workers exposed to PBDEs during computer dismantling were shown to have significantly higher blood levels of several PBDE congeners than nonexposed subjects. Available data generally suggest that current levels of PBDE are more than an order of magnitude lower than those of PCBs. However, attention must be paid to exposure of infants from continuously increasing levels of PBDEs in mothers' milk.

Toxicokinetics

Experimental Animals

Absorption and elimination/retention. Oral administration of ¹⁴C-labeled decaBDE (BDE-209) to rats resulted in fecal excretion of > 90% of the dose 2 days after administration. Elimination in urine and in expired air was less than 1% over a period of 16 days, and accessible data seem to suggest minimal absorption of decaBDE from the gastrointestinal tract (54,60,79). In a carcinogenicity study (80), ¹⁴C-labeled decaBDE was given in the diet to rats to quantify decaBDE absorption from the gastrointestinal tract.

Results indicated that for all dose levels (250–50,000 mg/kg) more than 99% of the radioactivity recovered was eliminated in the feces within 72 hr. Urinary excretion accounted for about 0.01% or less of the dose; tissue levels of radioactivity were near the limit of detection, and in the liver, the radioactivity was confirmed as decaBDE. Similarly, El Dareer and co-workers (81) showed that < 1% of the dose of a radiolabeled decaBDE given orally to rats was found in tissues (about half in the liver) after 24 hr.

In a 2-year accumulation study, rats were maintained on diets providing up to approximately 1.0 mg technical decaBDE/kg body weight (bw) per day (of which 77.4% was the decaBDE congener, 21.8% nonaBDE, and 0.8% octaBDE). Selected tissues were analyzed for total bromine content. In most tissues (serum, liver, kidneys, skeletal muscle, and testes) the bromine contents were not above background, but in the adipose tissue bromine concentration was 3-fold that of controls (0.1 mg/kg bw/day). Regarding elimination, the moderate bromine accumulation in the adipose tissue remained unaffected during 90 days of recovery, whereas bromine was cleared from the liver within 10 days of recovery (82,83).

These data suggest that the bioaccumulation potential of decaBDE is low, but the retention in body fat may be pronounced. In comparison, the bioaccumulation of an octabromobiphenyl (belonging to the PBB group) was much more pronounced (79). Possible metabolism and/or debromination of decaBDE may interfere with the results.

Von Meyerink and co-workers (84) studied the retention of different fractions of Bromkal 70 in perirenal fat from rats. Bromkal 70 (mainly pentaBDE) was given as a single oral dose of 300 mg/kg bw, and the rats were killed after 1–10 weeks. Concentrations of the different PBDEs were analyzed by high pressure liquid chromatography, and gas chromatography–mass spectroscopy was used to confirm the degree of bromination (the stereochemistry of the individual compounds was not elucidated). Half-lives for two hexaBDE congeners were 50 and 105 days, respectively, and for two different penta congeners, 42 and 25 days. Half-life of tetraBDE(s) was 19–30 days, depending on sex of the subject. Half-life was shorter in males than in females.

In a bioaccumulation study in pike (*Esox lucius*) (56), 12 different halogenated diaromatic compounds, including three PBDE congeners, were administered in feed. Gastrointestinal bioavailability was 95% for BDE-47 (highest for all compounds studied), 60% for BDE-99, and 40% for BDE-153, indicating a clear decrease in uptake with increasing bromination.

Generally, lower-brominated PBDEs appear to be accumulated in biota to a greater

extent than higher-brominated compounds. This is also evident from comparison of the Bromkal 70-5DE composition with the PBDE pattern in herring and seal: concentrations of tetraBDE (BDE-47) are increased in biota in relation to other congeners. Conversely, the relative concentrations were the same in Bromkal 70-5DE and in samples from herbivorous mammals in Sweden. According to Zitko (85), compounds with low bromine content are bioconcentrated more strongly from water than compounds with high bromine content. For example, PBBs with more than six bromine atoms were scarcely bioconcentrated; similar conditions may apply for PBDEs. In contrast, half-lives of PBDEs in adipose tissue of rats increase with the degree of bromination (84). It can be concluded that absorption of PBDEs, which favors lower-brominated congener groups, is an important determinant of bioaccumulation, at least in aquatic environments. Elimination of PBDE, on the other hand, may be slower for higher-brominated compounds, although they are less accumulative. However, data are sparse and somewhat contradictory.

Distribution. Tissue distribution of ¹⁴C-decaBDE was studied in rats 16 days after a single oral dose (54,60,79). Radioactivity was observed only in the adrenal glands (0.01% of administered dose) and in the spleen (0.06% of administered dose) but not in any other tissue studied.

In the above-mentioned high-dose experiment with oral ¹⁴C-decaBDE (80), the liver contained about 0.5 and 0.016% of the dose 24 and 72 hr, respectively, after dosing. Radioactivity extracted from the liver was found to be mainly the unchanged component. Traces of the label were found in the kidneys, spleen, lung, brain, muscle, fat, and skin. Distribution data after intravenous (iv) injection of labeled decaBDE indicate that feces collected during this period and the contents of the intestines altogether contained 74% of the dose, suggesting considerable biliary excretion. Radioactivity was also detected in the liver, kidneys, and lungs, and at lower concentrations in muscle, skin, and fat.

In a comparative study on radiolabeled BDE-47 in rats and mice (12,16), an effective absorption and accumulation in adipose tissue was shown. The study also indicated a marked species difference in degree of retention. In rats 86% of the oral dose (approximately 30 µmol/kg bw=14.6 mg/kg bw) was retained in the body within 5 days, compared to only 47% in mice. Radioactivity was about 3 times higher in fat than in liver in rats, whereas in mice the levels in the two tissues were comparable.

Metabolism. In studies by Norris and co-workers (54,60,79), rats were injected iv with ¹⁴C-decaBDE, after which the radioactive

compounds in feces were analyzed. Of the excreted fecal label, 63% were unidentified metabolite(s) of decaBDE and 37% were unchanged decaBDE. El Dareer and co-workers (81) obtained similar results. They suggested that extensive metabolism of the orally administered compound might take place in the gastrointestinal tract.

Studies with ¹⁴C-BDE-47 in rats and mice revealed five hydroxylated PBDE metabolites in feces and tissues, although BDE-47 was the major compound detected (12,16). A marked difference was found in urinary excretion between the mouse and rat. Within 5 days, rats excreted < 1% and mice excreted 33% of the dose in urine (the corresponding figures for fecal excretion, including nonabsorbed material, were 14 and 20%, respectively). The label in the mouse urine was highly hydrophilic and labile, and no specific metabolites could be identified. No debromination products of PBDEs were found. Thus, the metabolism of BDE-47 seems limited, at least in rats, but there are marked species differences in rodents in metabolism and excretion of this and probably other PBDE congeners.

Limited metabolism and excretion of another PBDE congener, BDE-99 (a pentaBDE), was observed in rats (86). Small amounts of mono-hydroxylated metabolites of penta- and tetraBDE were detected in feces, which indicates *in vivo* debromination. Mono- and dihydroxy pentaBDEs as well as two thio-substituted pentaBDEs were detected in bile.

Methoxylated PBDE congeners have been identified in Swedish fish and seal samples (13). These compounds may have been formed by *in vivo* methylation of hydroxylated PBDE metabolites. On the other hand, microbial formation or other biogenic sources are also possible.

In a toxicokinetic study (53), rainbow trout were administered technical decaBDE (containing small amounts of nona- and octaBDE) in the diet. PBDEs levels in muscle were monitored during a depuration period in clean water. The analysis revealed decreasing levels of decaBDE, whereas levels of BDE-153 increased continuously during the depuration period. The results indicate metabolic debromination of decaBDE to BDE-153 in fish.

Microsomal enzyme induction. PBDEs are able to induce both phase I and phase II xenobiotic metabolizing enzymes. Regarding the cytochrome P450 (CYP)-mediated phase I metabolism, CYP1A1 and CYP1A2 were induced, as indicated by the increased activity of liver microsomal 7-ethoxyresorufin *O*-deethylase (EROD) activity after Bromkal 70 exposure in Wistar rats (84) and in H-4-II cells (87). The other enzymes used as indicators of microsomal phase I activity, benzphetamine *N*-demethylase, *p*-nitroanisole

demethylase, arylhydrocarbon hydroxylase (AHH), and benzo[*a*]pyrene hydroxylase, were also induced by PBDEs (technical pentaBDE preparations in rats) (84,88,89). Some of the enzymes were induced in a long-term oral administration study at doses as low as approximately 1 μmol/kg/day, and the enzyme activities continued 30–60 days after termination of the exposure (89). The full-brominated decaBDE, however, appears to have low enzyme-inducing potency.

