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Review

Polybrominated Diphenyl Ethers (PBDEs): New Pollutants–Old Diseases

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ABSTRACT

Polybrominated diphenyl ethers (PBDEs) are a class of recalcitrant and bioaccumulative halogenated compounds that have emerged as a major environmental pollutant. PBDEs are used as a flame-retardant and are found in consumer goods such as electrical equipment, construction materials, coatings, textiles and polyurethane foam (furniture padding). Similar in structure to polychlorinated biphenyls (PCBs), PBDEs resist degradation in the environment. Less brominated PBDEs like tetra-, penta- and hexa- demonstrate high affinity for lipids and can accumulate in the bodies of animals and humans. Breast milk from North American women contained much higher amounts of PBDEs than levels in breast milk from Swedish women, indicating that North American exposures to PBDEs may be particularly high. Evidence to date suggests that tetra- and penta-BDEs are likely to be the more toxic and bioaccumulative of the PBDE compounds, compared to octa- and deca-congeners. PBDEs are sold as mixtures, under names such as "pentabromodiphenyl ether" and "octabromodiphenyl ether." The pentabromo product is a mixture of tetra-BDEs and penta-BDEs in approximately equal amounts. Pentabromo consists of PBDEs that are believed to be the most toxic. This mixture has been banned by the European Union, but is still used in North America. The United States is the leading producer and user of pentabromo. In August 2003, the State of California passed a bill to phase out the use of penta- and octa-PBDE by 2008. The toxicology of PBDEs is not well understood, but PBDEs have been associated with tumors, neurodevelopmental toxicity and thyroid hormone imbalance. The neurotoxic effects of PBDEs are similar to those observed for PCBs. Children exposed to PBDEs are prone to subtle but measurable developmental problems. It is presumed that PBDEs are endocrine disruptors, but research in this area is scant. Further studies are imperative in a multitude of health and environmental disciplines to determine the adverse effects and mode of action of this widespread emerging pollutant on human health.

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INTRODUCTION

In September 2001, the European Commission (EC) over the concern for human health and environmental safety, brought a proposal to the European Union (EU) that would ban the use of penta- and octa-brominated diphenyl ethers (BDE) fire retardants. The EU voted to accept the EC proposal to ban the use of penta-and octa-BDE by August 2004 and also to extend the ban to the use of deca-BDE by January 2006.[1]

To address how these and other chemicals effect human and and wildlife health when released into the environment, the EU recently established CREDO–Cluster of Research into Endocrine Disruption in Europe.[2] The study of brominated flame retardants is one of CREDO's four core projects.

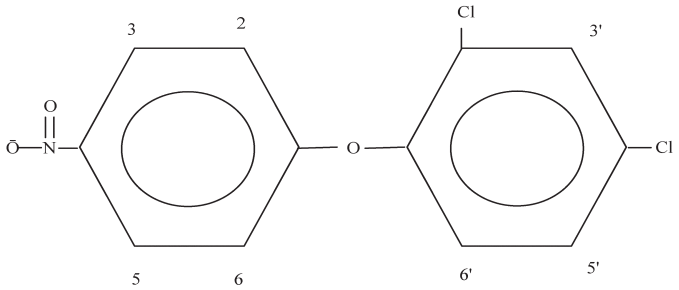
Polybrominated diphenyl ethers (PBDEs) are used in paints, plastics, foam furniture padding, textiles, rugs, curtains, televisions, building materials, airplanes and automobiles. PBDEs constitute 5% to 30% of some of these products by weight.[3,4-8] In 1999, approximately 98% of the global demand for penta-BDE was used in North America.[9,10]

Sweden has already imposed a stringent environmental labeling law that has forced some manufacturers to reduce PBDEs in their products.[3] This is in contrast to the United States, which does not regulate PBDEs because their environmental fate and human health risks have only recently begun to emerge. The Priority Toxic Pollutants list produced by the United States Environmental Protection Agency does not contain any of the brominated diphenyl ethers. However California, following the lead of the EU, recently became the first state to pass a bill that will phase out the use of penta- and octa-BDE by 2008.[11]

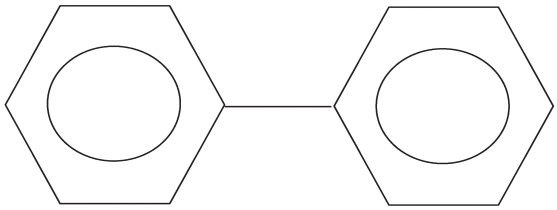
WHAT ARE PBDEs?

