Brominated Flame Retardants: Cause for Concern?

Linda S. Birnbaum[1] and Daniele F. Staskal[2]

[1]U.S. Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Experimental Toxicology Division, Research Triangle Park, North Carolina, USA; [2]University of North Carolina, Curriculum in Toxicology, Chapel Hill, North Carolina, USA

Brominated flame retardants (BFRs) have routinely been added to consumer products for several decades in a successful effort to reduce fire-related injury and property damage. Recently, concern for this emerging class of chemicals has risen because of the occurrence of several classes of BFRs in the environment and in human biota. The widespread production and use of BFRs; strong evidence of increasing contamination of the environment, wildlife, and people; and limited knowledge of potential effects heighten the importance of identifying emerging issues associated with the use of BFRs. In this article, we briefly review scientific issues associated with the use of tetrabromobisphenol A, hexabromocyclododecane, and three commercial mixtures of polybrominated diphenyl ethers and discuss data gaps. Overall, the toxicology database is very limited; the current literature is incomplete and often conflicting. Available data, however, raise concern over the use of certain classes of brominated flame retardants. ***Key words:*** **BFRs, brominated flame retardants, HBCD, hexabromocyclododecane, PBDE, polybrominated diphenyl ether, TBBPA, tetrabromobisphenol A.** ***Environ Health Perspect*** **112:9–17 (2004). doi:10.1289/ehp.6559 available via** ***http://dx.doi.org/*** **[Online 17 October 2003]**

Every year, fires kill more than 3,000 people, injure more than 20,000, and result in property damages exceeding an estimated $11 billion in the United States alone (Karter 2002). Fire incidence has dropped over the past 25 years, which is partly because of the fire prevention policies requiring the presence of flame retardant chemicals in many industrial products. In fact, the incidence of potentially preventable fires due to combustion of electrical equipment and furniture is lower in the United States than in Europe, at least in part because of the higher standards for protection against flammability in the United States (Dawson 2002). Thus, not only do flame retardants save lives and prevent harm, but they also reduce the economic cost of fires. In addition to their immediate detrimental impact, fires can also generate persistent environmental contaminants such as polyhalogenated dibenzo-*p*-dioxins and polyhalogenated dibenzo-*p*-furans, which are known to have the potential to adversely affect both human and environmental health (Birnbaum et al. 2003).

There are more than 175 different types of flame retardants, which are generally divided into classes that include the halogenated organic (usually brominated or chlorinated), phosphorus-containing, nitrogen-containing, and inorganic flame retardants. The brominated flame retardants (BFRs) are currently the largest market group because of their low cost and high performance efficiency. In fact, there are more than 75 different BFRs recognized commercially. Some, such as the polybrominated biphenyls (PBBs), are no longer being produced. The PBBs were removed from the market in the early 1970s because of poisonings in Michigan attributed to the inadvertent mixing of a bag of Firemaster FF-1, a commercial PBB mixture, into animal feed. This PBB contamination of animal feed resulted in loss of livestock, long-term impacts on the health of farm families in Michigan, and economic dislocation (Dunckel 1975; Fries 1985; Mercer et al. 1976). "Tris-BP," another BFR originally used in clothing, was shown to be mutagenic and nephrotoxic and was later removed from commerce (Dybing et al. 1980; Soderlund et al. 1980).

Despite these incidents, little toxicity information is present for nearly half of the existing BFRs. Many of these are new compounds that will require basic toxicity testing, at minimum, before they are released to the marketplace. It is also important to note that not all BFRs are alike: the only thing that many have in common is that they contain a bromine atom. However, they represent a major industry, involving high-production chemicals with a wide variety of uses (de Wit 2002). Recent reports have demonstrated that BFRs exist in the environment far from the locations where they are produced and/or used, and that the concentrations of some of the BFRs, both in the environment and in humans, are rapidly increasing (Alaee and Wenning 2002a). The widespread production and use of BFRs, and strong evidence of increasing contamination of the environment and people by these chemicals, heighten the importance of identifying emerging issues and data gaps and of generating a future research agenda. In this article we briefly review the issues surrounding the use of BFRs and identify scientific issues that need to be addressed by regulators and scientists alike. Other, more comprehensive reviews of the literature are available (Alaee and Wenning 2002b; Letcher and Behnisch 2003).

Bromine and BFR Use

Worldwide, approximately 5,000,000 metric tons of bromine are produced each year, with a market value exceeding US $2 billion annually [Arias 2001; Bromine Science and Environmental Forum (BSEF) 2000]. Since 1975, the worldwide bromine demand has increased significantly, averaging a 2% growth rate between 1990 and 2000 [Organisation for Economic Co-operation and Development (OECD) 1994]. As of 2000, BFRs accounted for 38% of the global demand share of bromine, a stark increase compared with 8% in 1975. There are five major classes of BFRs: brominated bisphenols, diphenyl ethers, cyclododecanes, phenols, and phthalic acid derivatives. The first three classes represent the highest production volumes. In fact, five BFRs constitute the overwhelming majority of BFR production at this time, although new compounds are being introduced constantly as others are eliminated from commerce. The five major BFRs are tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCD), and three commercial mixtures of polybrominated diphenyl ethers (PBDEs), or biphenyl oxides, which are known as decabromodiphenyl ether (DBDE), octabromodiphenyl ether (OBDE), and pentabromodiphenyl ether (pentaBDE). The structures for these chemicals are shown in Figure 1. HBCD, TBBPA, and PBDEs are used as additive or reactive components in a variety of polymers, such as polystyrene foams, high-impact polystyrene,

Address correspondence to D. Staskal, U.S. EPA, ORD, NHEERL, ETD, PKB, MD B143-05, Research Triangle Park, NC 27711 USA. Telephone: (919) 541-5484. Fax: (919) 541-9464. E-mail: staskal.daniele@epa.gov

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and epoxy resins [World Health Organization (WHO) 1994]. These polymers are then used in a medley of consumer products, including computers, electronics and electrical equipment, televisions, textiles, foam furniture, insulating foams, and other building materials.

More than 200,000 metric tons of BFRs are produced each year (BSEF 2000). The global market demand for BFRs in 2001, as reported by the BSEF (2003), is shown in Table 1. BFR production has increased dramatically over the past 20 years, with the largest relative increase at this time being in Asia. As of 2001, Asia consumed an estimated 56% of the total market demand, and the Americas and Europe consumed 29% and 15%, respectively (BSEF 2001). There are dramatic regional differences in the consumption patterns for the five major BFRs, which is demonstrated by the variations in BFR profiles in Table 1. For example, of the 117,950 tons of BFRs consumed by Asia in 2001, approximately 76% was TBBPA, 21% PBDEs, and 3% HBCD (BSEF 2001). In contrast, of the 53,900 tons used by the Americas, 34% was TBBPA, 61% PBDEs, and 5% HBCD.

The congener-specific breakdown of the PBDEs also shows large regional differences. DBDE is the most widely used PBDE globally, with equal use in America and Asia. PentaBDE is essentially only used in America, whereas OBDE remains a minor product worldwide. Some of these differences may be due to the voluntary ban on pentaBDE in Europe (formalized as of July 2003), which was followed by a European Union directive restricting the use of pentaBDE and OBDE in electrical and electronic equipment by 1 July 2006 (BSEF 2003). Early in 2003, the California Assembly moved to ban the use of OBDE and pentaBDE beginning in 2008 (California State Assembly 2003); recently, this bill has been approved as a California state law.

Tetrabromobisphenol A

TBBPA, the most widely used BFR, is used primarily as a reactive flame retardant in printed circuit boards but also has additive applications in several types of polymers. When used as a reactive component, the phenolic hydroxy groups react covalently, resulting in incorporation of TBBPA into the polymer. However, when TBBPA is used as an additive component, the BFR molecules are not part of the structure of the polymer itself and can be released into the environment more readily. The extent of BFR release into the environment is therefore dependent on whether the application is additive or reactive.

Despite TBBPA's reactive properties, both additive- and reactive-treated products have been shown to release TBBPA and metabolites into the environment. TBBPA has been measured in the air, soil, and sediment but is generally not found in water samples. TBBPA is highly lipophilic (log K_{ow} = 4.5) and is not very water soluble (0.72 mg/L). TBBPA was measured in the air near a production site at a level of 1.8 µg TBBPA/m^3 (Zweidinger et al. 1979). Studies in Japan have found TBBPA in soil and sediment at concentration ranges of 0.5–140 µg/kg (dry weight) and 2–150 µg/kg (dry weight), respectively (Watanabe et al. 1983a, 1983b). Data are very limited regarding the presence of TBBPA in biota, which may reflect its relatively short half-life in air, water, and sediment. Human TBBPA serum levels were measured by Jakobsson et al. (2002), who found TBBPA in 8 of 10 samples from computer technicians, at levels ranging from 1 to 3.4 pmol/g lipid.

Biodegradation studies conducted under varying conditions in several environmental media (soil, river sediment, and water) have indicated that TBBPA partially breaks down under both aerobic and anaerobic conditions, with variable degradation rates (Fackler 1989a, 1989b, 1989c). Judging from the range of half-lives obtained in those biodegradation studies, the compound's half-life approximates 2 months. In contrast, a 2-week biodegradation study in sludge under sewage treatment conditions showed no degradation (Chemicals Inspection & Testing Institute 1992). TBBPA also shows sensitivity to light, resulting in a photodegradation half-life in water of 6.6–80.7 days (dependent on season), and 0.12 days when absorbed onto silica gel and exposed to ultraviolet (UV) rays (WHO 1995). The half-life of TBBPA in fish is < 1 day, and in oysters is < 5 days (Fackler 1989b; WHO 1995).

There are a limited number of laboratory studies examining the metabolism of TBBPA. Two acute, high-dose studies in rats have reported that unmetabolized TBBPA (51–95% of dose) is rapidly excreted in the feces after a single exposure (Szymanska et al. 2001; WHO 1995). After intraperitoneal administration (250 or 1,000 mg/kg), Szymanska et al. (2001) observed peak concentrations of ^{14}C-TBBPA within the first hour in all tissues; highest concentrations were in the fat, followed by the liver, sciatic nerve, muscles, and adrenals. Furthermore, they found that a low percentage of the TBBPA dose was retained in fatty tissue (3–6%) and muscles (11–14%) after 72 hr, which suggests that TBBPA, or a metabolite, has the potential to bioaccumulate with repeated exposure. This is inconsistent with the short half-lives found in fish and oysters, which suggest TBBPA will not bioaccumulate. In a similar study by Larsen et al. (1998), 95% of the dose was excreted in the feces as parent compound in the first 72 hr. Similar results were obtained by Meerts et al. (1999) after oral exposure to pregnant rats on gestational days (GD) 10–16; 80% of the radioactivity was excreted in the feces within 48 hr.

Despite the high levels of parent compound in both tissue and excreta in these studies, there is also evidence for TBBPA metabolism. The analysis of the feces in the Szymanska et al.

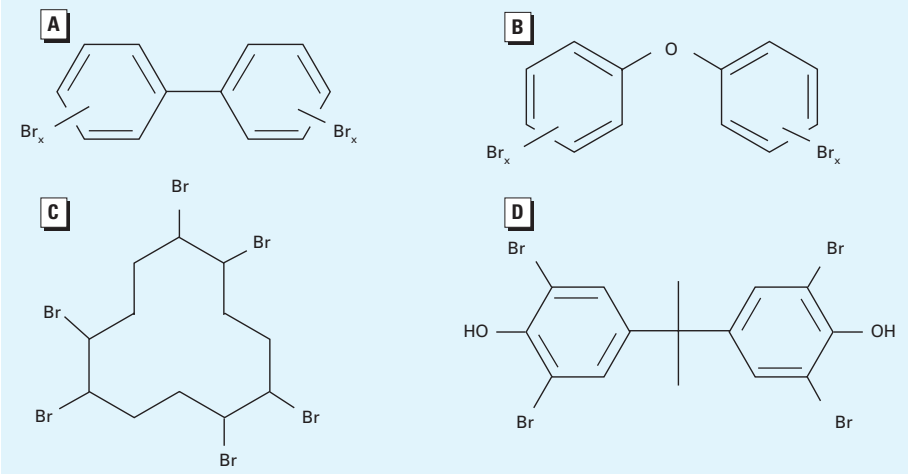

Figure 1. Chemical structures of (*A*) PBBs, (*B*) PBDEs, (*C*) HBCD, and (*D*) TBBPA.

Table 1. Major BFR volume (metric tons) estimates by region in 2001.

BFR	Americas	Europe	Asia	Rest of world
TBBPA	18,000	11,600	89,400	600
HBCD	2,800	9,500	3,900	500
DBDE	24,500	7,600	23,000	1,050
OBDE	1,500	610	1,500	180
PentaBDE	7,100	150	150	100
Total PBDEs	33,100	8,360	24,650	1,330
Total BFRs by region	53,900	29,460	117,950	2,430

Data from BSEF (2001).

(2001) study showed that 10% of the radiolabeled material in the feces was tribromobisphenol A, suggesting rapid elimination in the bile and possible debromination by gastrointestinal flora. Larsen et al. (1998) also investigated TBBPA metabolism in bile-cannulated rats; 71% of the dose was excreted in the bile. Upon analysis, three conjugated metabolites were found in the bile: a diglucuronide, a monoglucuronide, and a glucuronide-sulfate ester. This suggests that biliary conjugates are deconjugated and reabsorbed in the lower gastrointestinal tract and then reconjugated and reexcreted in the bile, which also results in elimination of parent TBBPA via the feces (Larsen et al. 1998).

Rodent studies have indicated that TBBPA is not acutely toxic because the single dose oral LD_{50} (dose lethal to 50%) is approximately > 5 g/kg in rats and > 4 g/kg in mice (WHO 1995). Dietary levels of 0.05–100 mg TBBPA/kg body weight/day in 30- and 90-day rodent studies did not produce any effects on behavior, appearance, food consumption, body weight gain, or mortality (Goldenthal EI. Unpublished data; Quast JF. Unpublished data; WHO 1995). To our knowledge, no long-term exposure data are available. Furthermore, *in vivo* studies have shown TBBPA not to be an inhalation or dermal toxicant, teratogen, or skin and eye irritant (WHO 1995).

The majority of adverse effects of TBBPA have been found *in vitro*. TBBPA is toxic to primary hepatocytes, most likely by destroying mitochondria (Boecker et al. 2001). This may not be surprising because its halogenated phenolic properties would suggest that it could uncouple oxidative phosphorylation. TBBPA exposure results in membrane dysfunction in isolated liver cells and inhibits the activity of a key mixed-function oxidase, cytochrome P450 2C9 (CYP2C9) (Boecker et al. 2001). TBBPA is also highly immunotoxic in culture, which is demonstrated by its ability to specifically inhibit the expression of CD25 at concentrations as low as 3 μM (Pullen et al. 2003). The expression of CD25 is essential for proliferation of activated T cells and is commonly used as a marker for T-cell activation. TBBPA's potent inhibition of this protein may have a profound effect on an organism's immunomediated defense against bacteria, viruses, and possibly cancer. This major BFR is also neurotoxic in cerebellar granule cells and rat brain synaptosomes, where it inhibits dopamine and generates free radicals (Mariussen and Fonnum 2002; Reistad et al. 2002).

Some of the most recent concerns regarding the potential for adverse effects of TBBPA focus on the possibility that TBBPA may act as an endocrine disruptor. The structural similarity of TBBPA to bisphenol A, a known weak environmental estrogen, has suggested that this chemical might have the ability to bind to the estrogen receptor and disrupt signaling. Meerts et al. (2001) examined the estrogenic potency of TBBPA and related compounds in three different cell lines looking for estrogen receptor–dependent luciferase reporter gene expression. TBBPA had little estrogenic effect, but lower brominated bisphenols were found to have estrogenic activity (Meerts et al. 2001). However, hydroxylated TBBPA metabolites have been shown to inhibit estrogen sulfotransferase activity *in vitro* (Kester et al. 2002). If such an inhibition were to occur *in vivo*, it could result in elevated levels of circulating estrogens because sulfation is a major elimination pathway for endogenous estrogenic hormones.

Endocrine disruption through disruption of thyroid hormone homeostasis has also been studied *in vitro*. TBBPA inhibited triiodothyronine (T_3) and transthyretin (TTR) binding (concentration range of 1×10^6 to 1×10^4 M), enhanced proliferation of rat pituitary GH3 cells and stimulated their production of growth hormone, and enhanced the proliferation of MtT/E-2 cells, whose growth is estrogen dependent (Kitamura et al. 2002). The results from these studies suggest that TBBPA is a cytotoxicant, immunotoxicant, and thyroid hormone agonist and has the potential to disrupt estrogen signaling, at least *in vitro*.

Disruption of thyroid homeostasis has been proposed to be the primary toxic effect of TBBPA, as well as the other BFRs. Perturbations of thyroid homeostasis are of special concern during development because slight changes in thyroid status of the mother have been associated with cognitive deficits in their children (Haddow et al. 1999). Circulating thyroid hormone levels can be affected by several mechanisms, including changes in synthesis, breakdown, distribution, and binding to the nuclear thyroid hormone receptor. There is no evidence that TBBPA affects the synthesis of thyroxine (T_4). Likewise, the major routes of clearance of T_4 involve glucuronidation and sulfation, and there is no evidence that these are affected by TBBPA. We do not yet have studies of TBBPA's effects on deiodination of thyroid hormones; this is a potential data gap in the toxicity pathway. Because TBBPA has the potential to compete with T_4 for binding to a key serum transport protein, TTR, it is possible that TBBPA's toxicity to the thyroid is related to the chemical's effects on the transport of T_4 in the blood. Meerts et al. (2001) has demonstrated *in vitro* that the binding affinity of TBBPA to TTR is greater than that of T_4 (up to 10 times more potent than T_4). The effects of TBBPA *in vivo* are limited. Meerts et al. (1999) also exposed pregnant rats to TBBPA from GD 10–16 and found no effects on maternal or fetal T_4, T_3, or TTR. However, TBBPA increased thyroid-stimulating hormone (TSH) levels (196%) in fetal plasma, suggesting that despite potent *in vitro* TTR binding, TBBPA acts via another mechanism (Meerts et al. 1999).

Hexabromocyclododecane

HBCD is a nonaromatic, brominated cyclic alkane used primarily as an additive flame retardant in thermoplastic polymers with final applications in styrene resins (National Research Council 2000b). It has also been used, although to a lesser extent, in textile coatings, cable, latex binders, and unsaturated polyesters. Its total production is about 16,700 metric tons per year, making it a relatively minor contributor to the total BFR economy (Table 1). However, it is used more extensively in Europe than in the Americas, where it has been substituted for some of the nonfoam applications for which PBDEs were formerly used. As is the case for the other major BFRs, HBCD is highly lipophilic, with a log K_{ow} of 5.6, and has low water solubility (0.0034 mg/L) (MacGregor and Nixon 1997; Stenzel and Markley 1997). Because of its size and halogenation, it also has a low vapor pressure (4.7×10^{-7} mm Hg) (Stenzel and Nixon 1997). Recent studies have shown that HBCD has a strong propensity to bioaccumulate, demonstrated by a bioconcentration factor of approximately 18,100 in fathead minnows, as well as fish-to-sediment ratios of up to 15 (Sellstrom et al. 1998; Veith and Defoe 1979). In fact, HBCD is not only bioaccumulative but is also persistent, with a half-life of 3 days in air and 2–25 days in water (Lyman 1990).

The commercial HBCD product is composed of three diastereomers: α-, β-, and γ-HBCD. Technical HBCD typically consists primarily of γ-HBCD; however, the isomeric profile varies depending on product application. At temperatures above 160°C, thermal rearrangements of the diastereomers can occur. HBCD is usually present in sediments as γ-HBCD (> 90%); however, small amounts of the α-diastereomer and even smaller amounts of the β-diastereomer have been found in some regions with high HBCD levels (De Boer et al. 2002). One interlaboratory study also examined α:β:γ ratios in eel at the locations found to have high levels of HBCD in the sediment; however, those isomer ratios do not mimic the environmental or commercial mixtures (De Boer et al. 2002). Rather, those results showed α:β:γ ratios in eel of 21:21:1 and 5:1:2, as measured in two separate locations with high sediment HBCD levels. These levls are consistent with the ratios of HBCD found in a harbor porpoise and cormorant, where only α-HBCD was detected. γ-HBCD is the prominent diastereomer in sediment, whereas α-HBCD is consistently the highest in biota, and β-HBCD always appears to be a very minor component. In sewage sludge, all three diastereomers are found in almost equal ratios (De Boer et al. 2002). The diastereomer ratios

in commercial HBCD were very different from the ratios in the environmental media and biota, providing clear evidence of environmental transformation of the industrial product. There is no information on the relative toxicity of the different HBCD isomers, or of a mixture resembling what has been found in wildlife and in people.

A limited number of studies have examined the ecotoxicity of HBCD. The EC_{50} (concentration effective in 50%) values in algae range from 9.3 μg/L to 0.37 mg/L, indicating the potential for high toxicity; however, these EC_{50} values are greater than the water solubility of this compound (Kemi 1999; OECD 2003). Studies with aquatic invertebrates have also resulted in toxicity values near the level of solubility. Studies in daphnia have demonstrated a life-cycle no-observable-effect concentration of 3.1 μg/L (OECD 2003), and more recent studies in rainbow trout have found an LC_{50} (concentration lethal to 50%) of 2.5 μg/L (OECD 2003). Negative results for mutagenicity in yeast and *Salmonella*, as well as lack of chromosomal aberrations in human peripheral blood lymphocytes, indicate that HBCD is not genotoxic (Brusick 1976; Shoichet and Ehrlich 1978; Zeiger et al. 1987).

Although the information on HBCD metabolism is extremely limited, industry studies suggest that HBCD is metabolized and excreted with a very short half-life (~2 hr) in rats after oral exposure (Hakk and Letcher 2003; Hale et al. 2002; National Research Council 2000b). The toxicity of HBCD has not been extensively studied; however, one study has reported a lowest-observable-effect level (LOEL) in rats of approximately 13 mg/kg/day based on liver effects after repeated exposures (National Research Council 2000a). In contrast, an industry study reported that the no-observable-adverse-effect level (NOAEL) for adverse changes in the liver was 1,000 mg/kg/day (Chengelis 1997). The same study reported significant decreases in circulating T_4 levels at 100 mg/kg/day, an effect clearly of concern given the potential for adverse effects on the developing organism from disruptions of thyroid homeostasis. Two other reproductive/developmental studies in rats treated with HBCD revealed essentially no developmental effects (NOAEL > 500 mg/kg/day) (Murai et al. 1985; Stump 1999).

In addition to the concern for effects on thyroid hormone levels, recent studies by Eriksson et al. (2002a) have demonstrated that early neonatal exposure of mice to HBCD can result in changes in spontaneous behavior, learning and memory defects, and a reduced number of nicotinic receptors. Coexposure to polychlorinated biphenyls (PCBs) resulted in an apparent increase in the response observed with either commercial mixture alone. Several *in vitro* studies have supported the thesis that HBCD has the potential to cause neurobehavioral alterations. Using cerebellar granule cells, Reistad et al. (2002) reported that HBCD was the most potent BFR tested this *in vitro* system, resulting in an LC_{50} of 3 μM. HBCD has also been shown to block the uptake of dopamine into rat brain synaptosomes *in vitro* (EC_{50} = 5 μM) (Mariussen and Fonnum 2002), which supports the thesis that HBCD has the potential to cause neurobehavioral alterations.

There are very few reports of effects of HBCD on people. No toxicokinetic data exist; however, there are a few reports of results from dermal exposure testing (National Research Council 2000b). In a human dermal study, no irritant effects were reported after exposure to the fabric (10% HBCD) for 6 days (McDonnell 1972). Results are contradictory regarding dermal sensitization effects of HBCD because some studies have found it to be a mild sensitizer, whereas others have not (National Research Council 2000b).

HBCD has been detected in workplace air samples at levels up to 1,400 μg/kg in dust (Leonards et al. 2001). Ryan and Patry (2002) also measured the concentration of total HBCD in human breast milk from several cities in Canada. The mean and median values from 30 individual women were 6.6 and 1.3 μg/kg lipid, respectively, with a range of 0–126 μg/kg lipid. These concentrations are low, but because HBCD has the potential to bioaccumulate and persist in the environment, there is cause for concern. Overall, the available literature on HBCD is incomplete and conflicting, emphasizing the need for more information on developmental effects, endocrine disruption, and longer term effects, including carcinogenesis.

Polybrominated Diphenyl Ethers

The PBDEs potentially involve 209 different congeners, varying in both number and position of bromination. By analogy with the PCBs, they are numbered using the same International Union of Pure and Applied Chemistry (IUPAC) system. However, there appear to be many fewer actual PBDE congeners in the commercial mixtures than the theoretical number possible, largely because many of the congeners lack stability and tend to debrominate. The same situation has been shown to be true of the PBBs. The PBDEs are major industrial products with a total worldwide production of approximately 67,400 metric tons/year (BSEF 2000). However, the use is not evenly spread over the industrialized world. The Americas account for slightly more than 50%, whereas all of Europe accounts for 12% (Table 1).

In fact, although the production of PBDEs has continued to increase in the United States and Canada, voluntary bans have resulted in a declining use in Europe. DBDE represents the major product in all markets, accounting for approximately 80% of the total PBDE production worldwide (BSEF 2000). Unlike the other commercial products, DBDE is a relatively pure mixture, composed of ≥ 97% brominated diphenyl ether (BDE) 209 (DBDE), < 3% nonabromodiphenyl (NBDE), and small amounts of OBDE. DBDE is used as an additive flame retardant primarily in electrical and electronic equipment, as well as in textiles, where it is applied as a polymer backcoat to the fabric. Commercial OBDE is a more complicated mixture with several congeners present: approximately 10–12% hexabrominated diphenyl ethers (HxBDE), 44% heptabrominated diphenyl ethers, 31–35% OBDE, 10–11% NBDE, and < 1% DBDE (WHO 1994). It is not clear whether any pentaBDEs are present in the commercial OBDE products. OBDE is a minor PBDE product, used as an additive in polymers for use in plastic housings and smaller components, such as office equipment.

The third commercial PBDE product, pentaBDE, or "pentabrom," is a viscous liquid used primarily in textiles as an additive in polyurethane foams, where up to 30% of the weight of the foam can be accounted for by this flame retardant (Hale et al. 2002). It also has minor uses in phenolic resins, polyesters, and epoxy resins. Although there is variation in commercial mixtures, penta mixtures are generally composed of 24–38% tetrabromodiphenyl (TBDE), 50–60% pentaBDE, and 4–8% HxBDE (WHO 1994). The major PBDE congeners are IUPAC nos. 47 (TBDE), 99 and 100 (pentaBDEs), and 153 and 154 (HxBDEs). BDEs 47 and 99 are the major congeners in the mixture, accounting for approximately 75% of the total mass. There is roughly twice as much BDE 99 as BDE 47 in the commercial mixtures, and approximately equal amounts of BDEs 153 and 154 (WHO 1994). The use of pentaBDE has decreased in response to a voluntary ban in Europe, which is to be followed by a formal ban of use in all applications for the European Union market that must be complied with by 2004 (BSEF 2003).

The PBDEs are reported to be extremely stable. However, several studies have investigated the photolytic lability of the individual congeners from the commercial products and found that when PBDEs are dissolved in organic solvents, debromination occurs in the presence of UV light (Eriksson et al. 2001a; Olsman et al. 2002; Tysklind et al. 2001). DBDE breaks down to lower brominated congeners (nona- to hexa-BDEs) with a half-life of < 15 min in toluene and approximately 15, 100, and 200 hr in sand, sediment, and soil, respectively (Tysklind et al. 2001). Eriksson et al. (2001a) determined that the reaction rate of photodecomposition seems to be dependent on the degree of bromination; the lower

brominated congeners degrade slowly (half-life > 1 day), whereas the octa and deca congeners decompose rapidly (5 hr and 30 min, respectively). Further analysis of the breakdown products has revealed that compounds with fewer than six bromine atoms all seem to be polybrominated dibenzofurans (PBDFs) (Eriksson et al. 2001a; Olsman et al. 2002). It is clear that debromination occurs in experimental conditions; however, whether this photodecomposition occurs in the environment is less certain. Studies involving analysis of sludge arrive at conflicting conclusions. Some investigators have suggested that DBDE may not undergo photolytic decomposition, based on mass-balance calculations (Schaefer and Fowles 2001). However, careful analysis of this study demonstrates the presence of lower brominated congeners in the sediments 32 weeks after initial application of radiolabeled BDE 209.

The environmental patterns of PBDEs in the air vary from the patterns in soil, sediment, and sludge. PBDEs strongly adsorb to these matrixes, and the congener patterns tend to reflect those in the commercial mixtures, except in sludge. Hale et al. (2002) has recently reported that PBDE concentrations in sewage sludge in the United States are as high as 33 mg/kg and reflect the congener makeup found in polyurethane foam. In contrast, point sources releasing DBDE have resulted in sediment with concentrations as high as 5 mg/kg. The lower brominated congeners (four to seven bromines) are more bioaccumulative and persistent, with bioconcentration factors > 5,000 (de Wit 2002). This is reflected by increasing concentrations in animals higher in the food web: concentrations in invertebrates are lower than those in fish, which are much lower than those in marine mammals (Alaee et al. 2002; Boon et al. 2002).

PBDE congener composition varies in different biologic specimens. Rice et al. (2002) have shown that fish from two different sites in the United States have distinct congener patterns, which may reflect their nearness to sources. In bass collected from the Detroit River, BDE 47 accounted for 76% of the total; in other cases, BDE 47 was as low as 17%. Although there was some variation among samples, the amounts of BDEs 99, 100, 153, and 154 were approximately equal. In carp collected in the Des Plaines River downstream of a facility using OBDE, there were large amounts of BDE 181 and BDE 183, as well as the unique congener, BDE 190 (all hepta congeners). In another fish study, Petreas et al. (2002) reported that BDE 47 represented approximately 50% of the total in fish from northern California, followed by approximately 30% BDE 100, 10% each for BDEs 99 and 154, and traces of BDE 153. Higher up the food chain, in harbor seals from San Francisco Bay, 75% of the PBDEs were BDE 47; the remainder of the PBDEs were approximately equally divided among BDEs 99, 100, 153, and 154 (She et al. 2002). These various data sets provide suggestive evidence for transformation of the commercial PBDE mixtures in biota and in the environment.

Perhaps the most interesting point concerning the breakdown of higher brominated PBDE congeners is that the congener composition does not create the same profile found in the commercial PBDE mixtures, which argues against the complete stability of these products. For example, recent analysis of fish tissue by Rice et al. (2002) revealed relatively high amounts of two hepta-BDE congeners, 181 and 190, which have not been detected as major components of any commercial mixture. Whether these are due to debromination of BDE 209, as suggested by the studies involving exposure of trout to a commercial DBDE mixture (Kierkegaard et al. 1999), remains to be determined.

The lack of consistency between congener patterns in the environment and human tissues and commercial products is a reflection of both the physical and chemical properties of this class of chemicals, resulting in differences in environmental fate and transport as well as metabolic differences. Although all of the PBDEs have low solubility (< 1 µg/kg) and high K_{ow} values (> 5), the lower congeners have substantially higher vapor pressures than do the highly brominated compounds. Therefore, BDE 47, which has four bromine atoms, is usually found at highest concentration in air samples. BDE 47 is followed by BDE 99, which is more prevalent in commercial pentaBDE mixtures. BDE 100, a minor constituent of commercial pentaBDE, is found at higher concentrations in air than are the more common HxBDEs, 153 and 154. The major components of OBDE and DBDE (i.e., the highly brominated congeners) are found at much lower concentrations because of extremely limited volatility. However, PBDEs have been shown to undergo long-range transport, evidenced by the increasing levels of several PBDE congeners in Canadian Arctic ringed seals (Ikonomou et al. 2002a).

All of the congeners of concern are persistent, with half-lives in air, water, and soil or sediment > 2 days, 2 months, and 6 months, respectively. Because of differences in bioaccumulation and persistence, the congener patterns in biota are different from the commercial products. Typically, levels of BDE 47 exceed those of BDEs 99 and 100, unless samples are taken from near potential source of environmental exposure, such as a manufacturing facility (Sjodin et al. 1999). This trend is in contrast to the commercial pentaBDE mixture, in which BDE 99 is the major congener. There are several potential sources of exposure in addition to the manufacture of these chemicals, primarily through the diet, but also during the application of PBDEs to textiles as well as volatilization and leaching during use. Bocio et al. (2003) recently analyzed PBDEs in foodstuffs from Spain, reporting that the dietary intake of PBDEs for an adult male was 97 ng/day and that the majority of exposure was from the lower brominated congeners (tetra and penta congeners) found in oils, fats, fish, shellfish, meat, and eggs. At this time, a large-scale study assessing dietary exposure in the United States is unavailable. In addition, studies from Hale et al. (2002) indicated particulate losses over use, and disposal may serve as an ongoing reservoir of environmental exposures.

Limited evaluations of the ecologic effects of PBDEs have been conducted. In general, the lower brominated mixtures are more toxic than are the higher congeners. PentaBDE is more toxic than OBDE, whereas DBDE is essentially nontoxic to invertebrates. Recent studies have shown that the $LC(EC)_{50}$ values in crustaceans are below 1 mg/L for BDEs 27, 47, 99, and 100, which classifies these chemicals as very toxic to aquatic organisms (Wollenberger et al. 2002). Data on PBDEs in fish are limited to a handful of studies. In rainbow trout fed BDE 47 or BDE 99 for 6 and 22 days, ethoxyresorufin *O*-deethylase (EROD) activity was inhibited, as was glutathione reductase (Tjarnlund et al. 1998). Stapleton et al. (2002) were able to show that PBDEs accumulate in carp; however, the congener pattern is different: BDE 47 is still dominant, but it is followed by BDE 154 and there is almost no BDE 99 bioaccumulation. Despite the low risk of toxicity of DBDE and OBDE to surface-water organisms and top predators, there may still be concern for wastewater, sediment, and soil organisms. In addition, there may be lower brominated congeners in the commercial OBDE mixture, as well as the potential for photolytic and/or anaerobic debromination and the formation of polybrominated dibenzo-*p*-dioxins and PBDFs.

Mammalian toxicity studies have been conducted in both rats and mice. The most extensive data set exists for DBDE, with studies ranging from acute to chronic laboratory studies. The U.S. National Toxicology Program (NTP) conducted 2-year feeding studies with DBDE (NTP 1986) and showed that high doses up to 50,000 ppm in the diet (5,000 g/kg/day) resulted in neoplastic nodules in the liver in both male and female rats; nodules were also apparent in male rats given a low dose (25,000 ppm). DBDE had similar effects on male mice but did not have these effects in female mice. Few effects other than the low incidence of tumors were seen.

Little information exists for reproductive effects. DE-71, a commercial penta mixture, was tested under the Endocrine Disrupter Screening Program according to the male and female Tier 1 pubertal protocols to detect thyroid active agents (Stoker et al. 2003). In

male rats, there was a delay in reproductive development evidenced by a delay in puberty and a decrease in ventral prostate and seminal vesicle weights at the high dose (60 mg/kg). This was accompanied by decreases in T_4 and T_3 and an increase in TSH, as well as effects on the liver, including increases in liver weight and EROD, pentoxyresorufin *O*-deethylase (PROD), and UDP-glucuronosyltransferase (UDPGT) activity at doses of 30 and 60 mg/kg (Stoker et al. 2003). These results suggest a 5-day LOEL of 30 mg/kg/day and a 31-day LOEL of 3 mg/kg/day in male rats based on decreases in T_4. In female rats, DE-71 caused a delay in the onset of puberty (60 mg/kg), decreases in T_4 (30 mg/kg), increased liver size (30 mg/kg), and induction of liver enzymes (Laws et al. 2003). Similar results were found by Lichtensteiger et al. (2003); the onset of puberty was delayed in female offspring after an 8-day exposure to BDE 99.

The greatest concern for the potential health effects of PBDEs comes from the reports of developmental neurotoxicity in mice. Several studies by Eriksson and co-workers have exposed mice neonatally to individual PBDE congeners resulting in developmental neurotoxic effects (Eriksson et al. 2001b; Viberg et al. 2002, 2003). Using a paradigm that they had developed for PCB developmental neurotoxicity, they were able to define a critical window of sensitivity [postnatal day (PND) 10] for PBDE exposure in neonatal mice, which also coincides with the period of rapid brain growth (Eriksson et al. 2002b). In this series of studies, several PBDE congeners were examined; however, the majority of the work focused on BDE 99. BDE 99 has been shown to impair spontaneous motor behavior, alter cholinergic transmitter susceptibility, and disrupt habituation capability (Viberg et al. 2002). Male NMRI mice exposed to BDE 99 and C57 BL6/J male and female mice exposed to BDEs 47, 99, 153, and 209 on PND 10 showed neurobehavioral alterations at doses as low as 0.4 mg/kg (Eriksson et al. 2001b, 2001c, 2002b; Viberg et al. 2002, 2003). In addition, results of some studies have shown that PBDE-treated animals exhibited a nonhabituating behavior profile similar to mice neonatally exposed to PCBs (Eriksson 1998; Eriksson and Fredriksson 1996). These deficits in learning and memory are observed in adulthood, and the effects worsen with age. This well-known series of studies produced very interesting results; however, they have recently been criticized for the lack of appropriate statistical analysis.

More recently, Branchi et al. (2002) examined the effects of perinatal BDE 99 exposure on CD-1 Swiss female mice using a different exposure paradigm and compared the results with concurrent studies conducted with the complex PCB mixture Aroclor 1254 (A1254). BDE 99 (0.6, 6, 30 mg/kg/day) or A1254 (6 mg/kg/day) was administered daily from GD 6 through PND 21. The mid-dose of BDE 99 reduced the number of pups per litter, and the high dose caused a delay in sensorimotor development. At adulthood, the A1254-treated animals were hyperactive, whereas all BDE 99–treated groups tend to be hypoactive, demonstrating that behavioral alterations can be different between PBDEs and PCBs. Neurotoxicology studies in rats with the commercial mixtures are also under way. Thus far, it has been shown that developmental exposure to DE-71 induces hepatic enzymes and hypothyroxinemia in both dams and offspring and alters some aspects of neurobehavioral development (Taylor et al. 2003). However, habituation of motor activity in rats was not altered after perinatal exposure to DE-71 (MacPhail et al. 2003).

The mechanisms for these behavioral and cognitive effects are not known. Some research has suggested that the observed neurotoxic developmental effects in mice may be associated with alterations in cholinergic receptors (Viberg et al. 2002). Other studies have investigated cell signaling involved in synaptic plasticity because these pathways have been shown to be affected by PCBs by stimulating the release of [^{3}H]arachidonic acid. Kodavanti and Derr-Yellin (2002) used cultured rat cerebellar granule neurons to investigate the effect of DE-71 (a penta mixture) and DE-79 (an octa mixture) on arachidonic acid release. Neurons exposed to the pentaBDE mixture, but not the OBDE mixture, shown alterations in arachidonic acid release due to activation of phospholipase A_2, which is similar to the effects observed with PCBs. Another group examined the effect of several PBDEs on cell death and free radical formation in cerebellar granule cells and found that DE-71 was more toxic than octa and deca congeners in inducing cell death (Reistad et al. 2002). Calcium homeostasis in neurons has also been shown to be disrupted by PBDEs (Wiegand et al. 2001). Such neurochemical changes in adults have been correlated with alterations in both behavior and cognition.

Yet another possibility involves the key role of thyroid hormones in the development of the brain. It is well known and documented that small decrements in maternal and fetal thyroid homeostasis cause neurologic impairments, including small decreases in the IQ of offspring (Haddow et al. 1999; Morreale 2001). Multiple studies have demonstrated that PBDEs can perturb the thyroid system in several experimental animal models, as well as in some *in vitro* test systems (Hallgren et al. 2001; Meerts et al. 2000; Zhou et al. 2002). Two theories exist to explain the mechanism by which PBDEs alter thyroid hormone homeostasis, both of which focus on decreases in T_4. Some research suggests that PBDEs cause enhanced excretion of T_4, whereas other research indicates that PBDEs may interfere with the thyroid hormone transport system by competitively binding with T_4, which prevents T_4 from binding with TTR.

Using commercial PBDE mixtures, Zhou et al. (2001) exposed weanling rats to DE-71, DE-79, and DE-83R at doses ranging from 0.3 to 300 mg/kg/day. After a 4-day exposure, total serum T_4 was decreased up to 80% for DE-71 and 70% for DE-79 at the highest dose. Developmental exposure (GD 6–PND 21) also dropped T_4 levels in the pups as well as in the dams (Zhou et al. 2002). The decrease in T_4 was associated with an induction of UDPGT, the key phase II metabolizing enzyme involved in the conjugation of T_4. Thus, the increased metabolism of T_4 results in enhanced excretion and thus a drop in the circulating levels. These results are consistent with studies from other laboratories demonstrating that exposure to specific congeners, such as BDEs 47 and 99, results in a decrease in serum T_4 in both rats (Hakk et al. 2002) and mice (Orn and Klasson-Wehler 1998).

The second mechanism suggested for the effects on T_4 involves competitive binding to TTR, a key protein involved in transport of T_4 through the blood and into developing tissues. One *in vitro* study showed that PBDEs, as parent compounds, do not compete with T_4–TTR binding and that only hydroxy metabolites of the PBDEs tested displaced T_4 from TTR (Meerts et al. 2000). For example, BDE 47 did not bind TTR *in vitro*, but metabolic conversion with CYP2B-induced microsomes gave rise to metabolites that competed with T_4. These experimental observations have been supported by the results of molecular modeling studies with PCBs (Chauhan et al. 2000). Whether the role of TTR in thyroid homeostasis is as important in humans as has been suggested from rodent studies is still unclear; although thyroid-binding globulin is the prominent transporter, TTR is essential to thyroid hormone transport to the developing fetus.

PBDEs have also been suggested to have other endocrine-disrupting effects. Using an *in vitro* model, Kester et al. (2002) demonstrated that hydroxy-PBDEs can inhibit estrogen sulfotransferase, leading to an apparent estrogenic effect. Whether PBDEs have any estrogenic activity *in vivo* has yet to be examined. In addition, some PBDE congeners, which are not environmentally relevant, have low affinity for the aryl hydrocarbon (Ah) (dioxin) receptor but are unable to induce dioxin response element binding (Chen et al. 2001). Zhou et al. (2002) found that repeated exposure of rats to DE-71, a commercial penta mixture, resulted in induction of EROD activity, a classic response to Ah receptor activation.

There have been only limited studies of the toxicokinetics of PBDEs. Because of high K_{ow} values, the PBDEs are expected to distribute

into the fat. However, data indicate that the concentrations of BDE 47 are greater than those of BDE 99 in adipose tissue, and these are much greater than those of BDE 209 (Choi et al. 2003; Covaci et al. 2002; Meironyte et al. 2001). Part of this is due to the relative absorption and persistence of these compounds, but part of this phenomenon may also be due to the fact that BDE 209, the fully brominated compound, is so large that it has difficulty moving at all. A similar situation has been observed with octachlorodibenzo-*p*-dioxin, the fully chlorinated dioxin (Birnbaum and Couture 1988).

Data are very limited in the scientific literature comparing uptake from oral, pulmonary, and dermal systems after PBDE exposure. By analogy to other persistent organic pollutants (POPs), it is likely that relative absorption may decrease at high concentrations; that the higher the degree of bromination, the poorer the absorption; that oral absorption will be similar to pulmonary absorption; and that dermal absorption will be quite limited. DBDE has historically been shown to be poorly absorbed after either oral or dermal exposure (Hughes et al. 2001; NTP 1986). However, recent studies in the rat have shown that DBDE can be absorbed (> 10% of the dose) orally and that highest concentrations are found in the plasma and highly perfused tissues (Morck et al. 2003). This group has also shown that approximately 10% of the dose was eliminated in the bile as hydroxy/methoxy metabolites with five to seven bromine atoms. In another recent study in rats, DBDE was readily absorbed from the gut with a bioavailability of approximately 26% (Morck et al. 2003). This research has also shown that hydroxylated octa- and nona-BDEs are the major phenolic metabolites and that DBDE follows a two-compartment elimination curve with an initial plasma half-life of 2 hr and a terminal half-life of 2.5 days in rats.

In a toxicokinetic study in male rats, it was shown that BDE 99 appears to be well absorbed (> 50%) (Hakk et al. 2002). Lipophilic tissues were the preferred sites for disposition, with highest tissue concentrations in adipose, adrenals, gastrointestinal tract, and skin. The metabolism of BDE 47 has also been studied in the rat and mouse at a single oral dose (Orn and Klasson-Wehler 1998). The distribution and excretion were surprisingly different between rats and mice: 14 and 20% of the compound was excreted in the feces, and < 0.5 and 33% via the urine, respectively. This suggests that mice may have a different metabolic capability for these chemicals compared with the rat. Of the remaining dose, high concentrations were found in adipose, followed by liver, lung, kidney, and brain in both species. Although most of the chemical found was parent compound, small amounts of hydroxylated metabolites were identified in the feces and tissues. Kinetic studies in pike have also found that BDE 47 is readily absorbed, reaching an uptake rate of 70 ng/g lipid/day (Stapleton et al. 2002). There is clearly a need to further investigate the toxicokinetic parameters of PBDEs.

Given that the PBDEs can be absorbed and metabolized, at least to some extent, and given the increasing production and use of these chemicals in North America, attention to the status of human is rapidly escalating. In Sweden, a human-milk–monitoring program has been in effect since the 1970s. When the PBDEs were first measured early in the 1990s, it became clear that the concentrations of these chemicals in human breast milk had been rapidly increasing over the past two decades (Meironyte et al. 1999). This trend peaked in 1997, after which levels began to decline in Sweden. Whether this was because of the voluntary ban on the production and use of penta congeners in Europe, which began in the early to mid 1990s, is not clear. In contrast, limited data from North America not only indicate that the concentrations of PBDEs have not peaked out in the Western Hemisphere but also that they are much higher than those ever reached in Europe. This observation was first highlighted by a comparison of the results of analysis of pooled samples from New York State; Austin, Texas; and Denver, Colorado (Betts 2002). Contemporary human milk samples from Sweden, Japan, Canada, and the United States were compared, resulting in large differences between Swedish and Japanese median levels (3.2 and 1.4 ng/g lipid, respectively) and Canadian and U.S. medians (25 and 41 ng/g lipid, respectively) (Betts 2002; Ryan and Patry 2002; Ryan et al. 2002). These investigators also compared the sum of seven congeners (28, 47, 99, 100, 153, 154, and 183) in individual human milk samples from Canada in 1992 and 2002 and observed that the median level had increased from 3.0 to 25 ng/kg lipid, with means growing from 15 to 64 ng/kg lipid over a 10-year period (Ryan et al. 2002). Although all of the congeners examined appeared to be increasing, the increase in BDE 47 was the most dramatic. Whether this is a product of debromination of more highly brominated PBDEs or reflects its greater persistence is not yet clear.

A variety of human samples from California have also been examined recently by Petreas and co-workers (Petreas et al. 2002, 2003; She et al. 2002). The mean concentration of BDE 47 measured in stored serum from women in California in the 1960s was approximately 2 ng/g lipid, compared with approximately 50 ng/g lipid in the serum of Laotian women living in California in the 1990s (Petreas et al. 2003). This value was slightly higher than measurements of actual adipose tissue levels in women born in the United States and living in California in the same time period. These results are consistent with Canadian tissue levels, indicating that exposure to PBDEs is resulting in much higher body burdens in North America than in Europe and Asia. This is likely because of the continued North American production and use of the penta formulation, which was voluntarily banned in other countries. More recently, Schecter et al. (2003) measured PBDEs in human milk from Texas in 2002, finding total PBDE concentrations up to 419 ppb, with a median concentration of 34 ppb. Specifically, BDE 47 had a median concentration of 18 ppb, followed by BDE 99, with a median value of 6 ppb. The increasing time trend for PBDEs in human samples is paralleled by data from Californian harbor seals demonstrating a dramatic increase from the 1980s to the 21st century (She et al. 2000, 2002). It is important to note that although the concentrations from humans have been increasing exponentially, human levels are still much lower than the concentrations found in fish or many marine mammals.

Some investigators have examined the congener composition of the human samples from California and noted that the profile is very different from any of the commercial mixtures. For example, the mass ratio of BDE 99 to BDE 47 is approximately 2:1 in the commercial penta mixture, but in the human samples there is approximately 2.5 times as much BDE 47 as BDE 99 (Mazdai et al. 2003; Petreas et al. 2003). BDE 100 is a small contributor in the commercial mixture, whereas in human samples the amounts of BDE 100 and BDE 99 are approximately equal. Likewise, although there is more BDE 153 than BDE 154 in the commercial penta mixture, these are found in essentially equal amounts in human tissues. Congener profiles in wildlife vary among species but generally mimic that found in human tissues. In some fish species, the patterns much more closely resemble commercial mixtures, whereas in others there are major differences. In ringed seals from the coast of British Columbia, for example, almost no BDE 99 was detectable, indicating that these animals likely have the ability to metabolize and eliminate this congener (Ikonomou et al. 2002b).

It is also important to note that levels of PBDEs are not correlated with the levels of PCBs. In most samples today, the concentrations of PCBs are still greater than those of the PBDEs. However, this may be changing because PBDEs are still in production. The lack of correlation of the two classes of chemicals indicates that they are coming from different sources and/or that there are differences in time sequence of exposure. The environmental and human levels of PCBs are decreasing in most of the world; in contrast, the levels of PBDEs appear to be increasing, at least in North America. The deca formulation, which is the

major PBDE product, is resulting in high concentrations in sediment and sludge; however, the environmental fate and potential for transport remain to be determined. In summary, it is clear that lower brominated congeners are moving in the environment and human tissue; whether the levels in wildlife and people are high enough to result in any effects is unclear.

Conclusions

The BFRs represent major industrial chemicals whose use has increased dramatically over the past few decades. They are produced to prevent fires and thus can have a direct and obvious benefit. However, concerns are being raised because of their persistence, bioaccumulation, and potential for toxicity, both in animals and in humans. Production and use patterns are different in various parts of the world. There is clearly a need for more systematic environmental and human monitoring to understand how and where these chemicals are being released into the environment, and what is happening to them once they enter the environment. What fate and transport processes are involved in their environmental movement? Are the commercial products breaking down in the environment or in biota? And if they are degrading, what are the resultant products? How are all of these chemicals getting into people? Is food the major pathway, as is true for many other POPs, or are there other potential sources? Once we understand what the exposure levels are in both people and wildlife, what should be our level of concern? Our toxicology database is inadequate to truly understand the risk. Many of the studies that do exist involve the commercial mixtures, which do not represent human exposure. We need studies that focus on the congeners, and potentially their metabolites and/or breakdown products, present in people and wildlife in order to understand the risk from exposure to BFRs.

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