The effects of BDE-47 and Aroclor 1254 on microsomal enzyme induction was studied in Sprague-Dawley rats (90). Induction of EROD and 7-methoxyresorufin-*O*-deethylase activities by BDE-47 was limited, in contrast to the marked induction (> 100-fold) in Aroclor-exposed animals. The effect on the pentoxyresorufin analog, known to describe CYP2B activity, was, on the other hand, almost the same after treatment with both BDE-47 and Aroclor 1254. If induction capacity is indicative of metabolic pathways of these compounds, the CYP2B enzymes may be important in the metabolism of PBDEs.

In a recent study using a recombinant rat hepatoma cell line H4IIE with a luciferase reporter gene, several PBDE congeners acted as Ah-receptor agonists (91). In this model potencies of the agonists were comparable to those of some mono-*ortho* PCBs. Some PBDE congeners also had antagonistic effects on TCDD-induced luciferase production.

Halogenated dioxinlike compounds typically induce CYP1A1 and 1A2. Therefore, enzyme induction may be due to impurities with Ah-receptor binding affinity present in technical PBDE mixtures. It was shown that PCDF impurities at concentrations < 1% could completely account for the observed EROD activity of all except one of 29 tested polychlorinated diphenyl ether (PCDE) congeners (92). This study demonstrated that in studies with halogenated DEs, it is important to control the presence of potent dibenzofuran and dibenzodioxin impurities, which even at low concentrations can account for considerable biologic activity attributed to the relatively high dosages required for DEs. The outcome of this study is in agreement with structural considerations suggesting that the nonplanarity of halogenated DEs results in a low binding affinity to the Ah receptor (93). Nevertheless, some studies have shown that pure PCDEs indeed are weak inducers of microsomal EROD and AHH activities in a congener- and conformation-specific manner (94–97).

In studies on phase II induction, three different PBDE fractions were tested; i.e., low (24% tetra, 50% penta) and high (45% hepta, 30% octa) brominated mixtures, and the decaBDE congener only. After daily oral administrations (14 days, 0.1 mmol/kg bw), both of the mixtures, but not the decaBDE,

resulted in long-lasting induction of uridine diphosphate glucuronyltransferase (UDPGT) activity in rats (88).

Human Data

As mentioned previously, PBDEs are found in human blood and tissues and in human breast milk. Data show that PBDEs are also absorbed and retained in man and that BDE-47 is the most abundant congener in most cases. Today, data are too limited to estimate the degree of human bioavailability and bioaccumulation. However, Sjödin (98) estimated the elimination half-lives of certain PBDE congeners in humans. Calculations were based on blood levels taken before and after vacation of workers in an electronics dismantling plant (72). By this method, the estimated half-lives of BDE-183 and BDE-209 were set to 86 days and 6.8 days, respectively. The levels of BDE-47 and BDE-153 were also determined in the same manner, but because no clear decrease during vacation could be observed, the half-lives could not be estimated.

These results suggest that the elimination half-lives of PBDEs increase with degree of bromination. This suggestion contrasts with results in rats, where the reverse seems to be true, at least regarding tetra- to hexaBDEs (84). Results on elimination of PBDEs increase with degree of bromination in humans are quite different than those found for PBBs and PCBs, where increases in halogenation generally extend elimination half-lives.

Toxicokinetics: Summary and Conclusions

DecaBDE is minimally absorbed from the gastrointestinal tract of mammals because of its relatively high-molecular mass, and therefore it is unlikely to bioaccumulate. In fish, however, uptake of decaBDE and subsequent debromination to lower-brominated PBDEs has been demonstrated. There is no information on uptake or elimination of octaBDEs in mammals. OctaBDEs are found in human adipose tissue and in aquatic sediments, but bioaccumulation is not likely to be substantial because of low absorption. PentaBDEs are found in biota, sediment, and sewage sludge samples. They are likely to be persistent and to bioaccumulate, and a bioconcentration factor of > 10,000 has been determined for carp. A commercial tetraBDE mixture accumulates and is persistent in many organisms in the environment.

Penta- and tetraBDEs are quite persistent in the environment. Some mammalian uptake and elimination studies suggest effective absorption and only moderate retention. Considerable species differences have been reported in metabolism and excretion of the tetraBDE congener BDE-47. The rat appears

to have a much slower metabolism and (urinary) excretion than the mouse. Formation of hydroxylated, thiol-substituted as well as debrominated metabolites of BDE-47 and BDE-99 has been demonstrated in rats. Methoxylated PBDE analogs have been found in samples from fish and seal. Possibly they are formed by *in vivo* methylation of hydroxylated PBDE metabolites or by microbiologic transformation.

Toxicology

No complete toxicologic evaluation is currently available on any of the commercially available PBDE mixtures or on any individual

congener. Most studies have been performed using commercial PBDEs that are more or less unspecified mixtures of congeners and isomers. Consequently, a limited amount of data is available about congener-specific effects. An important question concerning PBDEs is whether because of their structural similarity to the highly toxic polyhalogenated aromatic hydrocarbons, such as polyhalogenated biphenyls, dibenzo-*p*-dioxins, and dibenzofurans, PBDE effects could occur by the same mechanism(s) of toxicity. It is also important to determine if contaminants in technical PBDE mixtures exert toxic effects, and if so, through which mechanism(s).

In this section, we examine available toxicity data on PBDEs. On the basis of existing data, a lowest-observed-adverse-effect level (LOAEL) value for the whole PBDE group is proposed. The collected data are used in the next section, "Toxicological Evaluation."

Experimental Studies in Animals

Toxicologic information on PBDEs is based on both published studies and research reports made available recently by the chemical industry (2,7). A summary of the data from studies on the acute toxicity, irritation, sensitization, genotoxicity and other short-term effects of PBDEs is presented in Table 4. Available

Table 4. Summary of the acute toxicity, irritation, sensitization, genotoxicity, and porphyrinogenic activity of PBDEs.

Study	PBDE	Test system	Result	Reference
DecaBDE				
Acute toxicity	DecaBDE (commercial)	Rat, f (Sprague-Dawley)	> 2 g/kg bw	(2,54,79)
		Rat, m (Spartan)	> 5 g/kg bw	(2)
Dermal LD ₅₀		Rabbit, m+f (New Zealand white)	> 2 g/kg bw (exposure for 24 hr)	(2)
Inhalation LC ₅₀			> 48,2 mg/l (exposure for 1 hr)	(2)
		Rat, m+f (Spartan)		
Skin irritation	DecaBDE (commercial)	Rabbit, m+f (New Zealand white)	No irritation - slight erythema and edema (on abraded skin)	(2,54,79)
Chloracne activity	Saytex 102 ^a	Rabbit, m+f (New Zealand white)	Negative	(2)
	DecaBDE (commercial)		Negative	(2)
		Rabbit (not specified)		
Eye irritation	Saytex 102	Rabbit, m+f (New Zealand white)	Transient redness and chemosis	(2,54,79)
Skin sensitization	DecaBDE (commercial)	Human volunteers	Negative	(2,54,79)
Genotoxicity				
Mutagenicity	HFO 102 ^b	<i>S. typhimurium</i>	Negative	(2)
	Not specified	<i>S. cerevisiae</i>	Negative	(2)
	DecaBDE (commercial)	Mouse lymphoma L5178Y cells	Negative	(2)
Chromosomal effects	DecaBDE (commercial)	Chinese hamster ovary cells	Negative	(2)
	DecaBDE (commercial)	Rat bone marrow <i>in vivo</i>	Negative	(2,54,79)
	DecaBDE (commercial)	Chick embryo liver cells	Negative	(100)
Porphyrinogenic activity				
OctaBDE				
Acute toxicity	Not specified	Rat (not specified)	> 28 g/kg bw	(2)
		Rat, m (Charles River CD)	> 5 g/kg bw	(2)
Dermal LD ₅₀	OctaBDE (commercial)	Rabbit, m+f (albino)	> 2 g/kg bw (exposure for 24 hr)	(2)
Inhalation LC ₅₀	OctaBDE (commercial)	Rat, m+f (Charles River CD)	> 60 mg/L (exposure for 1 hr)	(2)
	Saytex 111 ^c		> 50 mg/L	(2)
		Rat (not specified)		
Skin irritation	OctaBDE (commercial)	Rabbit, m+f (albino)	No irritation - slight erythema	(2)
Eye irritation	OctaBDE (commercial)	Rabbit, m+f (New Zealand white)	No irritation - slight redness	(2)
Genotoxicity				
DNA damage	OctaBDE (commercial)	WI-38 human fibroblasts	Negative	(2)
		<i>S. typhimurium</i>	Negative	(2)
		<i>S. cerevisiae</i>	Negative	(2)
Chromosomal effects		CHO cells	Negative	(2)
Porphyrinogenic activity	OctaBDE (commercial)	Chick embryo liver cells	Strong porphyrinogenic effect	(100)
PentaBDE				
Acute toxicity	PentaBDE (commercial)	Rat, m (Charles River CD)	0.5 – 5 g/kg bw	(2)
		Rat, m+f (Wistar)	m: 7.4 g/kg bw	(2)
Dermal LD ₅₀		Rabbit, m+f (New Zealand white)	> 2 g/kg bw (exposure for 24 hr)	(2)
Inhalation LC ₅₀		Rat, m+f (Charles River CD)	> 200 mg/L (exposure for 1 hr)	(2)
Genotoxicity				
Mutagenicity	PentaBDE (commercial)	<i>S. typhimurium</i>	Negative	(2)
		<i>S. cerevisiae</i>	Negative	(2)
Porphyrinogenic activity	DE-71 ^d	Rat, m+f (Sprague-Dawley CD)	Highly increased concentrations of porphyrins in liver and urine after oral dosing at 100 mg/kg bw/day for 13 weeks.	(2)

Abbreviations: f, female; m, male.

^aSaytex 102 is a technical decaBDE product. ^bHFO 102 is a technical decaBDE product. ^cSaytex 111 is a commercial mixture containing pentaBDE, 0.2%; hexaBDE, 8.6%; heptaBDE, 45%; octaBDE, 33.5%; nonaBDE, 11.2%; and decaBDE, 1.4% (2). ^dDE-71 is primarily a mixture of tetra-, penta-, and hexaBDE containing low levels of tri- (> 1%) and heptaBDE (< 2%) (2).

information on subchronic and chronic toxicity, carcinogenicity, and teratogenicity is given in Table 5.

Acute toxicity and local irritation. In general, the acute toxicity of PBDEs (administered orally, dermally, or by inhalation) is low

(Table 4). The low toxic potency of fully brominated BDE-209 is likely to be explained by poor absorption after oral administration (54,60,79,80). Available data are not suitable for use in even limited structure-toxicity correlations. PentaBDEs

appeared to be more toxic after oral administration than octa- and decaBDEs, as they caused clear signs of toxicity and mortality primarily at high doses (oral LD₅₀ in rats 0.5–5 g/kg or 7.4 g/kg, depending on the study; Table 4). The clinical signs were

Table 5. Summary of the repeated dose toxicity, carcinogenicity and special toxicity studies on PBDEs.

Study	Species (strain)	PBDE (purity)	Dosage (mg/kg bw/day)	Effects (dose level for observed effect)	Reference
DecaPDE					
Subacute toxicity (14 days)	Mouse (B6C3F ₁)	DecaBDE (99%)	In diet: 0, 3,000, 7,500 or 15,000 ^a	No compound-related effects	(80)
	Rat (Fischer 344/N)	DecaBDE (99%)	In diet: 0, 500, 2,000, 5,000 or 10,000 ^a	No compound-related effects	(80)
Subacute toxicity (28 days) (30 days)	Rat (Charles River CD)	DecaBDE (commercial)	In diet: 0, 10, or 100 ^a	No compound-related effects	(2)
Subchronic toxicity (13 weeks)	Rat (Sprague-Dawley)	DecaBDE (77.4%), NonaBDE (21.8%), OctaBDE (0.8%)	In diet 0, 8, 80, or 800	Thyroid - hyperplasia (≥ 80); liver - enlarged (≥ 80); kidney - hyaline degeneration (≥ 80); hematocrit and red cell count - decreased (800)	(2,54,79)
	Mouse (B6C3F ₁)	DecaBDE (> 97%)	In diet: 0, 465, 930, 1,875, 3,750, or 7,500 ^a	No compound-related effects	(80)
Chronic toxicity, carcinogenicity (103 weeks)	Rat (Fischer 344/N)	DecaBDE (> 97%)	In diet: 0, 310, 620, 1,250, 2,500, or 5,000 ^a	No compound-related effects; liver weights not recorded, in subsequent studies; liver - enlarged (≥ 2,500)	(80)
	Mouse (B6C3F ₁)	DecaBDE (94–99%)	In diet: 0, 3,200, or 6,650 (males), 0, 3,760, or 7,780 (females)	Liver - hypertrophy, granulomas, adenomas, carcinomas (in males ≥ 3,200); thyroid - follicular cell hyperplasia, adenomas, carcinomas (≥ 3,200)	(80)
	Rat (Fischer 344/N)	DecaBDE (94–99%)	In diet: 0, 1,120, or 2,240 (males), 0, 1,200, or 2,550 (females)	Liver - adenomas (≥ 1,120), thrombosis, degeneration (in males 2,240); pancreas - acinar cell adenomas (in males 2,240); spleen - hyperplasia (in males 2,240); lymphoid tissue - hyperplasia (in males 2,240)	(80)
	OctaBDE				
Subacute toxicity (28 days)	Rat (Charles River CD)	OctaBDE (commercial)	In diet: 0, 10, or 100 ^a	Liver - enlarged, cytoplasmic eosinophilic round bodies (≥ 10); thyroid - hyperplasia? (100)	(2)
	Rat (Charles River CD)	OctaBDE (commercial)	In diet: 0, 10, 100, or 1,000 ^a	Liver - hepatocytes enlarged with cytoplasmic eosinophilic round bodies (≥ 10), whole liver enlarged (≥ 100), hepatocytes vacuolized with focal necrosis (1,000)	(2)
Subchronic toxicity (13 weeks)	Rat (Charles River CD)	OctaBDE (commercial)	In diet: 0, 10, 100, or 1,000 ^a	Liver - enlarged, cytoplasm granular (≥ 10), hepatocytes vacuolized, hyaline intracytoplasmic inclusions, hyperplastic nodules (≥ 100), accentuated lobulation, yellowish mottling, brownish discoloration, focal necrosis, centrilobular fibrosis, pigmented Kupfer cells (1,000); thyroid - enlarged (≥ 100), cellular changes (1,000); kidney - enlarged, cortical regenerative tubules, a single case of tubular nephrosis (1,000); hemoglobin, hematocrit, erythrocyte count - decreased (1,000); blood glucose - decreased (1,000); urine - orange discoloration (1,000); bw gain - decreased (≥ 100)	(2)
PentaBDE					
Subacute toxicity (28 days)	Rat (Charles River CD)	PentaBDE (commercial)	In diet: 0, 10, or 100 ^a	Liver - enlarged, cytoplasmic eosinophilic round bodies (≥ 10); thyroid - follicular hyperplasia? (≥ 10)	(2)
Subchronic toxicity (90 days)	Rat (Sprague-Dawley CD)	DE-71 ^b	In diet: 0, 2, 10, or 100	Serum thyroxin - decreased (≥ 10); thyroid hyperplasia - (≥ 10); liver - enlarged, hepatocytomegaly (≥ 10); liver and urine porphyrins - increased (100); serum cholesterol - increased (100); food consumption - decreased (in females 100); bw - decreased (100)	(2)
Special single dose toxicity	Mouse (C57BL/6)	DE-71 ^b	By gavage: 0, 0.8, 4, 20, 100, or 500	Serum thyroxin - decreased (≥ 0.8?)	(104)
Special repeated dose toxicity (14 days)	Mouse (C57BL/6)	DE-71 ^b	By gavage: 0, 18, 36, or 72	Serum thyroxin - decreased (≥ 18)	(104)
	Mouse (C57BL/6)	Bromkal 70-5 DE ^c	By gavage: 0, 18, or 36	Serum thyroxin - decreased (≥ 18) Liver somatic index - increased (36)	(130)
	Rat (Sprague-Dawley)	Bromkal 70-5 DE ^c	By gavage: 0, 18, or 36	Serum thyroxin - decreased (≥ 18) Liver somatic index - increased (36)	(130)
TetraBDE					
Special repeated dose toxicity (14 days)	Mouse (C57BL/6)	2,2',4,4'-TetraBDE (> 98%)	By gavage: 0 or 18	Serum thyroxin - decreased (18) Liver somatic index - increased (18)	(130)
	Rat (Sprague-Dawley)	2,2',4,4'-TetraBDE (> 98%)	By gavage: 0, 1, 6, or 18	Serum thyroxin - decreased (18)	(90)

?, it was not clear for the authors of the original report whether or not the compound was compound related.

^aThe daily dose (in mg/kg bw/day) is estimated based on dietary PBDE concentrations and the generally used average daily food consumption of 10 g/day in young rats, 20 g/day in older rats, and 3 g/day in mice. ^bDE-71 is primarily a mixture of tetra-, penta-, and hexaBDE containing low levels of tri- (> 1%) and heptaBDE (< 2%) (2). ^cBromkal 70-5 DE is a commercial mixture containing about 60% pentaBDE and 40% tetraBDE (2).

reduced growth, diarrhea, piloerection, reduced activity, clonic persistent tremors of forelimbs, red staining around eyes and nose, and continuous chewing. Acute toxicity of diBDE (purity and isomer profile not specified) has only been studied in mice after intraperitoneal (ip) administration (2,99). The ip LD₅₀ value of 125 mg/kg clearly was lower than those reported for the higher-brominated congeners in rats after oral administration. This difference, however, does not conclusively reflect a higher potency of diBDE; it may have resulted from different routes of administration and differences in species sensitivity.

Skin and eye irritation studies with octa- and decaBDEs revealed only slight or no local irritation in rabbits (2,54,79). DecaBDE was not chloracnegenic in rabbits (2). In human volunteers decaBDE did not cause skin irritation or skin sensitization (2,54,79).

Subacute/subchronic toxicity. Subacute/subchronic oral toxicity studies in rats have been carried out with deca-, octa- and pentaBDE preparations (Table 5). In general, effects were less pronounced with decaBDE than with the other two congener groups. Target organs were liver, kidney, and thyroid gland. These organs were generally enlarged with or without some degenerative changes. In addition, hepatocellular necrosis was observed in both oral and inhalation toxicity studies with octaBDEs. Toxic effects were noted at daily dietary doses of 10 mg/kg bw and above for penta- and octaBDE. DecaBDE was effective at 80 mg/kg bw in one study, whereas another study showed effects only at much higher doses or no effects at all (54,79).

Porphyrogenic activity. Chronic hepatic porphyria is a condition characterized by a liver disorder resulting in production and excretion of excess porphyrins. A commercial octaBDE preparation (10 µg/mL) was strongly porphyrogenic in cultured chick embryo liver cells after incubation for 24 hr (100). Exposure of rats to a commercial pentaBDE in the diet (100 mg/kg bw/day) for 13 weeks resulted in highly increased liver and urine concentrations of porphyrins [unpublished data, cited in IPCS (2)]. It is interesting to note that octa- and pentaBDEs share the porphyrogenic activity of dioxins, PCBs, and PBBs (101–103).

Immunotoxicity. In a study by Fowles and co-workers (104), immunologic (and other) effects of the PBDE preparation DE-71 [a mixture of tetra-, penta-, and hexaBDE with low levels of tri- (< 1%) and heptaBDE (< 2%)] were monitored using sheep erythrocyte (SRBC) plaque-forming cell response and natural killer (NK) cell activity. C57BL/56 mice were orally exposed to single DE-71 doses of up to 500 mg/kg, or to subchronic daily doses of 72 mg/kg bw over a 14-day

period, totaling 1,000 mg/kg bw. Suppression of the anti-SRBC response was seen only in the mice exposed subchronically; this exposure also resulted in decreased thymus weight. NK cell activity was not altered.

Immunotoxic potential of Bromkal 70-5DE (a commercial mixture containing about 60% of pentaBDE and 40% of hexaBDE) was compared with that of a commercial PCB preparation—Aroclor 1254—in Sprague-Dawley rats and C57BL mice (105). The animals were given the preparations at 10–36 mg/kg bw/day for 14 days by oral gavage. Mice were also exposed to BDE-47 and PCB-105. The study showed that the exposure to PCBs induces certain immunologic alterations in both species, but signs of immunotoxicity after PBDE exposure were observed only in mice. The reduction in splenocyte numbers in mice was markedly decreased after BDE-47 exposure (18 mg/kg/day). Moreover, Bromkal 70 treatment at 36 mg/kg resulted in decreased production of IgG antibodies from pokeweed-stimulated splenocyte cultures *ex vivo*.

In an *in vitro* study on cultured human lymphocytes, the effects of two pure PBDE congeners [BDE-47 and BDE-85 (2,2',3,4,4'-pentaBDE)] and three PCBs [2,3,3',4,4'-pentaCB (PCB-105), 2,3',4,4',5-pentaCB (PCB-118), and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153)] on cell proliferation were studied (106). None of the chemicals significantly altered the proliferative response compared with control cells. Not even the PCBs affected the lymphocyte proliferative response, although PCBs are commonly known to be immunotoxic *in vivo*. The known discrepancies between *in vivo* and *in vitro* effects of polyhalogenated aromatic hydrocarbons on immunologic parameters may be a result of indirect effects of these compounds on immune function *in vivo*, e.g., via possible Ah receptor-mediated hormone interactions (107). Consequently, if PBDEs and PCBs affect the immune system via the same mechanism(s), this method may have limited relevance for predicting the immunologic effects of PBDEs *in vivo*.

The immunosuppressive potencies of eight isomers of tetra-, penta-, or hexachlorinated DEs were determined using the mouse splenic plaque-forming cell (PFC) response to sheep red blood cell antigens (95). The isomers dose dependently decreased the number of PFCs, with ED₅₀ values between 0.19 and > 151 mg/kg (given as a single ip dose). The immunotoxic effect appears to be highly isomer specific, as there were remarkable differences between different isomers of penta- and hexachlorinated DEs.

Reproductive and developmental toxicity. Reproductive toxicity of PBDEs has been studied using commercial deca-, octa-, and pentaBDE preparations and Saytex 111, a

commercial mixture of PBDEs containing several congeners from penta- to decaBDE, of which the hepta- and octaBDEs are most abundant (45 and 34% of all congeners, respectively) (Table 6). One of the studies is a rat reproductive performance study with decaBDE. All other studies are teratogenicity studies, and only Saytex 111 has been studied in both rats and rabbits.

Effects of decaBDE on reproductive performance were studied in male and female Sprague-Dawley (Spartan) rats given commercial decaBDE in the diet in doses of 0, 3, 30, or 100 mg/kg bw/day (2,54,79). Group sizes were 20 males and 40 females (control group), 10 males and 20 females (the low- and mid-dose group) and 15 males and 30 females (the highest-dose group). Treatment began 60 days before 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 was given in doses of 0, 10, 100, or 1,000 mg/kg bw/day by oral gavage on gestational days 6–15; fetuses were collected by cesarean section on gestational day 21 (2,54,79). 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, positions and numbers of fetuses *in utero*, individual fetal weights, crown–rump lengths, and sex ratios were not affected by the treatment. However, significantly increased incidences of resorption were observed at the lower dose levels but not at the 1,000 mg/kg bw/day dose. In the absence of numeric as well as historical control data, the possibility of embryoletality cannot be ruled out. No external abnormalities were observed in fetuses, but soft tissue and skeletal examinations revealed an increased number of litters with pups with subcutaneous edema and delayed ossification of normally developed bones of the skull at the dose level of 1,000 mg/kg bw/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 1,000 mg/kg bw/day dose. Although this study is inadequately reported, it suggests that decaBDE is not teratogenic but clearly fetotoxic at dose levels not maternally toxic.

Teratogenicity of a commercial octaBDE preparation was studied in rats (strain and number of animals not specified) receiving the test compound by gavage at 0, 2.5, 10, 15, 25, or 50 mg/kg bw/day on gestational days 6–15 (2). Reduced maternal body weight gain and slightly increased cholesterol levels, but no histopathologic changes in livers or kidneys were observed at the 50 mg/kg bw/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 edema (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 the 50 mg/kg bw/day dose. No treatment-related effects were observed at 15 mg/kg bw/day or lower, but the findings at 25 mg/kg bw/day were not discussed. Therefore, the no-observed-effect level (NOEL) for maternal toxicity is 25 mg/kg bw/day and for fetal effects 15 mg/kg bw/day (2).

Teratogenicity of the commercial Saytex 111 mixture was studied in four groups of 25 Charles River (Sprague-Dawley) rats (63). They were administered corn oil suspensions of the test substance by gavage at 0, 2.5, 10, or 25 mg/kg bw/day on gestational days 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. It resulted in a dose-dependent reduction of fetal body weight at the two highest dose levels. At 25 mg/kg/day it 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).

Teratogenicity of Saytex 111 was also studied in groups of 26 New Zealand white rabbits by the Dow Chemical Company (108). The rabbits were administered the test substance by gavage at 0, 2, 5, or 15 mg/kg bw/day on gestational days 7–19, and the fetuses collected on gestational day 28. Approximately half of the fetuses in each litter were randomly assigned for soft tissue examination. In addition, all fetuses were examined for skeletal alterations. Maternal body weight showed a dose-dependent decrease that was statistically significant only at 15 mg/kg bw/day (93% of control weight).

Also, the absolute and body weight-related liver weights were increased at this dose level. One rabbit at 5 mg/kg bw/day and two rabbits at 15 mg/kg bw/day delivered their litters prior to gestational day 28. In addition, one rabbit at 15 mg/kg bw/day was killed after exhibiting signs of abortion. This animal had multiple resorption sites in the uterus. Except for these animals, the number of resorptions was not affected by the treatment. Signs of fetal toxicity were slight (nonsignificant) decreases in fetal body weights at 5 and 15 mg/kg bw/day and increased incidences of delayed ossification of the hyoid, dental process (at 5 mg/kg/day only), and sternbrae at 2, 5, and 15 mg/kg bw/day (statistically significant only at 15 mg/kg bw/day). Treatment-related fetal variants included increased incidences of retrocaval ureter and fused sternbrae at all dose levels of Saytex 111, with the maximum incidence at 5 mg/kg/day (statistically significant). These variants were absent from the concurrent

Table 6. Summary of the reproduction and developmental toxicity studies on PBDEs.

Study	Species (strain)	PBDE (purity)	Dosage (mg/kg bw/day)	Effect (dose level for observed effect)	Reference
DecaBDE					
Reproductive performance	Rat (Sprague-Dawley)	DecaBDE (77.4%), NonaBDE (21.8%), OctaBDE (0.8%)	In diet: 0, 3, 30, or 100	No compound-related effects	(2,54,79)
Teratogenicity	Rat (Sprague-Dawley)	DecaBDE (77.4%), NonaBDE (21.8%), OctaBDE (0.8%)	By gavage: 0, 10, 100, or 1000	Fetal toxicity - resorptions (100), subcutaneous edema, delayed ossification (1,000)	(2,54,79)
OctaBDE					
Teratogenicity	Rat (not specified)	DE-79	By gavage: 0, 2.5, 10, 15, 25, or 50	Fetal toxicity - late resorptions, weight decreased, anasarca, bent limb bones, reduced ossification, bent ribs (50); maternal toxicity - bw decreased, serum cholesterol increased (50)	(2)
Teratogenicity	Rat (Charles River Crb: COBS CD (SD) BR)	Saytex 111 ^a	By gavage: 0, 2.5, 10, or 25	Fetal toxicity - weight decreased (≥ 10, resorptions delayed ossification (25); fetal variations/malformations - enlarged heart, rear limb malformation (25)	(63)
	Rabbit (New Zealand white)	Saytex 111 ^a	By gavage: 0, 2, 5, or 15	Fetal toxicity - delayed ossification (≥ 2), weight decreased (≥ 5), resorptions? (15); fetal variations/malformations - retrocaval ureter (≥ 5), fused sternbrae (5); maternal toxicity - bw gain decreased, liver enlarged (15)	(108)
PentaBDE					
Teratogenicity	Rat (not specified)	PentaBDE (commercial)	By gavage: 0, 10, 100, or 200	Maternal toxicity - bw gain decreased (≥ 100); fetal toxicity - weight decreased (200)	(2)
Special developmental toxicity	Mouse (NMRI)	2,2', 4,4',5-PentaBDE	By gavage: 0, 0.8, or 12 on postnatal day 10	Developmental neurotoxicity - impaired habituation (locomotion, rearing, total activity) in adulthood; worsens with aging; impaired learning and memory functions (12)	(111)
Special developmental toxicity	Mouse (not specified)	2,2',4,4',5-PentaBDE	By gavage: 0 or 8 on postnatal day 3, 10, or 19	Developmental neurotoxicity - impaired spontaneous motor behavior in adulthood; nicotine-induced hypoactivity (8)	(113)
Special developmental toxicity	Rat (not specified)	DE-71 ^b	By gavage: 0, 1, 10, or 30 to dams on gestational day 6–postnatal day 21	Offspring toxicity - serum thyroxin decreased (≥ 1) Maternal toxicity - serum thyroxin decreased (30)	(132)
TetraBDE					
Special developmental toxicity	Mouse (NMRI)	2,2',4,4'-TetraBDE	By gavage: 0, 0.7, or 10.5 on postnatal day 10	Developmental neurotoxicity - impaired habituation (locomotion, rearing, total activity) in adulthood; worsens with aging (10.5)	(111)

^aSaytex 111 is a commercial mixture containing pentaBDE, 0.2%; hexaBDE, 8.6%; heptaBDE, 45%; octaBDE, 33.5%; nonaBDE, 11.2%; and decaBDE, 1.4% (2). ^bDE-71 is primarily a mixture of tetra-, penta-, and hexaBDE containing low levels of tri- (> 1%) and heptaBDE (> 2%) (2).

controls, but they were reported to have occurred at relatively high frequencies among some historical controls. This fact and the lower incidence at 15 mg/kg bw/day compared to 5 mg/kg bw/day led the authors (108) to consider these variants spontaneous. Nevertheless, we consider that the results indicate a PBDE-induced increase in the incidence of fetal variations. Isolated incidences of fetal malformations were observed in all groups including controls, but they were not considered to represent a teratogenic effect. We concluded that Saytex 111 caused fetal toxicity and variants at maternally nontoxic dose levels.

A teratogenicity study with a commercial pentaBDE preparation was carried out in rats (strain and number of animals not specified) (2). The test compound was suspended in corn oil and given by gavage at 0, 10, 100, or 200 mg/kg/day on gestational days 6–15. Maternal body weight gain was decreased at 100 and 200 mg/kg/day, and a slight (non-significant) reduction of fetal body weight was observed at 200 mg/kg/day.

Treatment of pregnant mice and rats with certain pure PCDE congeners on gestational days 6–15 resulted in embryoletality as indicated by the decreased number of litters or pups born to dams administered the 100 mg/kg/day dose (109). In mice, the most potent congeners were 2,3',4',6-tetraCDE and 2,2',4,5,6'-pentaCDE, but also 2,2',4,4',5,6'-hexaCDE and 2,2',4,4',5,5'-hexaCDE caused a slight but statistically significant effect. The other five congeners studied did not show any signs of embryotoxicity at dose levels up to 100 mg/kg/day. In rats, 2,3',4',6-tetraCDE, 2,2',4,5,6'-pentaCDE and 2,2',4,4',5,6'-hexaCDE were studied; all were embryotoxic in terms of number of pups born or pup weight. No structural hallmarks in the PCDE molecule related to embryotoxicity could be established. However, a common feature of the congeners causing prenatal mortality was at least two chlorine substituents at the *ortho* position (although not all congeners with this property caused prenatal mortality). Induction of CYP enzymes did not correlate well with the ability of the congeners to cause embryotoxicity.

Reproduction and developmental toxicity studies showed that in general fetuses are more sensitive to PBDEs than mothers, and that the increased incidence of developmental variants is a frequent fetal effect. Although it is known that maternal toxicity can influence fetal ossification (110), the fetal effects seem to appear at lower doses than those indicative of maternal toxicity (manifested as decreased bw gain and increased liver weight in some cases).

Neurotoxicity. The developing central nervous system is a potential target for toxicity of PBDEs. Neonatal mice given a single oral

dose of BDE-47 (10.5 mg/kg bw) or BDE-99 (12.0 mg/kg bw) on postnatal day 10 (coinciding with the rapid brain growth period) had permanent impairment of spontaneous motor behavior in adulthood (111). The latter congener also affected learning and memory functions. Further studies with BDE-99 confirmed these permanent behavioral effects (112,113). Furthermore, studies with ¹⁴C-BDE-99 revealed concentrations in the brains of 10-day-old mice similar to those observed for other substances (DDT and certain PCB congeners) that induced the same type of behavioral effects in earlier studies. The neurodevelopmental toxicity of PBDEs appears to involve changes in the cholinergic system and may also be related to altered thyroid homeostasis. The latter hypothesis is based on the fact that brain development is highly dependent on thyroid hormones (114). PCBs and PCDDs that, like PBDEs, alter the thyroid hormone homeostasis have been suggested to disrupt brain development, resulting in permanent neurologic damage (115,116).

Genotoxicity. The genotoxic potential of commercial grade deca-, octa-, and pentaBDEs has been examined in several, mostly unpublished, studies (2). Mutagenicity tests carried out on four strains of *Salmonella typhimurium* with a technical product of decaBDE (HFO-102) and commercial decaBDE with and without metabolic activation were negative. Similarly, studies in eukaryotic cells utilizing yeast (*Saccharomyces cerevisiae*) and the TK locus of the mouse lymphoma cell line L5178Y with and without metabolic activation were negative. Commercial decaBDE did not induce chromosomal aberrations or sister chromatide exchanges in Chinese hamster ovary cells with or without metabolic activation. Results were also negative in cytogenetic examination of bone marrow cells from parent rats exposed to decaBDE (at dose levels up to 100 mg/kg/day in a reproduction study) and their weanlings (54,79).

A commercial octaBDE preparation was found to be negative in unscheduled DNA synthesis assay in the human fibroblast cell line WI-38 with and without metabolic activation. It neither induced mutations in *S. typhimurium* or *S. cerevisiae* nor caused sister chromatide exchanges in Chinese hamster ovary cells with or without metabolic activation. Mutagenicity studies with a commercial pentaBDE preparation in four strains of *S. typhimurium* and in *S. cerevisiae* with and without metabolic activation were all negative (2).

In two assays for intragenic recombination at an endogenous mammalian cell locus, lower-brominated DEs (2-monobromoDE and 3,4-dibromoDE) as well as other brominated flame retardants (TBBP-A and HBCD) significantly increased the recombination frequency (117). The possible role of this type

of increased intragenic recombination in human diseases remains to be clarified.

In conclusion, these studies, although not complete state-of-the-art genotoxicity test batteries, suggest that none of the PBDEs examined are genotoxic. However, the possible increase in intragenic recombination, as observed for the low-brominated DEs, should be noted.

Carcinogenicity. Rodent carcinogenicity bioassays have been carried out only for decaBDE (2,118). A mouse study and a rat study have been reported in the National Toxicology Program (NTP) report (80) (Table 4), and a rat study of limited value has been conducted by the Dow Chemical Company (83).

In the NTP mouse study (80), decaBDE (purity 94–99%; no brominated dioxins or furans found) mixed in the diet was given to groups of 50 male and 50 female B6C3F₁ mice for 103 weeks; all survivors were killed at 112–113 weeks of age. The concentration of decaBDE in the diet was 0, 25, and 50 g/kg. The average daily exposure to decaBDE was estimated to be 3,200 and 6,650 mg/kg bw/day in low- and high-dose males, respectively, and 3,760 and 7,780 mg/kg bw/day in low- and high-dose females. Body weight development and survival of decaBDE-treated mice were comparable to those in controls. Liver granulomas were observed in low-dose males and liver hypertrophy in low- and high-dose males. 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 increased only nonsignificantly. Furthermore, follicular cell hyperplasia was increased at both dose levels in males and females.

In a study by the Dow Chemical Company (83), 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, and 1 mg/kg/day. The treatment did not have any influence on survival rates, appearance, body weights, feed consumption, hematology, urinalysis, or organ weights. There were no other discernible toxic effects, and no significant differences in number of rats developing tumors between the groups. The International Agency for Research on Cancer (IARC) Working Group pointed out that the dose levels were very low (2).

In the NTP rat study (80), groups of 50 male and 50 female Fischer 344/N rats

received decaBDE (purity 94–99%; no brominated dioxins or furans found) mixed in the diet for 103 weeks, all survivors were killed at 111–112 weeks of age. The concentration of decaBDE in the diet was 0, 25, and 50 g/kg diet, and the estimates for average daily doses of decaBDE were 1,120 and 2,240 mg/kg bw/day in low- and high-dose males, respectively, and 1,200 and 2,550 mg/kg bw/day in low- and high-dose females, respectively. Body weights of the decaBDE-treated rats were not significantly different from those of controls. After week 75 survival rates of the treated groups were lower than those of controls. In high-dose males, thrombosis and degeneration of the liver, fibrosis of the spleen, and lymphoid hyperplasia 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 tumor 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 tumor test for trend). However, no differences in incidences of hepatocellular carcinomas were detected among the groups. Significantly increased incidences 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 tumor test for trend). Additionally, high incidences of mononuclear cell leukemia were observed in treated and control rats of both sexes.

These studies have led to a conclusion that there is limited evidence for carcinogenicity of decaBDE in experimental animals, and that decaBDE is not classifiable as to its carcinogenicity to humans (Group 3) (118). The lack of genotoxicity suggests that the mechanism of the possible carcinogenicity of decaBDE would be epigenetic.

Ah receptor-mediated effects. Polyhalogenated aromatic hydrocarbons exert many different mechanisms of toxicity. One they share in common, however, may be the Ah receptor (AhR) binding effects (96). The best characterized and one of the most sensitive of the AhR-mediated phenomena is the induction of isoenzymes CYP1A1 and CYP1A2, but the role of AhR in mediating toxic effects is less understood. Recent studies in AhR-deficient mice, however, strongly suggest that at least TCDD-induced thymic atrophy and the most characteristic liver lesions would be mediated by the AhR (119).

Several studies have shown that PBDEs may induce several microsomal enzyme activities. One of these, EROD, is a marker of AhR binding. In a study by von Meyerinck and co-workers (84) the same levels of EROD induction were observed after exposure of rats to pentaBDE as after Aroclor

1254 treatment (both given as a single dose of 300 mg/kg bw). However, Hallgren and Darnerud (90) observed a much weaker induction by BDE-47 than Aroclor 1254 when given orally to rats in isomolar doses.

The AhR agonist and antagonist activities of a series of 17 PBDE isomers were recently studied using a recombinant H4IIE rat hepatoma cell line with a luciferase reporter gene, the CALUX-assay (91). Seven of the congeners induced luciferase expression, whereas nine congeners decreased TCDD-induced luciferase expression. Thus, some pure PBDE congeners acted via the AhR signal transduction pathway as antagonists, agonists, or both. Their potencies, however, were approximately six orders of magnitude lower than that of TCDD but comparable to those of some mono-*ortho* PCBs such as PCB-105 and PCB-118 (120). The above studies suggest that PBDEs may have certain AhR binding activities, although results deviate. However, it seems less likely that the AhR would have any major role in mediating toxic effects of pure PBDEs.

Effects on thyroid hormones. Several studies have demonstrated that exposure to dioxins and related compounds are associated with complex alterations in thyroid function (121–123). These alterations include two different basic mechanisms. First, there is increased elimination of thyroid hormones, especially thyroxine (T_4), primarily because of induced activity of UDPGT in liver, which leads to accelerated hepatic clearance of T_4 . This has been reflected consistently in decreased serum levels of total and free T_4 . Alterations of 5'-deiodinase activities may also change serum and tissue levels of thyroid hormones (124). Second, many organohalogen compounds structurally resemble thyroid hormones and therefore compete for binding to thyroid hormone receptors and transporter proteins (121,125,126). In fact, halogenated DEs appear to bind to the thyroid hormone receptor with higher affinity than planar ligands do (93), and therefore PBDEs are likely to be more potent thyroid agonists (or antagonists) compared with many other classes of organohalogen compounds. Hydroxylated PBDE metabolites are of particular interest because thyroid hormones are also hydroxylated DEs. Hydroxylated PBDE congeners 4'-OH-1,3,3',5-tetraBDE and 4'-OH-1,3,3',5,5'-pentaBDE that theoretically show the highest structural similarity with triiodothyronine (T_3) and T_4 , respectively, have the highest binding affinities to the thyroid hormone receptors (127). The binding affinities, however, were about two to three orders of magnitude lower than those of the endogenous ligands T_3 and T_4 . Another potentially significant property of hydroxylated PBDE metabolites is their ability to

disrupt the transportation of thyroid hormones by displacing them from the thyroxine plasma transporter, transthyretin (TTR). A preliminary study revealed that several microsomal PBDE metabolites (not identified) are potent competitors of T_4 binding to human TTR (128). Interestingly, metabolism of BDE-47 by phenobarbital-induced microsomes (mainly CYP2B) resulted in a strong increase in TTR binding, whereas β -naphthoflavone-induced microsomes (mainly CYP1A1) did not. Binding to TTR has been shown to be a general property for hydroxylated metabolites of PCBs and of other organohalogen compounds (123,129).

Recent studies have shown that PBDEs share the general property of several organohalogen compounds in lowering the serum total and free T_4 in mice and rats (90,104,130). Significantly decreased serum T_4 concentrations were found in C57BL/6 mice treated orally with a commercial pentaBDE mixture (DE-71), both after exposure to a single dose of 0.8–500 mg/kg bw and after daily exposure for 14 days to total doses of 250–1,000 mg/kg bw, i.e., 18–71 mg/kg bw/day (104). Similarly, Sprague-Dawley rats and C57BL/6 mice given daily oral doses of Bromkal 70 for 14 days at total dose levels of 0, 250, or 500 mg/kg bw (0, 18, or 36 mg/kg bw/day) showed significant dose-dependent decreased levels of plasma total T_4 (130). Rats proved to be more sensitive than mice. The plasma thyroid-stimulating hormone concentrations were largely unaffected. The pure congener BDE-47 was equally or more potent in decreasing serum total T_4 than the commercial pentaBDE in mice suggesting that this effect is not caused by impurities of the technical grade PBDE mixture. In addition, the technical grade PCB mixture Aroclor 1254 (containing about 5% pentaCB) and the pure congener PCB 105 (a mono-*ortho* PCB with some AhR binding affinity) were slightly more potent than the PBDEs in causing these effects in mice. In continued studies on Sprague-Dawley rats, daily oral doses of BDE-47 for 14 days resulted in significantly decreased serum levels of free T_4 levels at 18 mg/kg bw/day and gave a NOEL for this effect of 6 mg/kg bw/day (90). Moreover, BDE-47 induced a synergistic effect with technical preparations of PCBs or chlorinated paraffins in decreasing T_4 levels.

In addition to the decreased T_4 observed after treatment with lower brominated DEs, indirect evidence suggests that decaBDE may also affect thyroid function. Increased incidences of thyroid follicular cell hyperplasia as well as slightly increased incidences of follicular cell adenomas and carcinomas were observed in decaBDE-treated mice in the NTP carcinogenicity bioassay (80). Furthermore, workers

exposed to decaBDE, other PBDEs, and PBBs had increased prevalence of primary hypothyroidism, although serum analysis did not confirm the exposure to decaBDE (131).

In a recent preliminary report, exposure of pregnant rats to DE-71 from gestational day 6 to postnatal day 21 at 0, 1, 10, or 30 mg/kg bw/day was shown to decrease serum T₄ dose dependently in dams, fetuses, and offspring (132). In the offspring the decreases were 25, 50, and 70% at 1, 10, and 30 mg/kg bw/day, respectively, on postnatal days 4 and 14, but levels recovered to the control levels by postnatal day 36. Thyroid toxicity was also observed in rat pups prenatally exposed to polychlorinated DEs (133). Significantly decreased serum T₄ levels were observed in 16-day old pups given three PCDE congeners (2',3,4,6'-tetraCDE, 2,2',4,5,6'-pentaCDE, or 2,2',4,4',5,5'-hexaCDE) at maternal dose levels of 25–100 mg/kg/day on gestational days 6–15. The maximum decrease generally had been observed at the lowest dose level, and therefore the NOEL could not be determined. At lower doses the T₄ decrease was shown in absence of any other toxic effect, but the highest dose level (100 mg/kg bw/day) caused embryoletality as the number of litters and the number of pups were highly reduced. Decreased maternal T₄ was observed only after treatment with the tetra and penta congeners at 100 mg/kg/day. Serum T₃ levels were unaffected in both pups and dams. The decrease in T₄ levels did not correlate with the ability of the congener to induce CYP enzymes.

Collectively, these studies demonstrate that thyroid homeostasis is a sensitive target of PBDEs. Because the development of the central nervous system is highly dependent on thyroid hormones, alterations in thyroid homeostasis may result in permanent neurobehavioral defects (114,115). It may also be the primary cause of neurodevelopmental toxicity of PBDEs. Therefore, altered thyroid function, especially during development, is likely to be among the most important end points of toxicity in the risk assessment of PBDE.

NOELs and LOELs. Data from effects observed in experimental animals administered PBDEs orally have been compiled in Table 7. In this table, the NOELs and the LOELs of the various studies are given. In general, the NOEL values are considerably higher for the decaBDE group than for the lower-brominated technical PBDE preparations and pure BDE-47. The most sensitive end point of toxicity, as indicated by the LOEL values, was the decrease in serum T₄ concentration. A LOEL value of 0.8 mg/kg bw after a single dose of Bromkal DE-71 was observed in adult mice (104). In this study, however, a dose–response relationship was absent. In a recent preliminary report (132), a

LOEL value of 1 mg/kg bw/day was reported in rat offspring exposed to DE-71 *in utero* and lactationally. A LOEL of 2 mg/kg bw/day for fetal toxicity was found after exposure to the Saytex 111 mixture in rabbits (108). In adult rats exposed to DE-71 for 90 days, a NOEL value of 2 mg/kg bw/day was determined for decreased serum T₄, thyroid hyperplasia, and hepatocytomegaly (2). Moreover, a NOEL of 1 mg/kg bw/day for decaBDE (containing 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE) was derived from the Dow Chemical Company carcinogenicity study on rats (83). This dose level was the highest dose and it did not cause any toxicity. A general limitation of the studies on the technical PBDEs is that the purity was not always determined and the contaminants present were not evaluated for their possible modulation of the observed effect. Considering this, the studies on the pure BDE-47 congener (>98% pure) are of value, as they exclude the contribution of possible contaminants to the observed thyroxin-lowering effect, shown at the dose of 18 mg/kg bw (90,130). Also, in a preliminary report, extended studies by Eriksson and co-workers on neurobehavior showed effects of the single congener BDE-99 at 8 mg/kg bw (113).

Toxicity in Humans

DecaBDE is the only PBDE for which limited human data are available. Skin sensitization potential of decaBDE (Dow Chemical Company, Midland, Michigan USA); containing 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octaBDE) was studied in 50 volunteers (54,79). A 5% suspension of decaBDE in petrolatum was applied to the skin 3 times per week for 3 weeks, followed by a challenge treatment 2 weeks after the last application. No skin sensitization responses were observed during the study. Another skin sensitization study was performed on 80 male and 120 female volunteers exposed to two batches of decaBDE (purity not stated) (2). The volunteers were treated with nine induction patches at 2-day intervals and the test substance was kept in contact with skin for 24 hr. The induction regimen was followed by a period of 12 days without treatment, after which a new skin site was used for a 24-hr challenge patch. Skin reactions were observed at 24 and 48 hr after removal of the challenge patch. The study revealed no evidence of skin sensitization with either batch of decaBDE.

Workers exposed during manufacture to PBBs and PBDEs, including decaBDE, were reported to have higher-than-normal prevalences of primary hypothyroidism and significant reductions in conducting velocities in sensory and motor neurons but no other neurologic or dermatologic changes (131). It was not possible to conclude whether these

changes could be attributed to PBB or PBDE exposure, but no decaBDE could be detected in serum of the exposed workers.

Four epidemiologic studies have been conducted on workers at facilities where flame-retardant polymers were extruded (2). The workers were potentially exposed to brominated flame retardants, including PBDEs and in some cases also to polybrominated PBDDs and PBDFs. These studies found no adverse effects attributable to exposure to these chemicals.

Toxicology: Summary and Conclusions

Limited amounts of data are available about the toxicity of PBDEs. Most of the studies have been carried out using technical- or commercial-grade PBDEs, the purity of which has been known in several cases, but the isomer composition unknown. Moreover, often no data are available about possible halogenated dioxinlike impurities. A general concern about toxicity data is that many studies are documents that are difficult to obtain and may not have been subjected to examination by independent referees. Therefore, because the quality of these studies cannot be verified, their relevance in some cases may be questionable.

Available data suggest that the acute toxicity of PBDEs is low, they have at most only slightly irritating properties, and they are not skin sensitizers. No severe signs of toxicity were observed in subacute and subchronic toxicity studies. Target organs were the liver, kidney, and thyroid gland, which were enlarged and/or showed mainly minor histopathologic changes. Different PBDEs seemed to have similar toxicologic profiles, but in most studies decaBDE was less potent than the other congeners. PBDEs were not genotoxic in short-term tests. In carcinogenicity studies with decaBDE (at very high doses), increased incidences of hepatocellular and thyroid adenomas and carcinomas were observed in mice, and increased incidences of hepatocellular adenomas and acinar cell adenomas of the pancreas were observed in rats. Reproduction toxicity studies revealed increased sensitivity of pregnant animals and fetuses to PBDEs. Except for pentaBDE, toxic effects on fetuses were observed already at dose levels not toxic to mothers. Fetal toxicity was sometimes associated with low incidences of developmental variants. Neurobehavioral effects were seen in adult mice after single relatively low oral doses of tetra- and pentaBDEs were given neonatally during the sensitive brain growth period. Humans occupationally exposed to PBBs and PBDEs were found to have hypothyroidism and decreased conduction velocity of sensory and motor neurons, but the association of these effects with exposure to PBDEs was equivocal.

Available evidence suggests that in spite of certain structural similarity to dioxins, PBDEs are weak agonists of the AhR. In fact, observed AhR effects (e.g., CYP1A1 induction) may be at least partly attributed to their highly potent polyhalogenated dioxin or furan impurities. This coupled with the lack of obvious dioxinlike toxic effects suggests that the primary mechanisms of toxicity of

PBDEs are different from those of dioxins. However, it appears likely that halogenated DEs and their hydroxylated metabolites bind effectively to transport proteins for thyroid hormones, and that alteration of thyroid homeostasis by this and perhaps also other mechanisms may represent an important and characteristic mechanism of toxicity of PBDEs.

The most sensitive end points of toxicity determining LOAEL and NOEL values were the hepatomegaly with cytoplasmic eosinophilic "round bodies," fetal and maternal toxicity, and disturbances of thyroid homeostasis. Also, the recently discovered neurotoxic effect of several PBDE congeners at relatively low levels should be noted. These effects and their significance therefore should

Table 7. NOEL and LOAEL values of orally administered PBDEs in different toxicity studies.

Study	Species	PBDE (purity)	NOEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Effect	Reference
DecaBDE						
Subacute toxicity (14 days)	Mouse	DecaBDE (99%)	15,000	—	—	(80)
	Rat	DecaBDE (99%)	10,000	—	—	(80)
Subacute toxicity (28 days) (30 days)	Rat	DecaBDE (commercial)	100	—	—	(2)
	Rat	DecaBDE (77.4%), nonaBDE (21.8%), octaBDE (0.8%)	8	80	Thyroid - hyperplasia Liver - enlarged	(54,79)
Subchronic toxicity (13 weeks)	Mouse	DecaBDE (> 97%)	7,500	—	—	(80)
	Rat	DecaBDE (> 97%)	5,000	—	—	(80)
Chronic toxicity, carcinogenicity	Mouse	DecaBDE (94–99%)	—	3 200	Liver - hypertrophy, granulomas adenomas, carcinomas; thyroid - follicular cell hyperplasia, adenomas, carcinomas	(80)
	Rat	DecaBDE (94–99%)	—	1 120	Liver - adenomas	(80)
Reproductive performance	Rat	DecaBDE (77.4%), nonaBDE (21.8%), octaBDE (0.8%)	100	—	—	(54,79)
	Rat	DecaBDE (77.4%), nonaBDE (21.8%), octaBDE (0.8%)	—	10	Fetal toxicity	(54,79)
Teratogenicity	Rat	DecaBDE (77.4%), nonaBDE (21.8%), octaBDE (0.8%)	1,000	—	Maternal toxicity	(54,79)
OctaBDE						
Subacute toxicity (28 days)	Rat	OctaBDE (commercial)	—	10	Liver - hepatocytes enlarged, cytoplasmic eosinophilic round bodies	(2)
Subchronic toxicity (13 weeks)	Rat	OctaBDE (commercial)	—	10	Liver - enlarged	(2)
Teratogenicity	Rat	DE-79	15	50	Fetal toxicity	(2)
			25	50	Maternal toxicity	(2)
Teratogenicity	Rat	Saytex 111 ^a	2.5	10	Fetal Toxicity	(63)
			25	—	Maternal toxicity	(63)
Teratogenicity	Rabbit	Saytex 111 ^a	—	2	Fetal toxicity	(108)
			5	15	Maternal toxicity	(108)
PentaBDE						
Subacute toxicity (28 days)	Rat	PentaBDE (commercial)	—	10	Liver - enlarged, cytoplasmic eosinophilic round bodies; thyroid - follicular hyperplasia?	(2)
Subchronic toxicity (90 days)	Rat	DE-71 ^b	2	10	Serum thyroxin - decreased, thyroid hyperplasia; liver - enlarged, hepatomegaly	(2)
Teratogenicity	Rat	PentaBDE (commercial)	100	200	Fetal toxicity	(2)
			10	100	Maternal toxicity	(2)
Special development toxicity (maternal) exposure on GD 6-PND 21)	Rat	DE-71 ^b	—	1	Offspring toxicity: serum thyroxin decreased	(132)
			10	30	Maternal toxicity: serum thyroxin decreased	(132)
Special single dose toxicity	Mouse	DE-71 ^b	—	0.8	Serum thyroxin - decreased	(104)
Special repeated dose toxicity (14 days)	Mouse	Bromkal 70-5DE ^c	—	18	Serum thyroxin - decreased	(130)
	Rat	Bromkal 70-5DE ^c	—	18	Serum thyroxin - decreased	(130)
Special developmental toxicity, single dose on PND 10	Mouse	2,2',4,4',5-PentaBDE	0.8	12	Developmental neurotoxicity	(111)
Special developmental toxicity, single dose on PND 3, 10, or 19	Mouse	2,2',4,4',5-PentaBDE	—	8	Developmental neurotoxicity	(113)
TetraBDE						
Special repeated dose toxicity (14 days)	Mouse	2,2',4,4'-TetraBDE	—	18	Serum thyroxin - decreased	(130)
	Rat	2,2',4,4'-TetraBDE	6	18	Serum thyroxin - decreased	(90)
Special developmental toxicity, single dose on PND 10	Mouse	2,2',4,4'-TetraBDE	0.7	10.5	Developmental neurotoxicity	(111)

Abbreviations: GD, gestational day; PND, postnatal day.

^aSaytex 111 is a commercial mixture containing pentaBDE, 0.2%; hexaBDE, 8.6%; heptaBDE, 45%; octaBDE, 33.5%; nonaBDE, 11.2%; and decaBDE, 1.4% (2). ^bDE 71 is primarily a mixture of tetra-, penta, and hexaBDE containing low levels of tri- (> 1%) and heptaBDE (< 2%) (2). ^cBromkal 70-5DE is a commercial mixture containing about 60% of pentaBDE and 40% of tetraBDE (2).

be addressed in further toxicologic studies with PBDEs.

Toxicologic Evaluation

PBDEs are accumulating in sediment and biota and appear to bioconcentrate at least in aquatic ecosystems. Relatively high levels could be found in fatty fish, Baltic herring, for example. However, analyses of terrestrial mammals reveal low PBDE levels. This may imply that for humans exposure to PBDEs directly from the environment is low (except for occupational exposure), but exposure may occur indirectly through the intake of food from aquatic ecosystems. An area of concern is the increasing exposure of infants to PBDEs during lactation because of increasing PBDE levels in mothers' milk. Also, the possibility of long-term exposure from electronic equipment such as computers should however not be ignored. Data on PBDE levels in human tissues and fluids suggest an increasing time trend, although levels are still considerably lower than those of PCBs.

Data on rodents suggest that elimination of PBDEs from the body is species dependent (urinary excretion of BDE-47 is much higher in mice than in rats). No clear differences in body distribution between different congeners is seen in mice. Hydroxylated PBDE metabolites were detected in the mouse and the rat. The toxic potency of these metabolites is unknown, but it is suggested that hydroxylated PCB metabolites mimic both thyroid hormones and estrogens. There is evidence that debromination of PBDEs to lower brominated DEs occurs in rodents and fish.

As nonplanar compounds, PBDEs do not bind to the AhR with high affinity or exert dioxin-like toxicity. Part of the observed limited CYP1A1 induction may be explained by potent halogenated dioxin and furan impurities which, even if present only at low concentrations, may become significant in exerting these effects.

Effects on thyroid function, experimentally observed primarily as T_4 hypothyroidism, appear to be sensitive end points of PBDE toxicity. Interestingly, primary hypothyroidism has also been reported in humans after possible occupational exposure. Other effects include hepatotoxicity, developmental neurotoxicity, and embryotoxicity as well as maternal toxicity during gestation. Fetal effects observed in several studies were delayed ossification of bones, bent ribs and bones, and decreased fetal weight. Although not severe, such effects if found at relatively low exposure levels are cause for concern. Currently there are no reports about effects of PBDE exposure on the human fetus/offspring. However, the possibility of these effects on humans should be considered.

The NOEL values for fetal effects were found at < 2 to 15 mg/kg bw/day (commercial

octa- and pentaBDEs). A LOAEL of 8 mg/kg bw was seen in mice subjected to neurotoxicity tests (BDE-99). Also, the effects on liver and thyroid hormones occurred at relatively low doses (NOEL 2–18 mg/kg bw/day). Effects on thyroid hormones were observed at an even lower dose, 0.8 mg/kg bw (but in the absence of dose–response correlation), by Fowles and co-workers (104). In a recent preliminary study in rats, exposure to a commercial PBDE mixture resulted in a LOAEL of 1 mg/kg bw based on thyroid hormone effects. Consequently, if the most sensitive end points are chosen (although partly based on a preliminary report on a technical pentaBDE), a LOAEL value of 1 mg/kg/day is reasonable for compounds or mixtures belonging to the PBDE group. Using an extrapolation factor of 10, a NOEL of 0.1 mg/kg/day could be suggested for the PBDEs. More studies are needed, however, to provide a better basis for risk assessment of PBDEs and for producing a more solid LOAEL and NOEL.

The preliminary estimated dietary PBDE intake of 51 ng/day equals 0.7 ng/kg/day for a person weighing 70 kg. Comparison of the estimated dietary intake with the presented LOAEL value of 1 mg/kg/day results in a safety factor of $> 10^6$ with regard to the mean PBDE exposure from food. However, special dietary habits or other types of PBDE exposure may decrease this safety factor considerably.

Data Gaps and Future Research Needs

It is important to know the purity and impurity profiles of PBDEs used for kinetic and toxicity studies; these data should always be available. To avoid impurity problems, studies using isomer-specific pure congeners should be encouraged.

Further studies on PBDE time trends are needed to confirm and extend earlier observations. Results from ongoing studies are important in assessing resource needs for future PBDE studies. It is currently known that certain PBDE congeners accumulate in the environment, where others do not, but the reason for this discrepancy is not understood. Therefore, environmental transformation studies are needed to examine, for example, the degradation of decaBDE to penta- and tetraBDEs. It is also important to collect more data on human exposure, especially through food, but also through other routes.

There still are large gaps in data concerning PBDE toxicity. General toxicity studies should be performed on specific congeners of importance in terms of environmental levels and bioaccumulation, congeners such as BDE-47, -99, -100 and -153. There are also large data gaps in the field of toxicokinetics, i.e., the metabolism of PBDEs, metabolites formed,

and enzymes involved. The following characteristic and critical end points of PBDE toxicity should be studied further: mechanisms of thyroid toxicity, possible effects on other hormonal systems, and reproduction and developmental toxicity. The latter should concentrate especially on multigeneration studies and perinatal and postnatal toxicity and include neurotoxicity models. It is also important to perform cancer bioassays on the tetra- and pentaBDEs, as these PBDE groups are bioavailable and are often found in higher concentrations in the environment than decaBDE. Finally, studies on structure–activity relationships and interactions (including synergism, antagonism, and interactions with other halogenated aromatic hydrocarbons) of PBDE are important for the toxicologic evaluation of PBDEs.

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