PBDEs have been used since the 1960s. They are synthetic compounds used as additives to retard fire and flames in a variety of commercial and household products. The relatively weak carbon-bromine bond is thermally-labile. The thermal energy releases bromine radicals that intercept carbon radicals to decrease flame, while simultaneously reducing heat and carbon monoxide production.[3,5]

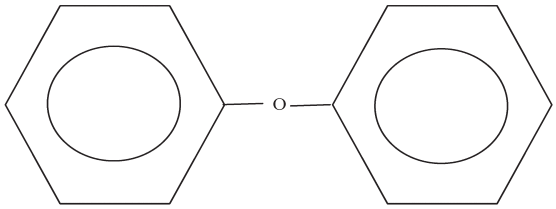
Commercial PBDEs are manufactured by bromination of diphenyl ethers resulting in a mixture of diphenyl ethers containing tetra-, penta-, hepta-, octa-, and deca-congeners in various percentages.[12-14] PBDEs are structurally similar to polychlorinated biphenyls (PCBs) (figure 1). There are 209 theoretically possible congeners divided into 10 congener



Herbicide Nitrofen



PCB or PBB depending on Chlorine (Cl) or Bromine (Br) substitution



Polybrominated diphenyl ether (PBDE)

Figure 1. A general structure of polybrominated diphenyl ether (PBDE), polychlorinated biphenyl (PCB), polybrominated biphenyl (PBB), and nitrofen. Name of the congener is representative of the total number of bromines (Br) or chlorines (Cl) and their respective position on each ring.

groups from mono- to deca-BDE. They are numbered according to the system originally designed for PCBs by the International Union of Pure and Applied Chemistry.[14,15]

Annual global production of PBDEs is estimated to be around 67,125 metric tons (13% penta-, 5.7% octa- and 82% deca-BDEs).[16,17] The eight worldwide manufacturers of PBDEs are located in the Netherlands, France, Great Britain, Israel, Japan and the United States. Bromine deposits in the United States are found principally in Michigan and Arkansas. Two companies, Albemarle Corporation, (formerly known as Ethyl Corporation, Richmond, VA) and Great Lakes Chemical Company (El Dorado, AR), both with their production facilities in Arkansas, manufacture more than 95% of the total organobromine compounds produced in the United States.[4,18,19] No brominated fire retardants are produced in Michigan.

PBDEs are commercially available in three technical mixtures as penta-, octa- and deca-brominated diphenyl ethers. Each mixture is not exclusively a pure combination of penta-, octa-, or deca-congeners, but rather contains a higher or lower amount of the brominated congeners.[13,19,20] For example, tetra-BDE is a mixture of 41% tetra-, 45% penta-, 7% hexa- and 7% to 8% unspecified PBDEs. Penta-BDE constitutes 50% to 60% penta, 24% to 38% tetra- and 4% to 8% hexa-BDE.[4,19]

PBDEs are seeded into, but are not covalently bound into polymer matrices. Over time, they diffuse out of the polymer matrix and become airborne and widely dispersed.[14,21,22] Polyurethane foam exposed to ambient outdoor conditions for 4 weeks becomes brittle, disintegrates and disperses penta-PBDE containing fragments.[23] PBDEs may be more prone to environmental degradation than are PCBs because carbon-bromine bonds are weaker than carbon-chlorine bonds.[24,25] The data on the extent of environmental degradation are inadequate. Nonetheless, PBDEs are persistent organic pollutants that remain in the environment for years without any significant degradation. The less brominated congeners are highly bioaccumulative and biomagnify in human, fish and other animal adipose tissues. It is speculated that PBDEs may cause a spectrum of chronic diseases from cognitive disorder to hormonal and liver dysfunction.[14,26-33]

More studies are needed to substantiate the evidence, as most of the current knowledge is based on animal studies in the lab. Some of the less brominated PBDEs are potential toxins. Their pervasiveness in the environment and human tissues resembles that of PCBs.[19] PBDEs are being called "the PCBs of the future."

ENVIRONMENTAL CONTAMINATION

PBDEs have been detected in coastal and estuarine environments. They have also been found in the air, soil, sediments, humans, wildlife, fish and other marine life, and sewage treatment plant biosolids.[14,34-39] They are released into the environment at industrial manufacturing sites as well as leached from common household products. The main non-point source of PBDEs is household trash (e.g., furniture, bedding, foam cushions, and electronics). In the United States, household waste is either deposited into landfills or incinerated. No information is currently available on how much incineration and/or leaching from the landfills contributes to environmental contamination. Incomplete incineration may contribute significantly to the environment. There are concerns that incomplete incineration and fire accidents produce brominated dioxins and furans which could be lethal in extremely low doses.[5,40]

Once airborne, PBDEs are dispersed varying distances deending upon meteorological conditions, airborne particle size and extent of bromination.[39] Moderate to highly brominated congeners are found in air samples relatively close to the source of pollution, while less brominated congeners travel greater distances from the same source.[41]

Evidence of photolytic and microbial degradation of octa- and/or deca-BDEs in the environment is lacking. It is assumed that these highly brominated PBDEs may degrade to less brominated congeners like tetra-, penta-, and hexa-BDEs in the environment. Deca- and octa-BDEs, are known to degrade photolytically to brominated dibenzofurans and dioxins in the lab and under high temperature caused by fires.[5,42-44] Studies directed to distinguish between PBDEs directly released and those arising from environmental breakdown may provide some answers in this regard.

Deca- and octa-brominated congeners have lower bioaccumulative and biological activities. More studies are needed to determine their fate in the environment and their subsequent health effects. Nonetheless, they remain a source of public health concern[3] in that they could degrade to less brominated, more toxic congeners in the environment after release. The less brominated congeners are believed to be more persistent in the atmosphere and can potentially move long distances.[6,45]

There are a few studies that have investigated the concentration of PBDEs in water.[38] It is believed that their presence in water does not pose health risks, as their solubility and volatility in water is very low limiting their redistribution.[38] However, PBDEs are strongly retained in sediments, soil and sewage sludge.[46]

BIOACCUMULATION IN NON-PRIMATES

In a study of different trophic levels of the North Sea food web, the lipid levels of six major tri-, tetra-, penta- and hexa-BDE congeners in fish were found comparable to the levels in marine invertebrates. Biomagnification of more than an order of magnitude occurred going from gadoid fish to marine mammals.[47]

Another study tested the levels found in chickens. The total concentration of PBDEs on a whole-weight basis in chickens ranged from 1.7 ng/g in North Dakota to 39.4 ng/g in

Arkansas. These concentrations were lower than levels reported on a lipid-weight basis in fish and fish eating mammals. The predominant congeners found were penta-BDEs.[48]

BIOACCUMULATION IN HUMANS

PBDEs have been found in human blood, serum, adipose tissue, breast milk, placental tissue and in the brain.[3,19,26,49,50] Contrary to octa- and deca-congeners, tri- to hexa-BDEs have a very high affinity for fat. They are resistant to metabolism and can bioaccumulate in adipose tissues from before birth until death.[25,51-55]

Human uptake is thought to be through inhalation, dermal absorption and consumption of contaminated food. The primary source of exposure to humans is believed to be consumption of contaminated fish, poultry, meat and dairy products. Occupational exposures may occur in computer and electronic warehouses, and formulation facilities. Dismantling and grinding polymer parts may increase the PBDE concentration in the air.[56]

The non-occupational occurrence of PBDEs in individuals from different developed countries is shown in table 1. The predominant congeners detected in Swedish human tissue samples were 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). Tissue levels ranged from 0.3 to 98.2 ng/g lipid.[3,52,57,58] Comparable levels of tetra- to hexa-BDEs were also found in human adipose tissues from other countries indicating a worldwide increase and bioaccumulation in humans.[55,59,60]

PBDEs have been increasing exponentially over the past 25 years in breast milk samples from Sweden.[3] A recent Polish study estimated a daily intake of PBDEs by adult humans at 51 ng/day, while breastfed infants accumulated more than twice that amount (110 ng/day).[49] The breast milk levels of North American women indicate the highest body burden in the world, 40 times higher than the highest levels reported for Swedish women. The average level of PBDEs found in breast adipose tissue of women from the San Francisco Bay area are the highest on record at 86 ng/g lipid.[61] The PBDEs detected in breast milk include tri-, tetra-, penta-, and hexa- but not hepta-, nona- or deca-congeners.[62]

Using human breast milk as a matrix, some European countries have successfully developed a body burden monitoring system for a variety of environmental contaminants, including PBDEs. It has been suggested that the same be done in the United States.[3,26,63,64]

PBDE TOXICITY

The toxicity of PBDEs is not as well understood as that of PCBs. PBDEs are endocrine disruptors and neurotoxins. They are believed to cause liver tumors, neurodevelopmental and thyroid dysfunctions. Exposure to polybrominated biphenyls (PBBs), close molecular analogs of PBDEs, has been associated with fatigue, reduced capacity to work, increased sleep, headache, dizziness and irritability. These symptoms often appear in combination with gastrointestinal syndromes including diminished appetite, weight loss, abdominal pain and diarrhea.[29] Exposure to PBDEs may present similar symptoms. At this time, no conclusive data is available.

Neurotoxicity

Children and young adults are more prone to developmental dysfunctions as a consequence of PBDE exposure. Neurodevelopmental toxicology has been linked to tetra- and penta-BDE congener exposure.[3,65] A single oral dose of

Table 1. Occurrence of PBDEs in non-occupational individuals from some developed countries.

Matrix	Location	PBDE Congeners	Reference
Breast adipose tissue	USA	tetra-, penta-, hexa-	33
Breast milk	Finland	tri-, tetra-, penta-, hexa-	105
Breast milk	Sweden	tetra-, penta-	106
Pooled breast milk	Sweden	tri-, 2* tetra-, 3* penta-, 2* hexa-	106
Adipose tissue	USA	hexa-, hepta-, octa-	55
Adipose tissue	Finland	tetra-, penta-, hexa-	105
Adipose tissue	Spain	tetra-, penta-, hexa-	59
Adipose tissue	Sweden	tetra-, penta-, hexa-	52
Blood serum	USA	tetra-, hexa-, hepta-, deca-	107
Blood serum	Sweden	tetra-	108
Placenta	Finland	tri-, tetra-, penta-, hexa-	105
Plasma	Sweden	tetra-	109

* Denotes the number of congeners detected, when more than one.

tetra- or penta-BDE on day 10 following birth permanently impaired spontaneous motor behavior, affected learning and memory, and had permanent behavioral effects in mice.[65-69] Penta-congeners have the most effect during a critical period of neonatal brain development in mice.[70] Studies using ^{14}C-BDE-99 indicated concentrations in 10-day-old mice brains comparable to PCBs that induced the same type of behavioral effects.[70]

Phospholipase A_2 (PLA_2) activity has been linked with learning and memory, and arachidonic acid (AA) has been identified as a second messenger involved in synaptic plasticity.[71] PBDE-71, a 2,3,4,6-congener, significantly stimulated ^{3}H-AA release at concentrations as low as 10 μg/ml, while an octa-BDE failed to do so even at 50 μg/ml. The release of ^{3}H-AA was observed after only 5 to 10 minutes of exposure of cerebellar granule cells in culture. Release of ^{3}H-AA was stimulated through a cytosolic PLA_2/Ca^{++}-independent PLA_2.

The neurodevelopmental toxicology of PBDEs appears to involve changes in the cholinergic system and may also be related to altered thyroid homeostasis. It is generally accepted that brain development is highly dependent on the thyroid hormone.

Thyrotoxicity

Hydroxy-PBDE congeners have structural similarities with the thyroid hormones 3,5-diiodothyronine (T_2), 3,3,5-triiodothyronine (T_3) and 3,3,5,5-tetraiodothyronine (thyroxine, T_4). They have been reported to bind human alpha- and beta-thyroid hormone receptors.[72] PCBs and PBDEs both alter thyroid hormone balance by disrupting brain development.[73-75] PBDEs also bind to cytosolic aryl hydrocarbon receptors, thyroid hormone receptors, and serum thyroid hormone binding proteins (i.e., transthyretin). Specific congeners may decrease, increase, or mimic the biological action of thyroid hormones owing to structural similarities to these compounds.

Short-term exposure to less-brominated PBDE congeners interferes with thyroid function and disrupts hormonal balance. Commercial formulations of penta-BDE reduce thyroid hormone levels and induce thyroid hyperplasia in rats. Penta-BDE also significantly reduced T_4 levels in mice.[76-78] PBDE-47, a tetra-BDE formulation that predominantly bioaccumulates in human and animal adipose tissue also reduced thyroid hormones levels in rats. The effects were additive when given simultaneously with PCBs and chlorinated paraffins.[31]

Highly brominated PBDEs can also cause thyroid hormone imbalance. Deca-BDE significantly increased the incidence of thyroid hyperplasia and tumors among male and female mice in a two-year feeding study.[79] Octa-BDE administered to rats for only 90 days resulted in thyroid changes.[4] At a deca-BDE and deca-bromobiphenyl manufacturing plant 4 workers among 35 exposed to the compounds exhibited clinical hypothyroidism. At least 1 of the 4 was exposed to deca-BDE alone, while no case of thyroid dysfunction was observed among 89 unexposed workers.[80]

The mechanism of thyroid hormone disruption is not clear. PBDEs may upregulate uridine diphosphate-glucuronosyl transferase (UDPGT), which increases the rate of T_4 conjugation and excretion.[3] Conversely, PBDEs and their metabolites may mimic T_4 and/or T_3. These latter hormones are hydroxy-halogenated diphenyl ethers. In metabolic studies of tetra-BDE, hydroxy-tetra-BDE metabolites were found. These hydroxy-PBDEs may reduce T_4 levels by binding to thyroid hormone transport protein (transthyretin), interfering with normal thyroid hormone transport, resulting in decreased total thyroxine levels.[72,81-83]

A structurally similar 2,4-dichloro-4-nitro-diphenyl ether preparation (nitrofen) that is used as an herbicide (figure 1) is also thought to induce derangement of thyroid function. Prenatal exposure to nitrofen resulted in a variety of congenital anomalies related to severe fetal lung hypoplasia. Congenital lung pathology associated with nitrofen exposure may be due to the down regulation of thyroid dependent transcription factor. Nitrofen non-competitively inhibits the binding of T_3 to the alpha-1 and beta-1 form of the thyroid hormone receptor *in vitro*.[84] Lung hypoplasia might represent a secondary sign for thyroid function disturbance during fetal development *in utero*.[84, 85]

Estrogenicity

PBDEs are also estrogen disruptors. In human T47D breast cancer cells stably transfected with an estrogen responsive luciferase reporter gene construct (pEREtata-Luc), 11 PBDEs showed estrogenic potencies. The highest estrogenic activity was observed for 2,2',4,4',6-, 2,4,4',6-, and 2,2',4,6'-congeners (PBDE-100, 75 and 51). Activity appears to require two ortho-(2,6)-bromine atoms on one phenyl ring and at least one para bromine atom and nonbrominated ortho-meta or meta carbons on the other phenyl ring.[86] The same structure-activity relationship has been suggested for PCBs in a competitive binding assay in which the PCB congener with the highest binding affinity for the estrogen receptor contained an unsubstituted phenol ring with a para-hydroxy group.[87]

Some hydroxy-PBDEs were more potent inducers than estradiol at higher concentrations. The concentrations of PBDEs leading to 50% induction varied from 2.5 to 7.3 μM. Several pure PBDE congeners as well as OH-PBDE are agonistic of both alpha- and beta-receptors and stimulate ER-mediated luciferase induction *in vitro*. This suggests that PBDEs may produce more potent pseudoestrogens upon *in vivo* metabolism that can compete with T_4 for binding to transthyretin.[81] Other estrogen receptor-mediated pathways affecting testis development,[88] hepatic enzymes activity,[89] and behavior[90] may be affected as well.

Carcinogenicity

PBDEs are alleged carcinogens in humans. One study implied an association between adipose tissue levels of 2,2',4,4'-tetra-BDE (PBDE-47) and the risk of non-Hodgkin lymphoma among Swedish hospital cancer patients.[57,58] Other studies have cited similar associations.[14,91,92] Polybrominated biphenyls (PBBs) that resemble PBDEs but lack an ester bond (-O-) between the two benzene rings, have also been linked with higher risks of developing lymphoma and breast cancer.[93, 94]

Radiolabeled tetra-BDE (^{14}C-PBDE-47) covalently forms reactive epoxide intermediates in rats and mice.[82] Mechanistic studies indicate that some congeners exhibit significant aryl hydrocarbon receptor (Ah-R)-mediated effects. Specifically, penta-congeners as opposed to tetra-congeners show high affinity for Ah-R. A standard assay for dioxin-like compounds involves the induction of ethoxyresorufin-o-deethylase (EROD). In rats, commercial grade penta-BDEs are more potent inducers of EROD than commercial PCBs like Aroclor 1254 (Monsanto Chemical Company, St. Louis, MO). The penta-BDE mixture was more active at lower concentrations than the model inducer 3-methylcholanthrene or most PCB mixtures.[3,95] These findings are in agreement with other studies indicating penta-BDE induces EROD. Penta-BDE suppresses Ah-R mediated immune response in mice.[78] BDE-47, a component of commercial penta-BDE mixture, is a major congener found in human and marine tissue. It also induces EROD activities in rats but to a lower degree than PCBs.[31]

Ah-R mediated activities of flame retardants have also been explored using rat hepatoma cell line H-4-II E. In this cell line a commercial penta-brominated formulation had Ah-R binding affinities 10^{-2} to 10^{-5} times that of dioxin (2,3,7,8-TCDD).[96] Induction of EROD was strongest with PBDEs 77, 100, 119, and 126, although the maximum EROD activity was less than those induced by dioxin.[97] In another study in which 17 specific PBDE congeners were used, 7 congeners acted as Ah-R agonists while 9 acted as antagonists when administrated with 2,3,7,8-TCDD. The agonist potencies of PBDEs were comparable to the potencies of some mono-ortho PCBs.[98]

Additional evidence that PBDEs behave like PCBs and dioxin-like compounds stems from the fact that simultaneous administration of tetra-BDE and PCBs results in induction of EROD. The effects of PBDEs and PCBs were synergistic, further suggesting that both the chemicals act through the same biological mechanism.[31]

PBDE Metabolism

PBDEs can induce both phase I and phase II xenobiotic metabolizing enzymes. Wistar rats exposed to Bromkal 70 (A German commercial penta-BDE mixture that is no longer manufactured), induced the cytochrome P450 (CYP)-mediated phase I metabolism enzymes CYP 1A1 and CYP 1A2 as indicated by the increased activity of liver microsomal 7-EROD.[95] Rat hepatoma cell line H-4-II E also indicated a similar increase in liver microsomal 7-EROD.[96] Phase II induction was studied by administrating a lower brominated congener mixture (24% tetra- and 50% penta-), higher brominated congener mixture (45% hepta- and 30% octa-), and deca-congener orally to rats for 14 days at a concentration of 0.1 mmol/kg body weight. Both mixtures, but not the deca-BDE, induce uridine diphosphate glucuronyl-transferase (UDPGT).[99] Bromkal 70 also induced UDPGT activity in rats at the highest dose and decreased hepatic vitamin A and serum T_4 levels.[30,100] The induced enzymes are thought to metabolize the PBDEs in liver.

Methoxy- and hydroxy- metabolites of PBDEs have been detected in aquatic and mammalian species.[101,102] PBDE-47 (2,2',4,4'-BDE) is transformed to HO-PBDEs in rats and mice.[82] Similarly, 3,5-dibromo-2-(2,4-dibromophenoxy) phenol, a hydroxy-BDE, was identified in blood plasma of Baltic salmon and a sponge (*Tedania ignis*) at levels comparable to the major PBDEs.[101,103]

Debromination of PBDEs is also believed to occur in biological systems. Debromination proceeds more easily than dechlorination since carbon-bromine bond is weaker than carbon-chlorine linkage.[24,25] Two debrominated monomethoxy metabolites were reported after orally dosing Sprague-Dawley rats with ^{14}C-labelled BDE-99.[102] Fish undergoing depuration exhibited higher ratio of BDE-154 to deca-BDE overtime indicative of debromination.[45] This biotransformation of PBDEs could advance through cytochrome P450 system by replacing the bromine with hydrogen in a process called reductive debromination[104] or by oxidative debromination.[102]

CONCLUSION

Polybrominated diphenyl ethers have become ubiquitous in the environment in developed Western countries. The extent and adverse health effects of their presence in the food chain, air, soil, sediments and consumer products is beginning to emerge. In the United States the levels of PBDEs in humans, animals, fish and the environment are rising. Very little information is available as to their human toxicity, carcinogenicity and behavioral effects. The few studies conducted on animal models are inconclusive. Tetra- to hexa-congeners appear to have the greatest effect on fish and mammalian nervous systems, thyroid and hepatic functions, endocrine and reproductive systems. They may be regarded as the PCBs of the future, but in contrast to point sources of PCB pollution, PBDEs are more widespread and enter the environment from more diverse sources. At this time, no regulatory efforts are being pursued in the United States at the federal level. California however, in August 2003, became the first state to pass a bill to phase out penta- and octa-BDE by 2008. The flame retardant industry argues that the benefits accrued through saving lives by fire prevention outweigh the costs incurred by any medical consequences. Over time however, this cost/benefit ratio is likely to shift. In the meantime, it is imperative that a more aggressive approach be taken to circumvent or regulate their use. More clinical and translational studies are needed in a multitude of

medical disciplines to determine how exposure to PBDEs effects humans. Studies to discover new alternatives to PBDEs and other similar fire retardants should be accelerated. Alternatives to PBDEs are being sought such as aluminum trihydroxide, magnesium hydroxide along with phosphorus and nitrogen based compounds.

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