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DEVELOPMENTAL NEUROTOXICITY OF POLYBROMINATED DIPHENYL ETHER (PBDE) FLAME RETARDANTS

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Abstract

Polybrominated diphenyl ethers (PBDEs) are a class of flame retardants used in a variety of consumer products. In the past 25 years, PBDEs have become ubiquitous environmental contaminants. They have been detected in soil, air, sediments, birds, marine species, fish, house dust, and human tissues, blood and breast milk. Diet and house dust appear to be the major sources of PBDE exposure in the general population, though occupational exposure can also occur. Levels of PBDEs in human tissues are particularly high in North America, compared to Asian and European countries, and have been increasing in the past 30 years. Concentrations of PBDEs are particularly high in breast milk, resulting in high exposure of infants. In addition, for toddlers, dust has been estimated to account for a large percentage of exposure. PBDEs can also cross the placenta, as they have been detected in fetal blood and liver. Tetra-, penta- and hexa BDEs are most commonly present in human tissues. The current greatest concern for potential adverse effects of PBDEs relates to their developmental neurotoxicity. Pre- or postnatal exposure of mice or rats to various PBDEs has been shown to cause long-lasting changes in spontaneous motor activity, mostly characterized as hyperactivity or decreased habituation, and to disrupt performance in learning and memory tests. While a reduction in circulating thyroid hormone (T_4) may contribute to the developmental neurotoxicity of PBDEs, direct effects on the developing brain have also been reported. Among these, PBDEs have been shown to affect signal transduction pathways and to cause oxidative stress. Levels of PBDEs causing developmental neurotoxicity in animals are not much dissimilar from levels found in highly exposed infants and toddlers.

Introduction

Fires are a major health and economic issue, killing yearly more than 3,500 people, injuring more than 18,000, and causing property damage in excess of $10.7 billion in the U.S.A. alone (Karter, 2006). The use of flame retardants corresponded with a drastic drop in fire incidence in the past 30 years. Among chemicals used as flame retardants, there are phosphorus- or nitrogen-containing compounds, and brominated compounds. Some of the latter, e.g. polybrominated biphenyls, were removed from the market following their contamination of animal feed in the 1970s (Dunckel, 1975). Others, such as tetrabromobisphenol A (TBBPA) and hexabromocyclododecane, are still widely used. A third major class of brominated flame retardants is that of polybrominated diphenyl ethers (PBDEs), extensively used in a variety of consumer products such as textiles, carpets, polyurethane foams, electronic cables, television

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sets and computers. Commercially used PBDEs were 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. PentaBDE, whose use was concentrated chiefly in North America, and octaBDE, were banned in the European Union in 2004, and in several states in the USA (e.g. California, Maine, Hawaii) in 2006; they will be banned in the state of Washington from 2008. In the United States, the producer of penta-and octaBDE has voluntarily ceased production in 2004. PentaBDE was added to polyurethane foams used in couches, chairs, automobile seats. OctaBDE was used primarily in plastics used for circuit boards or small appliances, while decaBDE is used in television and computer casings, as well as in textiles.

PBDEs are not fixed in the polymer product through chemical binding, and can thus leak into the environment. PBDEs are chemically similar to the long banned polychlorinated biphenyls (PCBs), and like PCBs, they are persistent organic pollutants, bioaccumulate in the environment and biomagnify up the food chain (Darnerud et al. 2001; Birnbaum and Staskal, 2004; She et al. 2004; Schecter et al. 2005a; Law et al. 2006). There are 209 possible types of PBDE congeners, numbered using the same system as the PCBs. The general structure of PBDEs is shown in Fig. 1, and the chemical names of some of the compounds discussed in this article are shown in Table 1. Widespread contamination of the environment by PBDEs, and their detection in wildlife, and most importantly in human tissues, have raised concerns on possible adverse health effects. As exposure appears to be highest in the young, a major current concern relates to the possible developmental effects of PBDEs (Branchi et al. 2003; Birnbaum and Staskal, 2004; McDonald, 2005). This article intends to discuss aspects of PBDE's toxicology related to their potential developmental neurotoxicity. Several other reviews on the general toxicology of PBDEs are available (Darnerud et al. 2001; de Wit, 2002; McDonald, 2002; Hardy, 2002; Birnbaum and Staskal, 2004; WDEH, 2006).

PBDEs as environmental pollutants

A number of studies have established the almost ubiquitous presence of PBDEs in the environment, in animals and in 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 (Darnerud et al. 2001; de Wit, 2002; Gill et al 2004; Hites et al. 2004; She et al. 2004; McDonald, 2005; Law et al. 2006; Hazrati and Harrad, 2006; Schecter et al. 2006a; Chen et al. 2007). As in the case with PCBs, they have a biomagnification potential in the food chain (Darnerud et al. 2001). However, in contrast to PCBs and other chlorinated compounds, whose levels in biota have been decreasing in the past three decades, levels of PBDEs have significantly increased (Darnerud et al. 2001). PBDEs have also been detected in human adipose tissue, serum and breast milk (Petreas et al. 2003; Sjodin et al. 2004; Schecter et al. 2005a; Furst, 2006). Five tetra-, penta- and hexa-BDE congeners (BDE-47, −99, −100, −153, −154) predominate in human tissues, usually accounting for 90% of the total body burden (McDonald, 2005). Still widely used decaBDEs (such as BDE-209) are also found in the environment (Law et al. 2006; Chen et al. 2007), where they can be broken down to the lower brominated congeners commonly found in humans (Soderstrom et al. 2004; WDEH, 2006); BDE-209 has been detected in some samples of human milk, and in certain foods (Vieth et al. 2004; Schecter et al. 2005a; Gomara et al. 2006).

Human exposure and body burden

Levels of PBDEs found in human tissues in North America are particularly alarming, as they are one to two orders of magnitude higher than those reported in Europe and Japan (Petreas et al. 2003; Schecter et al. 2003; Inoue et al. 2006). Sources of PBDE exposure can be found in the occupational setting, in the diet, and in the indoor environment. For example, with regard

to occupational exposure, in a group of computer dismantlers, serum levels of PBDEs were 26 ng/g, compared to 3.3 ng/g in a reference group of hospital cleaners (Sjodin et al. 1999). Among foods, fish has the highest content of PBDEs, followed by meat and diary products, with meat estimated to be the major source of PBDEs in the U.S. diet (Schecter et al. 2004; Hites et al. 2004; Jones-Otazo et al. 2005; Schecter et al. 2006a). In a small study, vegetarians (vegans) were found to have somewhat lower plasma levels of PBDEs (range 12.4 – 127 ng/g lipid) than the general U.S. population (4 – 366 ng/g lipid) (Schecter et al. 2006b). Above all, high PBDE levels have been found in human breast milk. Table 2 summarizes reported levels of PBDEs in human milk from different countries. It is readily apparent that levels in North America (U.S. and Canada) are much higher than those reported in Europe, Asia or Australia. Levels of PBDEs in breast milk have been increasing in the past 20–30 years (see Table 3), along with serum levels in the general population (Thomsen et al. 2002; Sjodin et al. 2004). Fig. 2 shows the levels of PBDEs in serum found in the United States in 1973 and in 2003. It is evident that while levels of dioxins, furans and PCBs have declined, those of PBDEs have substantially increased. Given the high levels found in breast milk, it has been estimated that a breastfed infant would be exposed to approximately 306 ng/kg/day of PBDE, as compared to about 1 ng/kg/day for adults (Schecter et al. 2006a; see also Table 4). Although PBDE contamination of food is currently higher in the USA than in other countries, diet alone cannot explain the higher levels of PBDEs in the general U.S. population (Jones-Otazo et al. 2005; Wilford et al. 2005; Schecter et al. 2006a; Fischer et al. 2006; Lorber, 2007). Several studies have indicated that house dust is a major source of exposure to PBDEs (Jones-Otazo et al. 2005; Wilford et al. 2005; Schecter et al. 2005b; Wu et al. 2007). For toddlers in particular, dust has been estimated to account for 80% to 93% of PBDE exposure (Wilford et al. 2005). A toddler would be expected to ingest approximately 100 mg/day of house dust (vs 50 mg for an adult; USEPA, 1997), a difference that is compounded by differences in body weight. Table 5 shows serum levels of PBDES found in a California family, where the toddler had the highest body burden. Indeed, in contrast to PCBs, whose concentration increases with age due to accumulation in adipose tissue, PBDE levels do not appear to vary with age in adults (Thomsen et al. 2002). Rather, the highest serum levels of PBDEs are found in infants and toddlers, as a result of exposure through maternal milk and house dust (Fischer et al. 2006; Table 4). PBDEs can also cross the placenta, and similar concentrations are found in maternal and fetal blood, as illustrated in Table 6. Levels of PBDEs ranging from 4 to 98.5 ng/g lipid have also been found in fetal liver (Schecter et al. 2007). In almost all cases, BDE-47, BDE-99 and BDE-153 were among the PBDEs found in highest amounts.

Toxicity of PBDEs

There is an acceptable body of information on the toxicity of PBDEs, particularly decaBDE, and a comprehensive discussion of PBDE toxicology is outside the goal of this article (see Darnerud et al. 2001; de Wit, 2002; Hardy, 2002; Gill et al. 2004; Birnbaum and Staskal, 2004; McDonald, 2002; 2005; WDEH, 2006). 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 instance, in subchronic toxicity studies in rat, NOEL (no-observed-effect-level) values are usually in the g/kg/day range for decaBDE, but less than 10 mg/kg/day for pentaBDE (Darnerud et al. 2001). PBDEs are not genotoxic (Hardy, 2002; Evandri et al. 2003), but an increased incidence of hepatocellular carcinomas and of thyroid adenomas have been observed in rodents upon exposure to BDE-209 (NTP, 1986; Darnerud et al. 2001). Reproductive toxicity has also been reported. Prenatal exposure to BDE-99 has been found to reduce sperm counts in adult rats (Kuriyama et al. 2005), and to alter the ultrastructure of the ovary cells in females (Talsness et al. 2005). Similar findings in the female reproductive system were seen with BDE-47 (Talsness et al. 2004), while BDE-209 (500–1500 mg/kg/day from GD 0 to GD 17) was reported to impair male rat reproductive

functions (Hsu et al. 2006). 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 (Chen and Bunce, 2003; Peters et al. 2006; Hamers et al. 2006). PBDEs may have endocrine disrupting effects, as they have been shown to interact as antagonists or agonists at androgen, progesterone, and estrogen receptors (Meerts et al. 2001; Hamers et al. 2006). For example, most PBDEs have antiandrogenic activity in vitro and in vivo (Stoker et al. 2005); 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 (Hamers et al. 2006). Hydroxylated BDEs are structurally very similar to thyroid hormones, and have been shown to displace thyroid hormones from the thyroxin plasma transporter transthyretin (TTR) (Meerts et al. 2000). PBDEs have also been reported to decrease levels of total and free T_4 in adult animals (Fowles et al. 1994; Hallgren et al. 2001), and following developmental exposure (discussed below). Various PBDEs have been reported to induce mixed-type monoxygenase in vivo. For example, DE-71 was reported to induce CYP1A1 and CYP2B in rats (Zhou et al. 2001), while BDE-47, −99, and −153 upregulate CYP2B and CYP3A, also in rat (Sanders et al. 2005). 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) (Pacyniak et al. 2007). Some PBDEs and their metabolites (e.g. OH-BDE-47) have been found to inhibit activity of CYP17, a key enzyme in the synthesis of testosterone, in vitro (Canton et al. 2006). PBDEs have also been shown to induce phase II metabolizing enzymes, such as uridine diphosphoglucuronosyl transferase (UDPGT; Zhou et al. 2002; Skarman et al. 2005) (see section on thyroid hormones for further discussion).

Developmental neurotoxicity of PBDEs

The current greatest concern for potential adverse health effects of PBDEs relates to their developmental neurotoxicity (Branchi et al. 2003; Birnbaum and Staskal, 2004; McDonald, 2005). Such concern is motivated by the following consideration: 1) Animal studies, carried out with different PBDEs, have indicated that pre-and post-natal exposures to PBDEs may cause long-lasting behavioral alterations, particularly in the domains of motor activity and cognitive behavior. Neurochemical changes have also been found following developmental exposure to PBDEs; 2) PBDEs affect thyroid hormone homeostasis, which may result in developmental neurotoxicity; 3) There is indication that young animals may have a reduced ability to excrete PBDEs, and pups have higher tissue (including brain) concentrations than the dams; 4) PBDEs are excreted in milk, and relatively high concentrations are found in North America; 5) Dust has been found to be a major source of exposure; 6) Infants and toddlers have the highest body burden of PBDEs, due to exposure via maternal milk and house dust.

Behavioral studies

A Swedish group has carried out most studies on developmental neurotoxicity of various PBDEs (see Table 7; Eriksson et al. 2001; 2002;Viberg et al. 2003a; 2003b; 2004a; 2004b; 2006; 2007a). Their experimental protocol involves direct exposure of neonatal mice or rats to PBDEs, as a single oral dose, usually on post-natal day (PND) 10. All PBDEs tested so far (BDE-47, BDE-99, BDE-153, BDE-183, BDE-203, BDE-206, BDE-209) were shown to cause long-lasting changes in spontaneous locomotor behavior. Fig. 3 shows a typical profile of locomotor activity in these experiments. Three variables are measured: horizontal locomotor activity, rearing, and total activity (Eriksson et al. 2001). Mice exposed to PBDEs display significant less activity than controls during the first 20-min. period, but are significantly more active during the third 20-min. period. Control mice display habituation, a decrease in locomotion, rearing and total activity variables in response to the diminishing novelty of the test chamber over 60-min. Thus, the investigators interpret their results (initial hypoactivity

and late hyperactivity) as a decrease in habituation caused by PBDEs (Eriksson et al. 2001). An alternative interpretation might be that the decreased activity at the beginning of the session is a possible sign of increased anxiety or arousal, and the elevated activity later in the session is simply the animals finally beginning to explore their environment, as controls did at the beginning of the session. In some cases, the observed behavioral changes appeared to worsen with age (e.g from 2 to 6 month of age; Viberg et al. 2003a; 2003b). Two of the PBDEs tested (BDE-209 and BDE-183, a heptaBDE) did not cause any behavioral change when administered on PND 10; however, they induced the usual changes in locomor activity (decreased habituation) when administered on PND 3 (Viberg et al 2003b; 2006). On the other hand, BDE-99 and BDE-203 (an octaBDE), caused such behavioral alteration when administered on both PND 3 and PND 10 (Eriksson et al. 2001;Viberg et al. 2006). The authors believe that PND 10, at the height of the so-called brain growth spurt, is the most sensitive period for disruption by PBDEs. In case of BDE-209, its ability to induce long-term behavioral changes only when administered on PND 3 has been attributed to its slow accumulation (or that of its metabolites) in the brain (Viberg et al. 2003b). Indeed, levels of [U- ^{14}C]BDE-209 increased from 24.2 nmol/brain on PND 3 to 42.8 nmol/brain on PND 10 (Table 1 in Viberg et al. 2003b). However, similar brain levels (47.8 nmol/brain) were also attained when [U-^{14}C] BDE-209 was given on PND 10 (Table 1 in Viberg et al. 2003b), and they increased even further (to 107.7 nmol/brain) by day 17. This apparent discrepancy may be due to BDE-209 metabolism; if so, metabolites of BDE-209, forming and/or accumulating in the brain over the PND 3–10 time period would be responsible for the observed neurotoxic effects. In case of BDE-99, 3–5% of the administered dose was found in brain (assessed as radioactivity, thus the presence of metabolites cannot be excluded), when exposure occurred on both PND 3 and PND 10 (Eriksson et al. 2002). Brain concentrations of BDE-99 on PND 10 were similar, after administration of the same dose (0.8 mg/kg) on PND 3 or PND 10 (10.7 and 7.2 pmol/g brain, respectively; Eriksson et al 2001; 2002). Thus, persistent similar levels of PBDEs on PND 10 would appear to be associated with long-term behavioral alterations. The susceptibility of this developmental window is also underscored by the fact that BDE-99 and BDE-209 did not cause any behavioral effect when administered on PND 19. In case of BDE-209 levels of brain radioactivity were lower (Viberg et al. 2003b), but for BDE-99 they were comparable to those found after administration on PND 3 or PND 10 (Eriksson et al. 2002). While most of the behavioral studies described so far were carried out in NMRI (Naval Medical Research Institute) mice, similar results were also reported in C57/Bl mice treated with BDE-99 (Viberg et al. 2004a), and in Sprague Dawley rats exposed to BDE-209 (Viberg et al. 2007a). In one study, gender differences in hyperactive behavior were investigated for BDE-99, and none were found (Viberg et al. 2004a).

The experimental protocol used by the Swedish investigators has been at times criticized, particularly as the litter is not used as the statistical unit. However, in a study with BDE-99 (reported only in abstract form; Eriksson et al. 2005) the investigators addressed this issue by showing that randomly selected animals from at least three litters, had the same statistical effect and power compared to the use of a litter based study. Issues have also been raised with regard to the experimental design utilized in these studies, which involves administration of a single dose of PBDEs directly to pups. Nevertheless, evidence from a number of other studies is overall supportive of their findings of alterations of locomotor activity following developmental exsposure to PBDEs (Table 7). In a study in rats, a single exposure to low doses of BDE-99 [0.06 or 0.3 mg/kg on gestational day (GD) 6], resulted in hyperactivity on PND 36 (only at the high dose) and on PND 71 (at both doses) (Kuriyama et al. 2005). Two studies by Branchi et al. (2002; 2005) examined the neurobehavioral development of CD-1 Swiss mice following oral developmental exposure of dams to BDE-99 from GD 7 to PND 21. In the first study, 0.6, 6.0 and 30.0 mg/kg/day of BDE-99 did not cause any alteration in the offspring in sensori-motor development, tested by a slightly modified Fox battery (Fox, 1965), with the exception of a delayed maturation of the climbing response in the high dose group (Branchi et

al. 2002). Also, no effects on ultrasonic vocalization and homing behavior were found. However, hyperactivity was found in the offspring on PND 34 and PND 60 at all dose levels, but not at a later age (PND 120). Decreased thigmotaxis, an evidence of reduced anxiety-like response, was observed on PND 60 only in the 6.0 mg/kg group (Branchi et al. 2002). In a follow up study, 18 mg/kg/day BDE-99 were administered to mice from GD 6 to PND 21 either by gavage, or by self administration through a syringe (Branchi et al. 2005). Hyperactivity was again observed in the offspring of both experimental groups, but only on PND 34 and not at later time points (PND 60–120). In both studies no gender differences were observed (Branchi et al. 2002; 2005). An increase in locomotor activity and a decrease in thigmotaxis were also found on PND 35 and 70 in offspring of rats exposed in utero (GD 6) to a low single dose of BDE-47 (0.7 mg/kg) (Kuriyama et al. 2004a). An additional study (reported, however, only in abstract form) investigated the developmental effects of DE-71. DE-71, given to rats from GD 6 to PND 21 (5, 30 or 100 mg/kg/day) was found to cause no changes in activity in the offspring when tested as adults (age not specified) (MacPhail et al. 2003). Rice et al. (2007) exposed C57BL6/J mice to BDE-209 postnatally from PND 2–15. They found a delay in the development of the palpebral reflex, and marginal effects on forelimb strength and struggling behavior in males. On PND 70, male rats were hyperactive, but no differences were observed at one year of age (Rice et al. 2007). Finally, motor activity alterations (hypo- or hyperactivity depending on the dose levels and the test) were also reported in the killifish, an estuarine minnow, upon exposure during the embryonic stage (Timme-Laragy et al. 2006).

In addition to changes in locomotor activity, some PBDEs (e.g BDE-99, BDE-153, BDE-203) were also found to cause cognitive impairment, as decreased spatial memory in a swim (Morris) maze was found upon a single postnatal exposure in mice (Eriksson et al. 2001; Viberg et al. 2003a; 2006). In another postnatal exposure study, Long-Evans rats were given the pentaBDE mixture DE-71 by gavage from PND 6 to 12 (Dufault et al. 2005). Starting on PND 30, animals were tested in a visual discrimination learning task, in which they performed significantly worse than controls. In contrast, DE-71 did not alter sustained attention or inhibitory control, though treated animals were sub-sensitive to the effect of the cholinergic muscarinic antagonist scopolamine on attention (Dufault et al. 2005). Finally, in a study (presented, however, only in abstract form) in which DE-71 was given to rats from GD 6 to PND 21 at the doses of 5, 30 and 100 mg/kg, tests of fear conditioning revealed a dose-dependent decrease in cue- but not context-based performance in male offspring tested as adults (Taylor et al. 2003).

Sex hormone-related behavioral effects have also been reported. In a study by Lilienthal et al. (2006), administration of BDE-99 on GD 10–18 at the dose of 10 mg/kg/day, was found to increase sweet preference in male rats on PND 120. Since sweet preference is normally higher in females, the investigators interpreted the finding as a feminization of this sexually dimorphic behavior by BDE-99. Alterations in the levels of circulating sex hormones (estradiol and testosterone) at weaning and in adulthood were also found in this study. In rats treated with BDE-99 under the same experimental protocol, Lichtensteiger et al. (2004) also reported a decrease in sexual behavior in females, while Kuriyama et al. (2005) did not find any alteration in sexual behavior in male rats prenatally exposed to a single low dose of BDE-99.

In summary, available behavioral studies indicate that all PBDEs tested in rodents under different exposure protocols cause alterations in neurobehavioral development. Mostly, changes are seen in the motor domain, with hyperactivity apparently being the most prominent effect, and in the cognitive domain, with reduced learning and memory. Still unclear is whether gender differences exist, as males appear to be more affected in some studies but not in others, and whether the hyperactivity is permanent (or even worsening with age; e.g. Viberg et al. 2003a), or only transient (Branchi et al. 2002; 2005; Rice et al. 2007).

Effects on thyroid hormones

Thyroid hormones are known to play a relevant role in brain development (Chan and Rovet, 2003; LaFranchi et al. 2005), and hypothyroidism has been associated with a large number of neuroanatomical and behavioral effects (Schalock et al. 1977; Haddow et al. 1999; Zoeller and Crofton, 2005). Several chemicals can disrupt thyroid function leading to a decrease in thyroxine (T_4). Among these are propylthiouracyl (PTU), which inhibits thyroid peroxidase (Zoeller and Crofton, 2005), perchlorate, which inhibits iodine uptake into the thyroid (Wolff, 1998), and various environmental contaminants (e.g. PCBs, polyaromatic hydrocarbons), that may act by inducing T_4 metabolism (Zoeller et al. 2007).

Various studies have found that PBDEs can perturb the thyroid system both in adulthood and during development. Fowles et al. (1994) first reported that adult mice exposed for two weeks to DE-71 had decreased levels of circulating T_4. Exposure of adult mice and rats to BDE-47 or to the pentaBDE mixture Bromkal 70-5DE, decreased serum total and free T_4 levels, without altering thyrotropin (TSH) levels (Hallgren et al. 2001; Hallgren and Darnerud, 2002). Exposure of two month-old C57BL/6 mice to BDE-47 for 4 days was found to cause a significant decrease of total T_4 levels (Richardson et al. 2006). With regard to developmental exposures (see Table 8), Zhou et al. (2001) reported that treatment of weanling female rats with DE-71 or DE-79, but not DE-83R (98% decaBDE), caused a reduction of serum T_4 levels, without altering those of triiodotyronine (T_3). In a subsequent paper, Zhou et al. (2002) found that exposure of rats to DE- 71 from GD 6 to PND 21 caused a significant decrease of serum T_4 in the dam on GD 20 and PND 22, and in the fetuses and pups on GD 20, PND 4 and PND 14, with a recovery by PND 36. A similar treatment with DE-71 in rats (GD 6-PND 18) was found to decrease serum T_4 levels in dams on PND 19, and in pups on PND 18, with a full recovery by PND 31 (Ellis-Hutchings et al. 2006). There were no changes in T_3 and TTR levels, but TSH levels in dams were increased. Upon exposure of mice to BDE-99 or Bromkal 70-5DE from GD 4 to PND 18 no changes in serum T_4 were found in dams on GD 17 and PND 20 (Skarman et al. 2005). In contrast, Bromkal 70-5DE, but not BDE-99, decreased serum T_4 concentration in pups on PND 11 and 18, but not on PND 37. Branchi et al. (2005) found a non significant decrease of serum T_4 on PND 22, following developmental exposure to BDE-99 in mice. Postnatal exposure of rats to BDE-209 was reported to decrease the serum levels of T_4 in male animals on PND 22 (Rice et al. 2007). Exposure to BDE-47 on GD 6 was found to decrease T_4 levels in dams on PND1, but not on PND 22 (Kuriyama et al. 2004b), and to decrease T_4 levels in pups on PND 14, but not on PND1 or PND 22 (Talsness et al. 2004). American kestrels (*Falco sparverius*) given a pentaBDE mixture *in ovum* , also displayed lower serum T_4 levels at 36 days of age (Fernie et al. 2005). Also, ranch minks (*Mustela vison*) fed a diet containing 5 or 10 ppm DE-71 for 11 weeks from weaning, had lower levels of T_4, as well as of T_3 (Martin et al. 2004).

Though these studies are quite consistent in showing a decrease in T_4 levels following exposure to PBDEs, less is known on possible underlying mechanisms. Current hypotheses 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. (2002) 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 (Barter and Klaassen, 1992). Induction of UDPGT was also found by Skarman et al. (2005) in mice. However, induction of UDPGT alone cannot explain the reduced T_4 levels induced by PBDEs. Indeed, in the Zhou et al. (2002) study, a decrease in T_4 levels was seen at a lower dose level (10 mg/kg/day) than that necessary to cause UDPGT induction (30 mg/kg/day). Hallgren et al. (2001) reported a similar finding in adult rats; additionally, in the same study, T_4 levels were also decreased in mice, where no induction of UDPGT was present. Similarly, in adult mice, the decrease in serum T_4 caused by BDE-47

was not paralled by an increase of hepatic UDPGT activity, though its hepatic mRNA levels were increased (Richardson et al. 2006). Also, changes in serum T_4 levels following gestational exposure to BDE-47 did not parallel changes in hepatic UDPGT activity (Kuriyama et al. 2004b).

An alternative/complementary hypothesis is that PBDEs may interfere with thyroid hormone transport. Meerts et al. (2000) reported that several PBDEs could interact with 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 (enriched in CYP 1A, 2B and 4A3), implicating one or more PBDE metabolites. Some hydroxylated PBDEs [e.g. 2, 6-dibromo -4- (2,4,6-tribromo-phenoxy) phenol], synthesized for their structural resemblance to thyroid hormones, were most potent in displacing T_4 from TTR. A high potency of 6-OH-BDE-47 (a metabolite of BDE-47; Darnerud et al. 2001) in displacing T_4 from TTR was confirmed by Hamers et al. (2006). While the exact role that this mechanism may play in the regulation of serum concentrations of T_4 is unknown, displacement of T_4 from TTR may lead to increased glucuronidation and a consequent lower level of T_4. Of interest is also that BDE-47 increases hepatic mRNA levels of TTR in adult mice (Richardson et al. 2006).

Concern has been expressed that PBDEs may contribute to thyroid and neurodevelopmental health effects in North America (Muir, 2005). Independent of the underlying mechanisms, the effect of PBDEs on thyroid hormone homeostasis may be of interest and significance. Behavioral studies in hypothyroidism (induced by developmental exposure to PTU from GD 3 to PND 20) have evidenced decreases in learning and habituation to maze tests, changes in anxiety-like behavior, and increases in locomotor activity in rats (Negishi et al. 2005). As indicated in a previous section, some of these effects are seen following developmental exposure to PBDEs. However, the PTU treatment caused T_4 level to fall below the limit of detection in offspring at PND 21 (Negishi et al. 2005), while decreases of T_4 following developmental exposure to PBDEs are less pronounced (10–60%). Nevertheless, in rats, a 60% decrease in T_4 levels has been associated with a 15-dB hearing loss (Crofton, 2004), and a good correlation between ototoxicity and decrease of T_4 has been established for PCBs (Crofton and Zoeller, 2005). Investigating potential ototoxicity of developmental exposure to PBDE would thus be of interest. It should also be pointed out that decrements in neurological development in children of mothers with 25% decrease in T_4 have been reported (Haddow et al. 1999), suggesting indeed that effects of PBDEs on thyroid hormones may contribute to their developmental neurotoxicity.

Biochemical studies following in vivo developmental exposure

There are only few studies that have investigated biochemical/molecular changes occurring in the central nervous system of animals following developmental exposure to PBDEs (Table 9). The rationale for some of these studies is not always clear, though some experiments appear to have been designed on the basis of previous findings with PCBs. Viberg and collegues found a decreased number of cholinergic nicotinic receptors in hippocampus of mice following postnatal exposure (single dose at PND 10) to BDE-99 and BDE-153 (Viberg et al. 2003a; 2004b). In both cases the decrease was in the range of 20–30%, and was observed only at the high dose level of PBDE. Strangely, however, levels of [^{3}H]-alpha-bungarotoxin binding in hippocampi of control animals differed by 3.5-fold in the two experiments (9.83 vs. 35.16 pmol/mg protein), though the only appreciable difference was the age of the animals (4 vs. 6 months). It is also unclear how these nicotinic receptor changes would correlate with the observed altered response to nicotine, which caused hyperactivity in 2 month-old control mice, but hypoactivity in mice exposed to BDE-99 on PND-10 (Viberg et al. 2002). A similar altered response to nicotine was also observed in 2 month-old rats exposed on PND 3 to BDE-209 (Viberg et al. 2007a). Similar changes in hippocampal nicotinic receptors and in response to

nicotine had been previously observed in mice exposed to a PCB (Eriksson and Fredriksson, 1996). In contrast to these findings, Bull et al. (2007) did not find any changes in nicotinic receptors in cerebral cortex of ranch mink (*Mustela vison*) following chronic developmental exposure to DE-71; muscarinic receptors, acetylcholinesterase activity, and acetylcholine levels were also unaffected (Bull et al. 2007).

In vivo exposure of mice to BDE-47 (6.8 mg/kg on PND 10) was found to reduce hippocampal long term potentiation and post-tetanic potentiation, and to decrease key postsynaptic proteins involved in glutamate receptor signaling [e.g. glutamate receptor subunits NR2B and GluR1, and autophosphorylated-active alpha Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)] at PND 17–19 (Dingemans et al. 2007). A decrease of CaMKII, in addition to decreases in the levels of brain derived neurotrophic factor (BDNF) and of Gap-43 (neuromodulin) were also found on PND 10 in mice exposed to BDE-209 on PND 3 (Viberg et al. 2007b). A proteomic analysis of hippocampus and striatum of mice 24 h after the administration of BDE-99 (12 mg/kg on PND 10) revealed changes in the levels of a number of proteins (Alm et al. 2006). Among these, Gap-43, which was increased in the striatum, and stathmin, which was decreased. Both are substrates of protein kinase C (PKC), which has been shown to be affected by PBDEs in vitro (Madia et al. 2004; Kodavanti et al. 2005; Kodavanti and Ward, 2005). Various enolases, as well as alpha synuclein were also increased in the hippocampus (Alm et al. 2006). In a study in rats, prenatal exposure to BDE-99 was shown to increase the activity of the glutamate -nitric oxide-cGMP pathway, as assessed by microdialysis (Llansola et al. 2007). This effect was possibly secondary to an increase in calmodulin and soluble guanylate cyclase, and would lead to increased production of nitric oxide in brain, which in turn may increase nitrosylation of proteins thereby altering their functions (Llansola et al. 2007).

Overall, the few and scattered studies available provide only limited information on possible mechanisms underlying developmental neurotoxic effects of PBDEs. More work is certainly needed in this area, particularly keeping in consideration the results of the behavioral studies (to investigate possible neurochemical substrates of behavioral changes), and of the in vitro studies (to validate the findings in vivo upon developmental exposure).

Biochemical studies in vitro

A number of studies (see Table 10) have examined potential effects of PBDEs in vitro, mostly in neuronal or astroglial cell preparations. As for the in vivo studies, many of the end-points studied in vitro were chosen as they had been shown to be affected by PCBs. Most effects are seen at micromolar concentrations of PBDEs. However, a study by Mundy et al. (2004) has indicated that, at least for BDE-47, concentrations present in the medium underestimate tissue concentrations by up to two orders of magnitude. For example, incubation of rat cortical neurons with 1 uM BDE-47 for 60 min, resulted in an intracellular concentration of 100 uM. As all PBDEs are highly lipophilic compounds, this observation may extend to other congeners as well. This study also noted that if serum was present in the incubation medium, accumulation of BDE-47 in cells was lower by 5-fold, suggesting that PBDEs may bind to serum proteins.

Studies in rat cerebellar granule neurons have shown that PBDEs can interfere with signal transduction pathways. DE-71 caused stimulation of arachidonic acid release by activating the phospholipase A_2 pathway (Kodavanti and Derr-Yellin, 2002). On a molar basis, DE-71 was as potent as the PCB mixture Aroclor 1254, and the minimal effective concentration of DE-71 was about 15 uM. In contrast, the octaBDE mixture DE-79 was inactive in this regard. DE-71 also increased the binding of a phorbol ester (^{3}H-PDBu), an index of PKC translocation (Kodavanti and Ward, 2005), but with less potency than Aroclor 1254. Again, DE-79 was ineffective. A subsequent examination of individual PBDE congeners showed that several PBDEs (BDE-47, BDE-99, BDE-77, BDE-100, BDE-153) could increase ^{3}H-PDBu binding at concentrations of 10 uM and higher (Kodavanti et al. 2005). The potency of PBDE congeners

appeared to correlate with their accumulation in neurons, with BDE-47 being the most potent (IC_{50} = 34 uM). Activation of various PKCs (alpha, epsilon, zeta) by BDE-99 was also observed in a human astrocytoma cell line (1321N1; Madia et al. 2004). In microsomal and mitochondrial preparations from rat brain (frontal cortex, hippocampus, cerebellum) DE-71 was found to inhibit uptake of $^{45}Ca^{++}$ (Kodavanti and Ward, 2005). Effective concentrations were as low as 5 uM, while DE-79 was devoid of inhibitory activity. Micromolar concentrations of BDE-99 were reported to increase Ca^{++} concentrations in rat astrocytes, PC-12 cells and human macrophages [Wiegand et al. 2001; Smolnikar et al. 2001 (abstract)]. Similarly, BDE-47 (20 uM) was reported to increase [Ca^{++}] in PC-12 cells (Dingemans et al. 2007). In contrast, DE-71 (30 uM) did not cause any Ca^{++} elevation in cerebellar granule cells (Reistad et al. 2006), and octaBDE (10–40 uM) did not alter Ca^{++} levels in mouse thymocytes (Sandal et al. 2004).

A number of studies have also examined the effects of PBDEs on cell viability. In rat cerebellar granule cells, DE-71 did not cause any release of lactate dehydrogenase (LDH) at up to 60 uM for 240 min (Kodavanti and Ward, 2005), while following the same incubation period, BDE-47 caused a small but significant increase of LDH release at 50 uM (Kodavanti et al. 2005). Similarly, in human astrocytoma cells, no cytotoxicity (assessed by measuring LDH release or Trypan blue exclusion) was found with up to 100 uM BDE-99 for 24 h (Madia et al. 2004). However, the mitochondrial activity that cleaves MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] was significantly decreased by BDE-99, with an IC50 of 46.5 uM (Madia et al. 2004). Further experiments in this glial cell line indicated that a PKC inhibitor (GF 109023X) or down-regulation of classical and novel PKCs by pre-incubation with a phorbol ester, did not affect the cytotoxicity of BDE-99 observed in the MTT assay (Madia et al. 2004). The membrane permeable calcium chelator BAPTA-AM also failed to affect BDE-99 cytotoxicity, suggesting that the observed effects on PKC and calcium homeostasis may not be involved in BDE-99 toxicity in astrocytoma cells.

In apparent contrast with the results of Kodavanti and Ward (2005), in rat cerebellar granule cells DE-71, but not DE-79, caused cytotoxicity (measured by the Trypan blue exclusion assay) at relatively low concentrations (IC_{50} = 7 uM) (Reistad et al. 2006). Cytotoxicity was partially reduced by an antagonist of the N-methyl D-aspartate (NMDA) receptor, and particularly by the lipid soluble antioxidant alpha-tocopherol, but not by a calcium chelator (Reistad et al. 2006). Interestingly, addition of an S9 fraction decreased the toxicity of DE-71, suggesting that possible metabolites possess lower cytotoxicity. An analysis of nuclear morphology and DNA laddering indicated that DE-71 caused apoptotic cell death, that was judged to be caspase 3-independent (Reistad et al. 2006). BDE-99 (50 uM) was also shown to cause apoptotic cell death and to increase levels of p53 in human astrocytoma cells (Madia et al. 2004).

As previously described, Reistad et al. (2006) found that neurotoxicity of DE-71 was prevented by an antioxidant; however, as they did not find any increase in the level of reactive oxygen species (ROS), they attributed the protective effects of alpha-tocopherol to an influence on membrane properties. However, the same authors found that in human neutrophil granulocytes, DE-71, as well as BDE-47, enhanced the production of ROS (Reistad and Mariussen, 2005). They also proposed, based on results with a number of inhibitors, that the effect of PBDEs on ROS was mediated through activation of tyrosine kinase, PI-3 kinase, PKC, phospholipase C, and intracellular calcium, leading to activation of NADPH oxidase, which plays a major role in ROS formation and the activation of the respiratory burst in these cells (Reistad and Mariussen, 2005). Another brominated flame retardant, TBBPA, also caused an increase of ROS levels in human neutrophil granulocytes, that may similarly involve tyrosine kinase, PKC, calcium and NADPH oxidase (Reistad et al. 2005). This same compound was further shown to increase intracellular [Ca^{++}], to increase ROS and to induce apoptotic cell death in rat cerebellar granule neurons (Reistad et al. 2007). The apparent discrepancy of these findings (similar effects of DE-71 and TBBPA in neutrophil granulocytes, different effects in cerebellar

granule cells) prompted a re-examination of the effects of DE-71 and other PBDEs in cerebellar granule neurons. These studies indicate that DE-71 causes cytotoxicity in mouse cerebellar granule neurons, with an IC50 (in the MTT assay) of 7.7 uM, almost identical to that reported by Reistad et al. (2006). The cytotoxicity of DE-71 was antagonized by the membrane permeable glutathione (GSH) delivery agent GSH ethyl ester, and by the antioxidant melatonin (Costa et al. 2007). DE-71 also caused a time-dependent increase in the levels of ROS, measured by DCF fluorescence. Furthermore, cell death induced by DE-71 was mostly apoptotic in nature. These findings were interpreted as indicating a role for oxidative stress in DE-71 neurotoxicity. Further evidence was provided by parallel experiments carried out in cerebellar granule neurons from *Gclm* (−/−) mice. *Gclm* (−/−) mice lack the modifier subunit of glutamate-cysteine ligase, the first and limiting step in the synthesis of GSH. As a result, cerebellar granule neurons from *Gclm* (−/−) mice have very low GSH levels compared to wild-type [*Gclm* (+/+)] mice (2.4 vs. 12.4 nmol/mg protein), and are more sensitive to the toxicity of agents causing oxidative stress, such as domoic acid (Giordano et al. 2006). In accordance with the hypothesis, cerebellar granule neurons from *Gclm* (−/−) mice were 8.5-fold more sensitive to the toxicity of DE-71 than neurons from *Gclm* (+/+) mice (IC_{50}s in the MTT assay = 0.9 vs. 7.7 uM). Further verification was provided by experiments in which cerebellar granule neurons from *Gclm* (+/+) mice were exposed to the GSH synthase inhibitor buthionine sulfoximine (BSO; 25 uM for 24 h), to decrease levels of GSH [from 12.5 to 3.7 nmol/mg protein, similar to the levels present in CGNs from *Gclm* (−/−) mice (2.4 nmol/mg protein)]. Under this condition, the toxicity of DE-71 was significantly increased (IC50 = 0.74 uM), and cerebellar granule neurons from *Gclm* (+/+) mice were as sensitive as CGNs from *Gclm* (−/−) mice, not treated with BSO. DE-71-induced increases in ROS levels and in apoptotic cell death were also more pronounced in cerebellar granule neurons from *Gclm* (−/−) mice than in their *Gclm* (+/+) counterparts.

Hippocampal neurons from wild-type mice were found to display lower GSH levels than cerebellar granule neurons (5.5 vs. 12.4 nmol/mg protein), and levels of GSH in hippocampal neurons from *Gclm* (−/−) mice were only 1.4 nmol/mg protein. Values of IC_{50} in the MTT assay for DE-71 in hippocampal neurons were 2.2 uM in *Gclm* (+/+) mice, and 0.31 uM in *Gclm* (−/−) mice. Hippocampal neurons thus appear to be more sensitive than cerebellar granule neurons to the toxicity of DE-71, possibly because of their lower GSH content. The ratio between the IC_{50}s in the two genotypes was 7.1, comparable to that observed in cerebellar granule neurons (Costa et al. 2007). Hippocampal astrocytes, whose levels of GSH in *Gclm* (+/+) mice were 21.4 nmol/mg protein, proved to be less sensitive to DE-71 toxicity (IC50 = 52.3 uM, similar to what was previously obtained in astrocytoma cells with BDE-99; Madia et al. 2004). These findings suggest that the neurotoxicity of DE-71, and that of other PBDEs (Giordano and Costa, unpublished) may involve oxidative stress, and is modulated by intracellular GSH content. In SH-SY5Y human neuroblastoma cells, Zhang et al. (2007) reported that BDE-47 (2–8 ug/ml) increases ROS levels, induces lipid peroxidation, and causes apoptotic cell death. These effects are not limited to nervous system cells. Indeed, an increase in oxidative stress, evidenced by increased lipid peroxidation and increased levels of oxidized glutathione (GSSG), was also found in liver of American kestrels (*Falco sparverius*) treated in ovo with a mixture of BDE-47, −99, 100, and −153 (Fernie et al. 2005). Increased levels of ROS were also found in human HepG2 hepatoma cells upon exposure to 10–100 uM BDE-209 (Hu et al. 2007), while postnatal exposure of mice to BDE-209 was reported to increase oxidative stress in sperm (Tseng et al. 2006).

Additional in vitro studies with PBDEs addressed aspects related to neurotransmitter uptake and release. Mariussen and Fonnum (2003) reported that DE-71 inhibited vesicular dopamine uptake in rat brain synaptic vesicles, with an IC_{50} of 8 uM. In contrast, DE-71 did not affect synaptosomal uptake of dopamine, GABA or glutamate. DE-79 and the decaBDE mixture DE-83R had no effect on vesicular or synaptosomal uptake (Mariussen and Fonnum, 2003).

Somewhat in contrast with these findings, Dingemans et al. (2007) reported that BDE-47 (20 uM) increased vesicular catecholamine release in PC-12 cells. The release of the neuropeptide vasopressin from hypothalamic preparations (tissue punches from the supraoptic and paraventricular nuclei) was shown to be inhibited by DE-71, BDE-47 and BDE-77 at micromolar concentrations (Coburn et al. 2007). Given the role of vasopressin in cognitive function (Gulpinar and Yegen, 2004), in addition to regulation of body fluid and cardiovascular function, it was suggested that neuroendocrine effect of PBDEs may play some role in developmental neurotoxicity (Coburn et al. 2007). Lastly, BDE-99 was found to stimulate the glutamate-nitric oxide-cGMP pathways in rat cerebellar granule neurons, thus confirming previous in vivo observations (Llansola et al. 2007).

Altogether, these in vitro studies indicate that PBDEs can elicit a number of effects on cell signaling and cell function. Such effects occur at micromolar concentrations that are similar to, or higher than those reported for PCBs. Clearly, research on potential mechanisms of PBDE neurotoxicity is only in its infancy, and further research is undoubtedly needed.

Toxicokinetic studies

Most aspects of the toxicokinetics of PBDEs have been summarized elsewhere (Darnerud et al. 2001; de Wit et al. 2002; Hakk and Letcher, 2003), and will not be discussed in detail. In adult rodents, lower brominated PBDEs (e.g. BDE-47, BDE-99, BDE-153) are usually well absorbed following oral exposure (Orn and Klasson-Wehler, 1998; Hakk et al. 2002; Staskal et al. 2006b). In contrast, absorption of decaBDE is much lower (10% of the dose) (Morck et al. 2003). PBDEs distribute to several tissues including the brain, and highest and more persistent concentrations are found in adipose tissue (Hakk and Letcher, 2003), however, this is not the case for BDE-209 (Morck et al. 2003). Tetra- and pentaBDEs are metabolized by mixed function oxidases to mono-and di-hydroxylated metabolites (Hakk et al. 2002; 2006; Hakk and Letcher, 2003; Malmberg et al. 2005; Marsh et al. 2004), while decaBDE is metabolized to lower brominated congeners (nona- and octaBDE) (Morck et al. 2003; Huwe and Smith, 2007). There appears to be a species difference in the rate of excretion, with a higher urinary excretion in mice (Orn and Klasson-Wehler, 1998). Gender differences are also observed, with males displaying a higher urinary excretion due to the binding of PBDEs to mouse major urinary protein (MUP), whose levels are much higher in males than females (Staskal et al. 2006b). The half-life of tetra- to hexa- PBDEs has been shown to range in mice and rats between 20 and 120 days (Hakk and Letcher, 2003; Geyer et al. 2004), with an increase proportional to the degree of bromination. In contrast, BDE-209 appears to be excreted more rapidly (Morck et al. 2003; Hakk and Letcher, 2003), though a half-life of 75 days has been reported in another study (Huwe and Smith, 2007).

Toxicokinetic studies with BDE-47 in developing mice (PND 10–28) have shown a reduced ability of young animals to excrete PBDEs, possibly due to a decreased urinary elimination, resulting in higher body burden compared to adults (Staskal et al. 2006a). In mice given BDE-47, BDE-85 or BDE-99, these compounds were shown to be secreted in milk, and suckling neonates had tissue concentrations higher than dams (Oskarsson and Moller, 2004; Darnerud and Risberg, 2006). In particular, levels of BDE-99 following maternal exposure in rats were found to be up to 17-fold higher in brain of pups compared to dams (Oskarsson and Moller, 2004). Administration of [^{14}C]-BDE-209 to pregnant rats resulted in low levels of radioactivity in the fetus (Riu et al. 2006), an observation also made by others with BDE-47, BDE-85 and BDE-99 (Darnerud and Risberg, 2006). However, Kuriyama et al. (2006) found that after a single administration of BDE-99 (0.06 or 0.3 mg/kg) to dams on GD 6, hepatic levels were much higher in pups than in dams on PND 1–22, suggesting that gestational exposure leads to long-term body burden. In support of this finding, Ceccatelli et al. (2006)

found that administration to rats of BDE-99 (1 or 10 mg/kg from GD 10 to GD 18) resulted in significant plasma and adipose tissue levels in pups at 120 days of age.

Overall, these toxicokinetics studies indicate that absorption, metabolism and excretion of PBDEs are congener-, species- and gender- dependent. Additionally, they show that substantial amounts of PBDEs are transferred to the pups through milk, and that pups have a decreased ability to eliminate PBDEs, leading to a higher body burden.

Relevance to humans

In the previous sections, as well as in Tables 7–10, the available information on PBDEs developmental neuroxicity, derived from animal and/or in vitro studies have been summarized. In contrast to the large data base on body burden (levels of PBDEs in serum, adipose tissue, breast milk), there is almost no information on possible adverse health effects in humans from PBDE exposure, including potential developmental neurotoxicity. Thus, any possible inference on potential risk for adverse nervous system effects in humans exposed to PBDEs in utero, or neonatally through breast milk or household dust, has to rely on animal data. In a traditional risk assessment approach, the applied dose would be the starting point for risk estimation. The NOEL values for PBDEs, determined in animal studies examining developmental neurotoxicity or thyroid hormone changes, range from 0.14 to 1.0 mg/kg/(day) (McDonald, 2005). In one case, the benchmark dose for BDE-99-induced changes in locomotor activity was calculated, and it was 0.31 mg/kg (Sand et al. 2004). By applying two safety factors (10x10) for interspecies extrapolation and intraspecies differences, and an additional factor (3) for insufficient data base, reference dose (RfD) values of 0.46 to 3.3 ug/kg/day (460–3300 ng/kg/day) are obtained. These values are not much dissimilar from the estimated exposure of infants to PBDEs (see Table 4). If one considers also the study by Kuriyama et al. (2005) with BDE-99, in which the dose of 0.06 mg/kg was the LOEL (low-observed-effect-level) for hyperactivity, applying all safety factors (10x10x10x3) provides a RfD of 20 ng/kg/day. By considering interspecies toxicokinetic differences, based on differences in half-lifes (Geyer et al. 2004;McDonald, 2005), which amount to about 50 fold, the safety factor for interspecies extrapolation could be 50 instead of 10. The resulting RfDs would then be 92–660 ng/kg/day, in the actual range of infant exposure (through breast milk), and close to the levels of toddler exposure through household dust and the diet.

Another approach consists in comparing body burden across species. This approach bypasses the need to quantify exposure from different routes and to consider species-specific toxicokinetics aspects, as body burden data are an integrated measure of exposure from all routes (McDonald, 2005). For example, following prenatal exposure to BDE-99 (1 mg/kg from GD 10 to GD 18) plasma levels of pups at PND 120 were 0.95 ng/ml (Ceccatelli et al. 2006). Assuming a total lipid content of rat plasma of 2 mg lipid/ml, this corresponds to 475 ng BDE-99/g lipid. It should be noted that the study by Ceccatelli et al. (2006) examined effects on gene expression in the uterus, rather than alterations in the nervous system; however, upon identical exposure, changes in sexual behavior and sweet preference were also found (Lichtensteiger et al. 2004; Lilienthal et al. 2006). Levels in human plasma as high as 580 and 460 ng/g lipid have been reported in maternal and fetal blood, respectively (Table 6; Mazdai et al. 2003). In the Fischer et al. (2006) family study, the toddler was found to have plasma PBDE levels of 418 ng/lipid (651 ng/g lipid if considering also BDE-209). These examples may represent a worst-case scenario, but indicate that adverse developmental effects are seen in animals at exposure levels relevant to humans, at least in North America. In another study, plasma levels of BDE-47 necessary to elicit a decrease of circulating T4 were found to be 421 ug/g lipid (Darnerud et al. 2007). This value would be about three orders of magnitude higher than levels found in humans. However, this study was carried out in adult rats, and sensitivity of developing animals may be higher.

As indicated earlier, an additional consideration is that in contrast to rodents, where total body half-lives of all PBDEs is in the order of several days or months, the terminal total body half -lives in humans have been estimated to be much longer, in the order of years for lower brominated congeners (e.g. BDE-47, 1.8 y; BDE-99, 2.9 y; BDE-154, 3.3 y; Geyer et al. 2004), while it is in the order of days to months for octa- to decaBDEs (Sjodin et al. 1999; Thuresson et al. 2006).

Whether the high levels of PBDEs in infants and children may result in adverse health effects, and specifically, in neurotoxicity, as would be predicted based on animal studies, is not known. In a study in Taiwan (Chao et al. 2007), 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. The daily intake of PBDEs for a breastfed infant was estimated as 20.6 ng/kg/day in this study, far below the estimated exposure levels in Canada (280 mg/kg/day; Jones-Otazo et al. 2005) or in the United States (306 ng/kg/day; Schecter et al. 2006a). In another study comparing maternal and fetal blood PBDE levels, no correlation was found with serum T_4 concentrations (Mazdai et al. 2003). