The PBDEs: An Emerging Environmental Challenge and Another Reason for Breast-Milk Monitoring Programs

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Levels of the polybrominated diphenyl ethers (PBDEs), a class of widely used flame retardants, appear to be rising rapidly in human tissues, as evidenced by studies of human breast milk. The case of the PBDEs illustrates the value of breast-milk monitoring programs in identifying important emerging pollutants, and highlights why such monitoring programs are needed in the United States. A review of the use, occurrence, and toxicity of PBDEs indicates many parallels between some PBDEs, PCBs, and other polyhalogenated persistent organic pollutants, and suggests that the PBDEs may be a significant environmental challenge in the future. *Key words*: breast-milk monitoring programs, flame retardants, persistent organic pollutants, polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorinated diphenyl ethers, structure–activity relationships, toxicity. *Environ Health Perspect* 108:387–392 (2000). [Online 15 March 1999]
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A family of brominated flame retardants called the polybrominated diphenyl ethers (PBDEs) has been increasing exponentially over the past 25 years as contaminants in breast milk samples from Sweden; their levels have doubled every 5 years (Figure 1) (*1*). PBDEs are now found as residues in sediments, wildlife (marine mammals, fish, and bird eggs) and humans (milk, serum, and adipose tissue). Lipophilic and metabolically resistant, the PBDEs share many of the properties that make them long-lived, bioaccumulating, environmental pollutants with the organochlorine pesticides (e.g., DDT), polychlorinated biphenyls (PCBs), and polychlorinated dibenzo-*p*-dioxins and furans. The increasing levels of PBDEs in breast milk illustrate how breast-milk monitoring programs (BMMPs) can act as warning systems and alert us to new forms of persistent organic pollutants (POPs).

Once alerted, new questions arise. What are the PBDEs? Where do they come from? What concerns should we have over their presence in the environment or in breast milk?

Briefly, PBDEs are flame-retardant additives in high-impact plastics, foams, and textiles (5–30% of these products by weight) (*2*). They are structurally related to the PCBs (Figure 2) and, like PCBs, are produced commercially as mixtures. However, PBDE mixtures contain fewer congeners than commercial PCB mixtures and enter the environment in a different way. PCBs, in general, enter the environment directly from point sources (e.g., broken capacitors) as a complete commercial dielectric mixture. PBDE mixtures, in contrast, are noncovalently bound additives in plastics and textiles that are selectively released over the products' lifetimes. What little is known of PBDE toxicology resembles that of the PCBs. Some of the persistent and bioaccumulative PBDE congeners seem likely to cause cancer and thyroid and/or neurodevelopmental toxicity, based on the available PBDE toxicology data and on structure–activity relationships with PCBs, polychlorinated diphenyl ethers (PCDEs), and other compounds.

At present, residue levels of PBDEs in biota are lower than (1/10–1/100th) levels of PCBs. However, the exponential increase in PBDEs found recently in breast milk may be a harbinger of things to come: PBDEs may be the PCBs of the future. PBDEs are an excellent example of why BMMPs are needed in the United States.

Polyhalogenated POPs

Polyhalogenated POPs are a superfamily of compounds with long 2- to 10-year half-lives [e.g., 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has a half-life of 7.5 years] (*3–6*). Members of this superfamily include the PCDD/PCDFs, PCBs, PCDEs, and polychlorinated naphthalenes (PCNs), as well as the polybrominated biphenyls (PBBs) and PBDEs (International Union of Pure and Applied Chemistry no. 209) (Table 1). Each subfamily consists of many congeners (Table 1) that share the subfamily's chemical backbone but with different numbers and positions of halogen substituents (Figure 2). Not all of the congeners in each subfamily are classified as POPs, i.e., are stable and persistent. For example, only 17 of the 210 PCDDs/PCDFs persist in humans. The polyhalogenated POP superfamily also contains approximately 20 of the organochlorine pesticides.

