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REVIEW

Polybrominated diphenyl ether (PBDE) flame retardants: environmental contamination, human body burden and potential adverse health effects

Lucio G. Costa[1, 3], Gennaro Giordano[3], Sara Tagliaferri[1], Andrea Caglieri[2], Antonio Mutti[2]

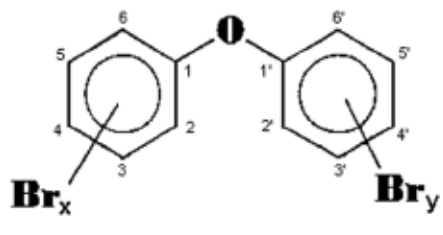
[1] Department of Human Anatomy, Pharmacology, and Forensic Science; [2] Department. of Clinical Medicine, Nephrology and Health Sciences, University of Parma Medical School, Parma, Italy; [3] Department of Environmental and Occupational Health Science, University of Washington, Seattle, WA, USA

Abstract. Polybrominated diphenyl ethers (PBDEs) are an important class of flame retardants, widely used in a variety of consumer products. In the past several years, PBDEs have become widespread environmental pollutants, and have been detected in water, soil, air, animals and human tissues. Exposure occurs in particular through the diet and the indoor environment. Infants and toddlers have the highest body burden, due to exposure via maternal milk and through house dust. Tetra-, penta- and hexa-BDEs are the congeners most commonly found in humans. Recent concerns on possible adverse health effects of PBDEs are focusing on their potential endocrine disrupting effects and on developmental neurotoxicity. (www.actabiomedica.it)

Key words: Polybrominated diphenyl ethers; flame retardants; endocrine disrupting chemicals; developmental neurotoxicity; oxidative stress; risk assessment

Introduction

Flame retardants are used in a variety of industrial and consumer products and have contributed in the past few decades to a reduction in the incidence of fires. Among fire retardants, several are brominated compounds, such as tetrabromobisphenyl A (TBBPA), hexabromocyclododecane, and polybrominated diphenyl ethers (PBDEs) (1). PBDEs are chemically similar to the long banned polychlorinated biphenyls (PCBs); there are 209 possible types of PBDE congeners, numbered using the same system as the PCBs. PBDEs have been marketed as one of three mixtures, known as pentabrominated BDE, octabrominated BDE, and decabrominated BDE. DecaBDE is the most widely used PBDE globally, and is still produced in the USA and in Europe, while pentaBDE and octaBDE have been recently banned in the European Union and in several states in the USA, and are no longer produced in these countries (2).



BDE-47: 2,2',4,4'-tetrabromodiphenyl ether
BDE-99: 2,2'4,4',5-pentabromodiphenyl ether
BDE-100: 2,2',4,4',6-pentabromodiphenyl ether
BDE-153: 2,2',4,4',5,5'-hexabromodiphenyl ether
BDE-154: 2,2',4,4',5,6'-hexabromodiphenyl ether
BDE-209: Decabromodiphenyl ether

Figure 1. General chemical structure of PBDEs ($x + y$ = 1-10) and chemical names of major PBDE congeners mentioned in the text

In contrast to TBBPA, which is chemically bonded into the polymer product, PBDEs are "additive" flame retardants, i.e. they are simply blended with the

polymers, and are thus more likely to leach out of the product into the environment. Like PCBs in the past, in the last twenty years, PBDEs have become ubiquitous persistent organic pollutants; they bioaccumulate in the environment, biomagnify up the food chain, and have been detected in significant amounts in animals as well as humans (3-5). This brief review will discuss current knowledge on environmental contamination by PBDEs, body burden in humans, and particularly in children, and potential adverse health effects, as evidenced so far by animal studies.

PBDEs: environmental contamination

A large number of studies have established the almost ubiquitous presence of PBDEs in the environment, in animals and humans. PBDEs have been detected in outdoor air, sediments, sludge, soil; in indoor air and house dust; in several food commodities; and in birds, marine species, fish and terrestrial animals (4, 6-12). PBDEs have also been detected in human adipose tissue, serum and breast milk (13-16). In contrast to PCBs and other chlorinated compounds, whose levels in biota and in human tissues have been decreasing over the past three decades, levels of PBDEs have significantly increased (13, 14, 16, 17). Five tetra-, penta- and hexa-BDE congeners (BDE-47, -99, -100, -153, -154) predominate in biota and in human tissues. Still widely used decaBDE (BDE-209) is also found in the environment (4, 12), where it can be broken down to the lower brominated congeners commonly found in humans (18, 19). BDE-209 has also been detected in certain foods, in breast milk, and in the placenta (15, 20, 21) and debromination of BDE-209 to lower brominated congeners has been observed in rats (22).

Sources of exposure and body burden in humans

PBDEs have been detected in human serum and adipose tissue in individuals from all around the world. In Europe and Asia levels are usually below 5 ng/g lipid, while those in North America have been found to be as high as 200 ng/g lipid (9, 15, 23). Levels of PBDEs found in human tissues in North America are thus particularly alarming, as they are one to two orders of magnitude higher than those reported in Europe and Japan (13, 24, 25). PBDEs can also cross the placenta, and similar concentrations are found in maternal and fetal blood (26-28). Levels of PBDEs ranging from 4 to 98.5 ng/g lipid have also been found in fetal liver (29). In almost all cases, BDE-47, BDE-99 and BDE-153 are among the PBDEs found in highest amounts.

Main sources of PBDE exposure are the diet and the indoor environment, though occupational exposure has also been documented. Among foods, fish, meats, and dairy products contain the highest concentrations of PBDEs (Table 1). In the U.S., fish has the highest content of PBDEs, followed by meat and dairy products; however, given the food consumption patterns in this country, meat is estimated to be the major source of PBDEs from the diet (9, 20, 30-32). In other world regions, such as in Europe, fish is a major source of dietary exposure to PBDEs. Independent of the specific food source, exposure to PBDEs through the diet is only slightly higher in the U.S. (60-84 ng/day), than in Europe (38-97 ng/day), (20, 31). Thus, diet alone cannot fully explain the higher levels of PBDEs found in human tissues of children and adults in North America (23, 31, 33).

In case of infants, diet is the major determinant of exposure. Significant levels of PBDEs have indeed been found in human breast milk, particularly in North America (Table 2). For example, mean levels of PBDEs (all congeners) in human milk in 2002-05 were (in ng/g of lipid): 3.7 in Europe, 1.57 in Japan,

Table 1. PBDEs in selected foods

Foodstuff	Spain	United States
Oil	15-2958	ND
Eggs	13-557	85
Milk	3-166	8-290
Butter	74-1588	485
Cheese	15-137	11-683
Chicken	16-1501	129-283
Pork	7-2518	41-1378
Beef	ND	105-258
Ham	15-1009	ND
Salmon	77-880	141-3082
Fatty fish	211	437-2450
Sardines, tuna	24-511	16-3276
Shellfish	3-677	108

Data are expressed in pg/g. Adapted from Gomara et al. (20) and Schecter et al. (31)

Table 2. PBDEs in human milk

World region	PBDE levels (range)	Year(s)
Europe		
Sweden	0.9-28	1996-2001
Finland	0.9-5.9	1994-1998
Russia	0.5-1.7	2003-2004
Poland	0.8-8.4	2004
Czech Republic	0.3-1.4	2003
France	1.4-11.6	2005
Italy	1.6-4.1	1998-2001
Germany	0.8-24.6	2001-2003
North America		
United States	4-419	2001-2004
Canada	0.9-956	2001-2005
Asia		
Japan	0.1-291	1999-2004
China	1.5-17	ND
Indonesia	0.5-13	2001-2003
Oceania		
Australia	6.1-18.7	2002-2003

Levels of PBDEs are in ng/g lipid. Table adapted from Costa and Giordano (2), where original references are indicated

and 73.9 (range 6.2-419) in the USA (16, 24, 25). Levels of PBDEs in breast milk have been increasing in the past 20-30 years, along with serum levels in the general population (2, 17), though a slight decline has started to emerge in the recent years. Given the high levels present in milk, it has been estimated that a breastfed infant in the U.S. would be exposed to 1500 ng/day of PBDEs (31).

Several studies have indicated that a major source of exposure to PBDEs is represented by house dust (34-38). Household cats, exposed to PBDEs partially through the diet and through house dust, have been found to have serum levels of PBDEs that were 20-100 fold higher than the mean levels in U.S. adults, and have been suggested to serve as "sentinels" for indoor exposure to PBDEs (39). For toddlers in particular, dust has been estimated to account for 80% of PBDE exposure (37). A recent study by Allen et al. (40) also indicated that children are exposed to PBDE levels 3-4 -fold higher than adults, and that house dust accounts for >80% of exposure (Table 3). In a study of a Californian family, serum levels of PBDEs were reported to be 651 ng/g lipid in a 1.5 year old toddler vs 87 ng/g lipid in the father (33). Thus, in contrast to PCBs, whose concentration increases with age due to accumulation in adipose tissue, PBDE levels do no appear to increase with age (17). Moreover, the highest serum levels of PBDEs are found in infants and toddlers, as a result of exposure through maternal milk and house dust (33).

As said, occupational exposure to PBDEs may also occur. For example, in a group of computer dismantlers in Sweden, serum levels of PBDEs were 26 ng/g lipid, compared to 3.3 ng/g lipid in a reference group of hospital cleaners (41). In a more recent study in China, workers at an electronic dismantling facility were found to have mean serum levels of BDE-209 of 83.5 ng/g lipid (with a peak of 3436 ng/g lipid), compared to 5.7 ng/g lipid in a reference group. Residents within a 50 km radius from the dismantling facility showed also relatively high serum BDE-209 levels (18.5 ng/g lipid) (42). In a group of adolescents working and living at a waste disposal site in Managua, Nicaragua, serum levels of PBDEs (mostly BDE-47) as high as 1250 pmol/g lipid were reported (43).

General toxicology of PBDEs

There is an acceptable body of information on the general toxicology of PBDEs, particularly de-

Table 3. Relative contribution of major routes of exposure to PBDE intake in the United States

Source	Adult				Child			
	Non-209 BDEs	% of intake	BDE-209	% of intake	Non-209 BDEs	% of intake	BDE-209	% of intake
Air	5.6	11.0	3.5	22.4	3.2	2.0	2.0	2.9
Food	33.3	65.3	6.5	41.7	24.9	15.7	6.0	8.7
Dust*	12.1	23.7	5.6	35.9	130.5	82.3	60.8	88.4
Total	51.0	100	15.6	100	158.6	100	68.8	100

PBDE exposure is expressed in ng/day. Adapted from Allen et al. (40)

caBDE, but for several emerging end-points of toxicity, information is still limited (6-8, 10, 19, 44-46). PBDEs have low acute toxicity, with oral LD50s of >5 g/kg. Upon chronic exposure, target organs are the liver, the kidney and the thyroid gland. Different PBDEs appear to have similar toxicological profiles, with decaBDE being less potent than other lower brominated congeners. For example, in subchronic toxicity studies in rat, no-observed-effect-levels are usually in the g/kg/day range for decaBDE, but less than 10 mg/kg/day for pentaBDE (6, 44). Toxicokinetic studies in adult animals have indicated that absorption, metabolism and excretion of PBDEs are congener-, species- and gender-dependent (6, 7, 47). For example, lower brominated congeners are metabolized to mono- and di-hydroxylated metabolites (e.g. 6-OH-BDE-47), which may have toxicological relevance (see below), and appear to bioaccumulate in serum (43), while decaBDE may be metabolized to lower brominated congeners. Male mice have a higher rate of urinary excretion compared to female mice or rats. Young animals have a reduced ability to excrete PBDEs, which contributes to a higher body burden (48).

PBDEs do not appear to be genotoxic (49, 50), but an increased incidence of hepatocellular carcinomas and thyroid adenomas have been observed in rodents upon exposure to BDE-209 (6, 44). PBDEs can be fetotoxic, but usually at maternally toxic doses, and there is no evidence of teratogenicity. Despite the structural similarities to PCBs, PBDEs do not appear to activate the Ah receptor-AhR nuclear translocator protein-XRE complex, although they can bind to the Ah receptor (51-54). However, various PBDEs have been reported to induce mixed-type monoxygenase in vivo. For example, DE-71 (a pentaBDE mixture) was reported to induce CYP1A1 and CYP2B in rats (55), while BDE-47, -99, and -153 upregulate CYP2B and CYP3A, also in rat (56). In a recent study in mice, BDE-47, -99, and -209 were found to induce expression of CYP3A11 and CYP2B10 by activating the pregnane X receptor (PXR) (57). PBDEs have also been shown to induce phase II metabolizing enzymes, such as uridine diphosphoglucuronosyl transferase (UDPGT) (58, 59). Inhibition of CYP activity by PBDEs has also been reported. For example, several hydroxylated PBDEs were found to inhibit CYP19 (aromatase), a key enzyme in steroidogenesis, in human placental microsomes (60).

PBDEs as endocrine disruptors

PBDEs have endocrine disrupting effects, as they have been shown to interact as antagonists or agonists at androgen, progesterone, and estrogen receptors (53, 61-63). For example, most PBDEs have antiandrogenic activity in vitro and in vivo (64); tetra-to hexa-BDEs have potent estrogenic activity in vitro; heptaBDE and 6-OH-BDE-47, a metabolite of BDE-47, have anti-estrogenic activity (53, 54). Reproductive toxic effects of PBDEs have been reported. Prenatal exposure to BDE-99 was found to reduce sperm counts in adult rats (65), and to alter the ultrastructure of the ovary cells in the females (66). Similar findings in the female reproductive system were also seen with BDE-47 (67), which also caused a decreased in ovarian weight and alterations in folliculogenesis and serum estradiol concentrations (68), while BDE-209 was reported to impair male rat reproductive functions (69).

PBDEs have also been reported to decrease levels of total and free T_4 in adult animals (70-72), in adolescent animals (73), and following developmental exposure. Given that thyroid hormones are known to play a relevant role in brain development (74, 75), and that hypothyroidism has been associated with a large number of neuroanatomical and behavioral effects (76-78), this latter effect has been particularly investigated. Zhou et al. (55) reported that treatment of weanling female rats with DE-71 or DE-79 (an octaBDE mixture) caused a reduction of serum T_4 levels. In a subsequent study, Zhou et al. (59) found that exposure of rats to DE-71 from gestational day (GD) 6 to postnatal day (PND) 21 caused a significant decrease of serum T_4 in the dam, and in the fetuses and pups on GD 20, PND 4 and PND 14, with a recovery on PND 36. A similar treatment with DE-71 in rats (GD 6-PND 18) was found to decrease serum T_4 levels in dams and in pups on PND 18, with a full recovery on PND 31 (79). Postnatal exposure of rats to BDE-209 was reported to decrease the serum levels of T_4 in male animals on PND 22 (80), while BDE-209 exposure from GD 0-17 was found to decrease T_3, but

not T_4 levels on PND 71 (81). A single pre-natal exposure to low doses of BDE-47 or BDE-99 (on GD 6) was found to decrease T_4 levels in pups (67, 82). However, a single exposure or rats to BDE-47 on PND 10, which resulted in behavioral toxicity (83, 84), did not cause any alterations in serum T_4 and T_3 levels (85). Possible mechanisms underlying the effects of PBDEs on thyroid functions relate to an enhanced metabolism and excretion of T_4 as a result of exposure to PBDEs, or to an interaction of PBDEs with the thyroid hormone transport system. Zhou et al. (59) found that the decrease in T_4 was associated with induction of UDPGT, a key phase II metabolizing enzyme involved in conjugation of T_4. Such increased metabolism results in enhanced excretion and hence in reduced circulating levels of T_4 (86). However, induction of UDPGT alone cannot explain the reduced T_4 levels induced by PBDEs, since decreased levels of T4 were also seen in the absence of UDPGT induction (59, 71, 81, 87, 88). An alternative/complementary hypothesis is that PBDEs may interfere with thyroid hormone transport. Meerts et al. (89) reported that several PBDEs could interact with transthyretin (TTR), one of the thyroid hormone-binding proteins in plasma, thereby displacing T_4. However, such interaction only occurred in the presence of phenobarbital-treated microsomes, implicating one or more PBDE metabolites. Some hydroxylated PBDEs, in particular 6-OH-BDE-47, were most potent in displacing T_4 from TTR (53, 54, 89). Displacement of T_4 from TTR may lead to increased glucuronidation and a consequent lower level of T_4.

PBDEs as developmental neurotoxicants

The current greatest concern for potential adverse health effects of PBDEs relates to their developmental neurotoxicity (2, 10, 45, 90). Such concern is supported by the fact that infant and toddlers have the highest body burden of PBDEs, due to exposure via maternal milk and house dust (2), and that a number of animal studies have provided indications of long-lasting behavioral alterations, particularly in the domains of motor activity and cognitive functions, upon pre- and postnatal exposures to PBDEs (Table 4). A series of studies have shown that exposure of neonatal mice and rats to various PBDEs (BDE -47, -99, -153, -183, -203, -206, -209) as a single oral dose, in most cases on PND 10, causes long-lasting changes in spontaneous behavior, mostly characterized as hyperactivity (decreased habituation), and disrupts performance in learning and memory tests (e.g. Morris water maze) (83, 91-96). In some cases, the observed behavioral changes appeared to worsen with age (92, 93). Evidence from a number of other studies is overall supportive of such findings. Hyperactivity has been reported following developmental exposure of rats and mice (various treatment schedules; see (2)) to BDE-99, BDE-47 and BDE-209 (65, 80, 84, 97-99). Cognitive impairment has also been reported following postnatal exposure to DE-71 (100) and to BDE-209 (101). Gender-dependent alterations in sweet preference, paralleled by changes in sex hormones have also been reported upon exposure to BDE-99 (102).

In contrast with the large database on body burden (levels of PBDEs in serum, adipose tissue, breast milk), there is almost no information on possible developmental adverse effects in humans from PBDE exposure. In a study in Taiwan (103), elevated PBDE levels in breast milk were correlated with lower birth weight and length, lower head and chest circumference, and decreased Quetelet's (body mass) index. In another study in Scandinavia, milk PBDE levels were associated with an increased incidence of cryptorchidism in newborn boys (104). Any possible inference on potential risk for adverse nervous system ef-

Table 4. Developmental neurotoxicity of PBDEs: animal studies

Exposure	PBDE	Behavioral effects	Reference
Pre-natal	BDE-47, -99	Hyperactivity	65, 97
Post-natal	BDE-47, -99, -153, -183, -203, -206, -209, DE-71	Hyperactivity, decreased habituation, impaired learning	80, 83, 84, 92-96, 100, 101
Pre- and post-natal	BDE-99	Hyperactivity	98, 99

fects in humans exposed to PBDEs in utero, or neonatally through breast milk or household dust, needs to be extrapolated from animal data. By using a standard approach of dividing NOEL values for the appropriate safety factors, Reference doses (RfDs) of 92-660 ng/kg/day can be calculated (2). These values are in the actual range of infant exposure in the U.S. (through breast milk; ~300 ng/kg/day) (31), and close to the levels of toddler exposure through household dust and the diet (50 ng/kg/day) (23). Comparison of body burden across species leads to similar conclusions, i.e. levels in animals shown to cause adverse developmental behavioral effects are in the same range of high human exposures (2).

Information on possible mechanisms of PBDE developmental neurotoxicity is still limited. As recently indicated (2), two general, and not mutually exclusive, ways of action are emerging: one related to the effects of PBDEs on thyroid hormones, and the other one involving the possible direct effects of PBDEs on the developing brain. Independent of the underlying mechanisms (see previous section), the effect of PBDEs on thyroid hormone homeostasis may be relevant in the context of developmental neurotoxicity. Behavioral studies in hypothyroidism [induced by developmental exposure to propyl thiouracyl (PTU)] have evidenced decreases in learning and habituation in maze tests, changes in anxiety-like behavior, and increases in locomotor activity in rats (105). As indicated above, some of these effects are seen following developmental exposure to PBDEs. Furthermore, thyroid hormone deficiency has been found to cause structural abnormalities in the hippocampus and the cerebellum (78), and to increase apoptosis in the cerebellum (106). PTU treatment causes T_4 level to fall below the limit of detection in offspring (105), while decreases of T_4 following developmental exposure to PBDEs are less pronounced (10-60%). Nevertheless, decrements in neurological development in children of mothers with 25% decrease in T_4 have been reported (77), suggesting that effects of PBDEs on thyroid hormones may contribute to their developmental neurotoxicity.

PBDEs may also exert direct neurotoxic effects in neuronal and glial cells. Few studies have investigated biochemical/molecular changes occurring in the central nervous system of animals following in vivo developmental exposure to PBDEs (2). For example, Eriksson et al. reported changes in cholinergic nicotinic receptors in the hippocampus upon exposure to BDE-99 and -153 (92, 107). The same investigators found changes in the expression of CaMKII, GAP-43 and BDNF following postnatal exposure to BDE-209 (108), and of GAP-43 and other proteins upon exposure to BDE-99 (109). Similar changes in CaMKII were also found upon exposure to BDE-47, which also altered the expression of glutamate receptor subunits (110). The glutamate-nitric oxide-cGMP pathway was altered by prenatal exposure to BDE-99 (111). Additional information has been provided by in vitro studies on neuronal or astroglial cells. Interference of PBDEs with signal transduction pathways have been reported. For example, various PBDEs were shown to cause translocation of protein kinase C (PKC), stimulation of arachidonic acid release, and inhibition of calcium uptake in cerebellar granule neurons (112-114). Effects of different PBDEs on calcium buffering mechanisms have also been seen in microsomes and mitochondria isolated from several brain regions of adult male rats (115). Activation of various PKCs by BDE-99 in human astrocytoma cells, and increases in calcium concentrations in astrocytes, macrophages and PC-12 cells, by BDE-99 and BDE-47 have also been reported (110, 116-118). BDE-99 has been shown to cause apoptotic cell death in human astrocytoma cells (116), and a similar effect has also been observed with DE-71 in cerebellar granule cells (119), and with BDE-47 in hippocampal neurons and human neuroblastoma cells (120, 121). In neuronal cells, PBDE neurotoxicity was prevented by antioxidants (119) suggesting that PBDEs may induce oxidative stress. Several recent reports, indeed indicate that PBDEs cause oxidative stress in vitro (Table 5). DE-71 and BDE-47 were shown to cause oxidative stress in human neutrophil granulocytes (122), an effect shared by other brominated fire retardants (123, 124). BDE-47 was reported to induce oxidative stress in SH-SY5Y human neuroblastoma cells (121, 125), in rat hippocampal neurons (120), and in fetal liver hematopoietic cells (126). Similar results were obtained in human hepatoma cells (Hep G2) with BDE-209 (127). An increase in lipid peroxidation and in the levels of oxidized glutathione

Table 5. Oxidative stress induced by PBDEs in vitro

PBDE	Cell system	Reference
BDE-47	Human fetal liver hematopoietic stem cells	126
BDE-47	Mouse cerebellar granule cells	Giordano and Costa, unpublished
BDE-47	Human SH-SY5Y neuroblastoma cells	121, 125
BDE-47	Rat hippocampal neurons	120
BDE-47	Rainbow trout RTgill-W1 cells	132
BDE-209	Human hepatoma (Hep G2) cells	127
DE-71	Mouse cerebellar granule cells	129
DE-71	Human neuroblastoma SK-N-MC cells	Tagliaferri, Caglieri et al., unpublished

(GSSG) have also been found in liver of American kestrels (*Falco sparverius*) treated in ovo with a mixture of BDE-47, -99, 100, and -153 (128). Furthermore, prenatal exposure to BDE-99 has been shown to increase levels of nitric oxide, possibly secondarily to an increase in calmodulin, which may lead to increased nitrosylation of proteins (111). Preliminary findings in the authors' laboratory also indicate that PBDEs cause oxidative stress in mouse cerebellar granule neurons and hippocampal neurons, and that their neurotoxicity is modulated by intracellular glutathione (129). In addition to oxidative stress caused by a direct effect of PBDEs on neuronal cells, it is also relevant that hypothyroidism itself may induce oxidative stress, as evidenced by increased hydroxyl radicals, lipid peroxidation and protein carbonyl levels in PTU-treated rats (130). However, as earlier mentioned, a recent study has shown that a single exposure of mice to BDE-47 (10 mg/kg on PND 10; the same protocol utilized in the Eriksson, Viberg et al. studies) causes neurobehavioral effects (delayed neuromotor ontogeny and long-term hyperactivity), without altering serum levels of T_3 and T_4 (84, 85). These findings would support the hypothesis that both thyroid hormone-mediated, and direct effects of PBDEs can occur, depending on the exposure paradigm. The two general ways of action are not mutually exclusive.

Conclusions

In the past several years, PBDEs have become widespread environmental pollutants, and body burden in the general population has been increasing, due to exposure through the diet and through house dust. Of particular concern is the high body burden in infants and children and the evidence, provided so far by animal studies, that PBDEs may be developmental neurotoxicants and endocrine disruptors. These concerns have led to the ban of several of these compounds in different countries. DecaBDEs have also been banned in some countries (e.g. Sweden) and in some states (e.g. Maine, Washington) in the U.S. Flame retardants in general have greatly contributed to a decrease in the incidence of fires, thus saving lives, injuries and property damages. Thus, PBDEs are likely to be replaced by other chemicals, whose potential adverse effects on the environment and human health are still unknown. Because of their persistence, PBDEs, like the long-banned PCBs, are expected to be around for quite some time; hence, it would be in the public interest to acquire more information on PBDEs' potential adverse health effects. Several issues still remain and need to be investigated (2). Among these, there is the need for epidemiological studies in humans to determine whether body burden of PBDEs may be associated with adverse health effects, particularly in the domains of neurobehavioral development and reproductive effects. Also, information on potential mechanisms of PBDE toxicity is still limited. Mechanistic studies would provide important information for a better assessment of the likelihood of PBDE adverse health effects, would define the toxicity of individual congeners, and would indicate whether interactions among PBDE congeners and between PBDEs and other environmental pollutants, e.g. PCBs (131) may occur.

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Correspondence: Lucio G. Costa
Dept. of Human Anatomy, Pharmacology
and Forensic Science
University of Parma Medical School
Via Volturno 39
43100 Parma (Italy)
Tel. 0521 903851
Fax 0521 903852
E-mail: lucioguido.costa@unipr.it