POPs have three chemical characteristics that make them intrinsically hazardous: they are stable (persistent), they are fat-seeking, and they have the potential to act as endocrine disruptors. The stability and lipophilicity of POPs causes them to biomagnify up the food chain, increasing in concentration at each successively higher trophic level. Once polyhalogenated POPs are released into the environment, they invariably find their way into the mother, where they pass transplacentally to the developing fetus or through the breast milk to the nursing infant.

Some POPs can bind to receptors and act in a hormonelike manner to cause biologic effects at low doses. For example, the 2,3,7,8-substituted PCDDs/PCDFs, PCNs, and coplanar PCBs bind as ligands to a cytoplasmic hormone-receptor-like molecule called the aryl hydrocarbon (Ah) receptor. This Ah receptor ligand-bound complex migrates from the cytoplasm into the nucleus and alters the expression of genes coding for different metabolizing enzymes (e.g., cytochrome P450s). Other POPs such as the PBDEs have the potential to bind to the Ah or other receptors and act via hormonelike mechanisms.

Recent studies indicate that a number of polychlorinated POPs are endocrine disruptors. Several have estrogen-like activities, whereas others, the dioxin-like POPs, have antiestrogenic activities (*7–10*). Health effects as diverse as shortened duration of lactation in mothers (*11*) and neurodevelopmental cognitive–motor deficits and intellectual impairment in children (*12–17*) have been attributed to polyhalogenated POPs. For PCDDs/PCDFs, contaminant levels in breast milk (*18–21*) and human health effects (*19,22–24*) have recently been reviewed. For TCDD, there are a plethora of health effects (*7,25*), ranging from chloracne to cancer (*19*) and altered sex ratio (*26*).

POPs have shorter half-lives in rodents than in humans (e.g., TCDD half-life in rodents is 10–20 days and in humans is 5–10 years). After corrections are made for species differences in residence times, human exposures to TCDD are closer to the dose levels that produce effects in animal studies (*27*).

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Ironically, it is the fetus and the nursing infant that receive significant exposures or the greatest body burdens of environmental POPs. As evidence of fetal exposures, the infant at birth has levels of TCDD that are up to 25% of maternal levels (*28–31*), and *in utero* exposures to background levels of some POPs are associated with adverse effects [e.g., cognitive-motor deficits (*12,13,15–17*)]. Breast-fed infants are effectively at the top of the food chain. Their daily intake of TCDD, for example, is typically 50-fold higher than that of adults, on a body weight basis (*32–34*), and they absorb 90% of the ingested TCDD (*35*).

This level of uptake of polyhalogenated POPs by the fetus and the nursing infant raises concerns about the potential for adverse health outcomes. POP body burdens may adversely affect reproduction in the mother or adversely affect the development of the fetus, infant, or child, exposed either *in utero* and/or via breast-feeding (*11–17,25,26*). Prenatal, and not lactational, exposures appear to be important sources of some of the adverse health effects of POPs seen in infants [e.g., cognitive-motor deficits from PCBs (*12*)].

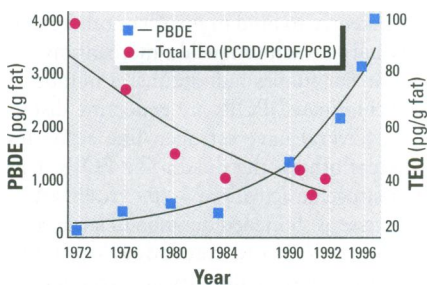

Figure 1. Organohalogen compounds in human milk in Sweden. Abbreviations: PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofuran; PCB, polychlorinated biphenyl; TEQ, toxic equivalent. Adapted from Norén and Mieronyté (*1*).

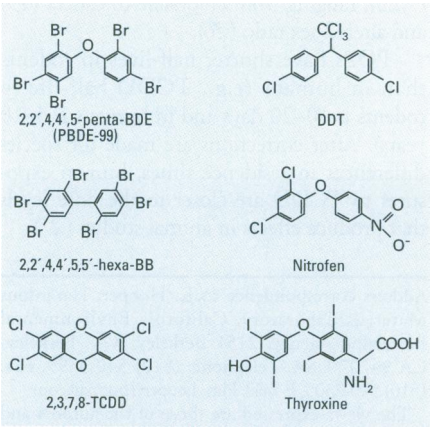

Figure 2. Examples of polybrominated diphenyl ethers and structurally related compounds. Abbreviations: hexa-BB, hexabromobiphenyl; penta-BDE, pentabromodiphenyl ether; TCDD, tetrachlorodibenzo-*p*-dioxin.

There is also evidence that breast-fed infants, even at the highest background exposures, fare better than nonbreast-fed infants with comparable exposure in cognitive and motor development (*15,36*). Thus, breast-feeding continues to be considered beneficial to the infant, although careful studies of longer term outcomes (e.g., cancer) from ingesting contaminants in breast milk have not been conducted. Thus, at present, POP contaminants in breast milk are useful as markers of maternal body burdens as well as lactational and *in utero* exposures.

BMMPs

Breast-milk monitoring is a convenient noninvasive means of estimating body burdens of polyhalogenated POPs in the mother, fetus, and breast-fed infant or child. POPs enter humans chiefly as contaminants in animal-derived food (fish, poultry, beef, eggs, and dairy products). Once ingested, POPs sequester in body lipids, where they equilibrate at roughly similar levels on a fat-weight basis between adipose tissue, serum, and breast milk. POP contaminants in breast milk increase with maternal age [e.g., TCDD (*18,37,38*)] and decrease with the number and duration of lactation periods (e.g., TCDD levels in breast milk decrease roughly 25% after each successive breast-fed child) (*18,39,40*).

BMMPs have many uses. They provide data on baseline body burdens for women during the perinatal period and, with the use of breast milk consumption data, provide estimates of POP levels in infants and children. BMMPs identify hot spots of POP contamination, and congener patterns can help to identify the sources of the POP contaminants. BMMPs identify at-risk populations of mothers, infants, and children for follow-up health outcome studies. Using time-trend data, BMMPs can also identify new POPs of emerging concern, and can assess the effectiveness of regulatory strategies to limit exposures to POPs (e.g., pollution prevention or hazardous waste management). Thus, time-trend data from the Swedish BMMP, as reported by Norén et al. (Figure 1), identified PBDEs as a growing concern. The Swedish data also demonstrated a 70% decrease in PCDD/PCDF/PCB body burdens over the past 25 years (*1*), presumably as a result of effective regulatory actions.

Breast milk and adipose tissue, like sediments in rivers or lakes, act as storehouses of POPs. POP levels in breast milk, as with sediments, reflect past environmental conditions. BMMP data complement monitoring data from air, water, soil, or food.

BMMPs have operated in several countries (Sweden, Germany, The Netherlands, and New Zealand) over the last 20–30 years, and have helped to identify PCBs and PBDEs as important human contaminants. Standardized collection and analytical protocols (*41*) now exist for analyzing many POPs in breast milk. Currently, there is no systematic monitoring of breast milk contamination in the United States, and little is known of PBDE breast milk levels or body burdens in the United States.

PBDEs

As with other POPs, PBDEs are transferred via breast milk from the mother to the offspring. Evidence of this transfer comes from pilot whales. Juvenile pilot whales, which subsist primarily on mother's milk, had 2- to 3-fold higher levels of 19 PBDE congeners (tetra- to hexa-BDE: 3 vs. 1 ppm) than adults (*42*).

Identity, use, and production. The PBDEs are structurally similar to the PCBs and PBBs (Figure 2), with the same nomenclature and number (209) of congeners. Since the 1960s, PBDEs have been added as flame-retardants to thermoplastics (e.g., high-impact polystyrene) that are used in electrical appliances, TV sets, computer circuit boards and casings, and building materials. PBDEs are also found in foams and upholstery in home and business furnishings; in interiors in cars, buses, trucks, and airplanes; and in rug and drapery textiles (*2,43*). Some manufacturers have begun to reduce PBDE levels in products (e.g., computer monitors) to earn the Swedish TCO99 environmental label.

Three major commercial mixtures of PBDEs are produced: deca-BDEs (mostly deca-BDE with some nona- and octa-BDE congeners), octa-BDEs (mostly hepta- and octa-BDE congeners), and penta-BDEs (mostly penta- and tetra-BDE congeners). Fully brominated deca-BDE is the major product, accounting for 75% of the PBDE production. The commercial PBDEs generally contain fewer (< 10) congeners than do commercial PCB mixtures (e.g., roughly 80 congeners in the Aroclor 1254 or 1260 mixtures). Worldwide PBDE production is estimated at roughly 80 million pounds per year (*2*). In the United States, commercial penta-, octa-, and deca-BDE were each produced or imported at greater than one million pounds per year in 1990, 1994, and 1998 (*44*).

Environmental fate. PBDEs are likely to be more susceptible to environmental degradation than PCBs because bromine is a better "leaving group" than chlorine; i.e., the carbon–bromine bond is weaker than the carbon–chlorine bond. Thus, whereas PCBs were used as thermally resistant dielectrics, PBDEs are used as flame retardants because they are somewhat thermally labile, and break down with heat to release bromine

radicals that quench the radical cascade of the combustion and fire-spreading processes.

The environmental fates of the PBDEs are not well documented. Most of the analytical methods used at present detect only the lower molecular weight (MW) (< 800 MW) tetra- to hepta-BDE congeners, and the fates of the higher MW (octa- to deca-BDE) congeners and the major commercial mixture (deca-BDE) are unclear.

The fate of deca-BDE in the environment needs further study. Even though the deca-BDE has lower bioaccumulative potential (*43*) and lower biologic activity (*45*) than the lower PBDE congeners, it is still a source of public health concern. Away from sunlight, deca-BDE likely persists in soils and sediments. In sunlight, the deca-BDE readily degrades to the lower brominated congeners (e.g., tetra- to hexa-BDEs) (*43,46,47*), which themselves readily bioaccumulate [the tetra- and penta-BDE bioaccumulate almost as well as the PCBs (*48,49*)]. Currently, it is unclear what proportion of the tetra- to hexa-BDEs in the environment are breakdown products of the deca-BDE congener and what proportion comes from the commercial penta-BDE mixtures.

Tissue levels: humans. Although PBDEs have been measured in humans, animals, and environmental samples for some years (*2*), the exponential increase of tetra- to hexa-BDEs in Swedish breast milk has galvanized interest. In the Norén study (Figure 1), milk samples were pooled from native Swedes living in the Stockholm region, with the proportion of primiparae (55–65%) and the average age of donors kept reasonably constant (*1*). Numbers of mothers in the pools varied from 75 to 116 during 1972–1985 and from 20 to 40 during 1990–1997 (*50*). 2,2′,4,4′-tetra-BDE was the major congener (60–70%), and it was present at approximately 2.3 ng/g lipid in 1997 (*1,51*). Another recent Swedish breast milk study found wide interindividual variability in PBDEs levels from 39 first-time mothers (1.1–28.2 ng/g fat), with mean levels similar to those reported in the pooled samples in the Norén study (*52*).

The predominant congeners in human tissues are the three *ortho-para*-(2,4-) substituted congeners: 2,2′,4,4′-tetra-BDE (PBDE-47); 2,2′,4,4′,5-penta-BDE (PBDE-99); and 2,2′,4,4′,5,5′-hexa-BDE (PBDE-153). These were present in recent human adipose tissue samples from Sweden at levels ranging from 0.3 to 98.2 ng/g lipid (*53,54*). Similar levels of the tetra- to hexa-BDEs were found in adipose tissue samples from Spain (*55*), Israel (*56*), and the United States (*57*). This raises the possibility that exponential increases in PBDEs are occurring worldwide.

In the few studies that have measured deca-BDE in environmental samples, deca-BDE is less prevalent in biota than the lower brominated congeners. PBDE congener patterns in humans may provide information on the nature or pathway of the PBDE exposures, much in the manner of the DDE:DDT ratio. Low tetra:deca BDE ratios suggest direct, recent, or occupational exposures to the parent product. Higher ratios may indicate an environmental pathway, where exposures stem from PBDEs that have leached from commercial products and that have been degraded in the environment.

Deca-BDE levels in human samples may be more likely to arise from direct exposures. For example, whereas breast milk samples had high tetra:deca-BDE ratios, serum samples from dismantlers at an electronics-recycling plant had low tetra:deca-BDE ratios (*58*). The levels of five PBDE congeners, including deca-BDE, in the serum taken from the dismantlers were significantly higher than levels in samples taken from clerks in the same plant or from a control group of hospital cleaners. Thus, deca-BDE, even with its high MW, is bioavailable.

Tissue levels: animals. PBDE levels have been measured in marine and terrestrial life. These analyses have primarily been conducted on samples taken from the North Atlantic Ocean and from Northern Europe. The predominant congeners are the tetra- to hexa-BDEs. Levels of PBDEs on a nanogram per gram lipid basis include: cod liver (3–170), herring (100), trout (100–170), eel (14,000–17,000), pike (27,000), guillemot egg (2,000), osprey (0.16–19,000), cormorant liver (28,000), seal blubber (2.6–1,470), sperm whale (79–136), pilot whale (843–3,160), reindeer (0.5), and moose (1.7) (*2,53,59,60–65*).

Current levels of PCBs or DDTs are considerably higher (10- to 500-fold) than PBDE levels. For example, levels of PCBs or DDTs (in nanogram per gram lipid) in Northern Europe were roughly 10-fold higher than PBDEs in herring, 300- to 400-fold higher in grey seals, and approximately 40-fold higher in osprey (*63*). However, if the trends in contaminant levels in human milk (Figure 1) and the environment continue, PBDEs will replace PCBs/DDTs as the major environmental POP over the next 15–30 years.

Table 1. PBDEs and other polyhalogenated POPs.

	Properties						Toxicity			
Chemical class, specific congeners	Congeners in class (*n*)	Use (functional property)	Commercial mixtures (no. congeners in product)	Half-life, rodent (days)	Half-life, human (years)	Human body burden, pg/g lipid, (TEQ)	Ah receptor activity	Cancer, animal or human	Neuro-develop-mental	Thyroid
PCDDs/PCDFs	75/135	Contaminants	NA	1–60	2–10	(20)	+/+	+/+	+/+	+/+
TCDD				10–30	8	3–5 (3–5)	+	+	+	+
PCBs	209	Dielectrics	e.g., Aroclor	6–28	2–6	1,500,000 (20)	+	+	+	+
Co-planar PCB		(thermally	1254, 1260	7–9			+			
Mono-*ortho*-PCB		stable)	(> 40)				+		+	+
Hexa-(PCB-153)[a]				431–478			–		+	
PBBs	209	Flame retardant	e.g., Firemaster	160–480	8–11	≤ 50,000	+	+		+
Hexa-(PBB-153)[a]		(releases Br)	BP-6 (> 30)[b]		4–97					
Deca-BB[c]							–			
PCDEs	209	Contaminants	NA				+		+	+
Penta-(PCDE-99)				6		2,000–8,000				
Hexa-(PCDE-153)						2,000–8,000	+			
PBDEs	209	Flame retardant				1,000–100,000	+		+	+
Tetra-(PBDE-47)[a]		(releases Br)		20–30		Tetra-hexa	+		+	+
Penta-(PBDE-99)[a]			Penta- (~ 10)	25–47			+[d]		+	+
Hexa-(PBDE-153)[a]				45–120			+[d]			
Deca-BDE[c]			Octa-							+
			Deca- (< 10)	< 1[e]				+/–		+

Abbreviations: Ah, aryl hydrocarbon; NA, not applicable; TEQ, toxic equivalency. +, positive study; –, negative study; +/–; marginally positive. Cells left blank indicate no data.
[a]Examples of major congeners commonly found in human tissues. [b]Monsanto Corporation, St. Louis, MO. [c]Most-produced congener of class. [d]Commercial grade penta-BDE was positive (primarily contains PBDE-47, -99, and -153). [e]The short half-life of deca-BDE is likely due to a very low (~ 0.3%) rate of absorption. However, adipose tissue bromine levels in rats fed deca-BDE remained unchanged for 90 days after cessation of exposure [reviewed in (*2*)], indicating a long terminal half-life.

Little is known of environmental levels of PBDEs in the United States. PBDE levels (di- to hepta-BDE) in whole homogenates of Lake Ontario trout were between 200 and 300 pg/g lipid (*66*). Recent PBDE levels in the muscle tissue of other Great Lakes fish averaged 3,000 ng/g lipid (the sum of six prominent congeners) (*67*).

Toxicology. PBDEs have some structural similarities to the PCBs and PBBs, the DDT family, the herbicide nitrofen, the PCDDs/PCDFs, and thyroxine (T_4) (Figure 2), and they appear to share some toxicologic properties as well. The available data suggest that the lower (tetra- to hexa-) PBDE congeners are likely to be carcinogens, endocrine disruptors, and/or neurodevelopmental toxicants.

Deca-BDE, the major commercial product, is expected to be one of the least active congeners because of its poorer bioavailability. Likely due to its high MW, deca-BDE is poorly absorbed by ingestion (approximately 0.3%) and is rapidly eliminated in rodents (half-life < 1 day) (*68*). This contrasts with the lower brominated congeners, which are almost completely absorbed and have half-lives in rodents that are comparable to or longer than TCDD (20–30 days for a tetra-BDE or 45–119 days for two hexa-BDEs in rats) (*69,70*). Activities of several enzymes induced by a commercial penta-BDE mixture in rats remained significantly elevated for 30–60 days after the last exposure, again suggesting long half-lives for the lower brominated congeners (*45,71*). Because the half-lives of these congeners in rodents are comparable to that of TCDD (*69*), the lower PBDEs are also likely to persist in humans.

Among commercial PBDE mixtures, those containing lower congeners are stronger inducers of liver enzymes in rats [i.e., penta-BDE > octa-BDE > deca-BDE (*45,71*)]. This is similar to the relative activities of the structurally related PBBs, where the lower congeners are generally more active. For the PBDEs, the greater activities of the lower congeners may be due to their greater bioavailability or to their higher affinities for receptor proteins.

Cancer. Human data on PBDE carcinogenicity are limited. One study cited an association between adipose tissue levels of PBDE-47 and the risk of non-Hodgkin lymphoma (NHL) among Swedish hospital patients (*54*). Other studies cited similar associations for PCB levels and the risk of NHL (*72*), and for PBB levels and the risk of lymphoma and breast cancer (*73,74*).

In animals, only the fully brominated and poorly absorbed (0.3%) deca-BDE has been tested for carcinogenicity in long-term studies (*68,75*). In mice, results from the National Toxicology Program bioassay (*68*) were marginally positive. Deca-BDE produced statistically significant increases in hepatocellular adenomas and carcinomas (combined) in male mice, but the increases were within the range of historical controls. Marginal increases in thyroid gland follicular cell adenomas or carcinomas (combined) were observed for male and female mice. PCBs and dioxin-like compounds disrupt thyroid hormone balance.

Stronger effects of deca-BDE were seen in rats, with significant dose-related increases in liver neoplastic nodules (adenomas) in both males and females. An earlier bioassay in rats, using fewer animals and much lower doses of deca-BDE, found no statistically significant increases in tumors (*75*), as might be expected. Liver tumors were the primary tumors observed in rodent cancer bioassays of PCBs and PBBs, which are structurally related to the PBDEs.

Evidence for Ah receptor mechanism. Although PBDEs have not been tested for their ability to bind to the Ah receptor, mechanistic studies indicate that some PBDE congeners exhibit significant Ah receptor-mediated (e.g., dioxin-like) effects, with penta-DBE activity greater than tetra-DBE activity. In rats for example, commercial-grade penta-BDE was a more powerful inducer of ethoxyresorufin-*o*-deethylase (EROD) activity, a standard assay for dioxin-like compounds, than commercial PCBs (Aroclor 1254). The penta-BDE mixture was active at lower levels (3 mg/kg) than the model inducers, 3-methylcholanthrene, or most PCB mixtures (*69*). In mice, commercial penta-BDE induced EROD activities and suppressed the immune response, which are consistent with Ah receptor-mediated effects (*76*).

PBDE-47, the major congener in human and marine tissues, also induced EROD activities in rats (6 mg/kg for 2 weeks), albeit less powerfully than PCBs (Aroclor 1254) (*77*). The tetra-BDE has less dioxin-like activity than the commercial penta-BDE product [comparing the results of von Meyerinck et al. (*69*) and Hallgren and Darnerud (*77*)].

Ah receptor-mediated activities of PBDEs also have been investigated using the rat hepatoma cell line H-4-II E. A commercial formulation of penta-BDE induced EROD levels in the H-4-II E cells with an estimated potency of one-millionth that of TCDD (*78*). In a study of 17 specific PBDE congeners, 7 congeners acted as Ah-recep-tor agonists and 9 congeners acted as antagonists when co-treated with TCDD (*79*). The potencies of the agonists were comparable to the potencies of some mono-*ortho* PCBs (*79*).

The PCDEs similarly induce EROD, also with penta activity greater than tetra activity (*80,81*). These observations agree with molecular modeling predictions of the interactions between PCDEs and the Ah receptor, where chlorines in the *ortho* positions are predicted to enhance binding to the receptor of the more highly chlorinated PCDEs (*82*). Thus, the enzyme induction data and modeling predictions for the PCDEs support the Ah receptor-mediated activity of the PBDEs.

Additional evidence for PBDE dioxin-like activity comes from the induction of EROD by coadministration of tetra-BDE and PCBs (Aroclor 1254). The effects of PBDE and PCBs were additive, suggesting that the two POP families operate through similar mechanisms (*77*).

Genotoxicity. The genotoxicity profiles of PBDEs and PCBs are similar. As with the commercial PCB mixtures, the deca-, octa-, and penta-BDE commercial mixtures were not mutagenic in *Salmonella typhimurium* (*2,68,83*). As with two technical mixtures of PCBs, two PBDE technical mixtures of mono- or di-BDEs induced genetic recombination in two mammalian cell lines, whereas the tetra-BDE mixture was positive in one cell line (*84*). In recent metabolic studies of [^{14}C]PBDE-47 in rats and mice, tetra-BDE was covalently bound to macromolecules in various tissues, with evidence for a reactive epoxide intermediate (*70*).

Endocrine effects. The lower PBDEs disrupt thyroid hormone balance. In rats, commercial-grade penta-BDE (2, 10, or 200 mg/kg/day for 90 days) reduced thyroid hormone levels and increased incidences of thyroid hyperplasia, with effects at all dose levels (*83*). In mice, the penta-BDE also significantly reduced T_4 levels 8 days after a single exposure and at the lowest dose tested (0.8 mg/kg) (*76*). PBDE-47, the major congener in human and animal tissues, reduced thyroid hormone levels in female rats at a dose of 18 mg/kg (*77*). The effects of tetra-BDE in reducing levels of thyroid hormones were additive with coadministered PCBs (Aroclor 1254) or chlorinated paraffins (*77*).

Higher PBDE congeners also have the potential to disrupt thyroid hormone balance. Deca-BDE produced statistically significant increases in the incidences of thyroid hyperplasia and marginal increases in the incidences of tumors of the thyroid among male and female mice in 2-year feeding studies (*68*). Commercial octa-BDE administered to rats for 90 days resulted in thyroid changes (*2*). Also, 4 of 35 production workers in a deca-BDE and deca-BB manufacturing plant manifested clinical hypothyroidism, with one case reportedly exposed only to deca-BDE. No cases of thyroid dysfunction were observed among 89 age- and sex-matched unexposed workers (*85*).

Studies of the structurally related PCDEs offer some supporting evidence that PBDEs disrupt thyroid hormone balance. Three

specific congeners (2′,3,4,6′-tetra-CDE; 2,2′,4,5,6′-penta-CDE; and 2,2′,4,4′,5,5′-hexa-CDE) administered to pregnant rats resulted in reductions of T_4 levels in dams and in offspring exposed *in utero* (*86*).

The mechanism of PBDE-induced thyroid hormone disruption is unclear. PBDEs may induce UDP-glucuronosyltransferases, which increases the rate of T_4 conjugation and excretion. Alternatively, PBDEs or their hydroxy metabolites may mimic T_4 or T_3 because these hormones are hydroxy-halogenated diphenyl ethers (Figure 2). This mechanism is supported by observations from metabolic studies of tetra-BDE, in which hydroxy-tetra-BDE metabolites were found (*70*). Hydroxy-PBDEs (as with hydroxy-PCBs) may reduce T_4 levels by competing with T_4 for the thyroid hormone transport protein, transthyretin (*86*).

Developmental toxicity. Neurodevelopmental toxicity has been reported for a tetra-BDE congener, PBDE-47, and a penta-BDE congener, PBDE-99, the major congeners in human tissues. PBDE-47 (0.7 mg) and PBDE-99 (10.5 mg) administered to mice on postnatal day 10 resulted in permanent aberrations in motor behavior that worsened with age. Neonatal exposure to PBDE 99 also reduced learning and memory in adult mice (*87*). Similar effects occurred in mice that were neonatally exposed to some of the *ortho*-substituted PCBs and coplanar PCBs (*87*).

Commercial formulations of penta-, octa-, and deca-BDEs give equivocal results in developmental studies. Although increases in embryo mortality and delayed skeletal formation were observed, these effects were accompanied by maternal toxicity in all of the studies except one (with octa-BDE) (*2,43*).

Structurally related compounds, including PCDEs, nitrofen, and PCB/PBBs, cause developmental effects. A penta- and a tetra-CDE decreased the number of litters born, the perinatal growth, and pup survival in mice when administered from gestational days 6–15 (*88*). Nitrodiphenyl ethers, including the herbicide nitrofen (2,4-dichlorophenyl-4′-nitrophenyl ether) caused pronounced perinatal and postnatal toxicity, which are believed to be thyroid hormone-mediated outcomes [reviewed by Rosiak et al. (*88*)]. Moreover, PCBs and PBBs are well recognized as developmental toxicants (*89*). In mechanistic and structure–activity studies, the di- to penta-CDE congeners showed greater activity than *ortho*-PCBs in perturbing Ca^{2+} neuronal homeostasis and other effects associated with *ortho*-PCB neurobehavioral toxicity (*90*).

Conclusion

The observation of rising levels of PBDEs in Swedish breast milk illustrates how BMMPs can serve to warn us of new or unrec-ognized POPs. The BMMP time-trend data have spurred research in the last year on the occurrence and toxicity of PBDEs. Monitoring programs are needed to determine PBDE levels in U.S. populations. In addition, BMMPs are needed in the United States to fill data gaps for other POPs, especially for PCDDs/PCDFs and PCBs. No BMMPs exist to monitor PBDE levels or time trends in the United States.

PBDE toxicology is incomplete. Ecologic, neurodevelopment, and thyroid function studies and 2-year rodent cancer bioassays are needed for some congeners, including PBDE-47 and the commercial formulations of penta- and octa-BDEs. Even in the absence of further studies, however, it seems clear that less toxic alternatives to persistent PBDE flame retardants are desirable, given the suggestive parallels between PBDE and PCB toxicology.

Several studies found that prenatal, and not lactational, exposures to polyhalogenated POPs were critical for childhood cognitive-motor deficits. If this is true, the health of the fetus and the infant can be protected only by limiting *in utero* exposures to POPs, which can be accomplished only by limiting the mother's exposures. Given the proclivity of POP compounds to persist, seek out fat, and biomagnify up the food chain, it is hard to see how the mother's exposures can be limited except by broad preventative strategies (e.g., replacing POPs with biodegradable or environmentally friendly alternatives) (*34*). Concentrations of POPs in breast milk serve as markers for *in utero* and lactational exposures. In conjunction with BMMPs, these markers will allow us to assess POP body burdens and monitor the progress of our preventative strategies.

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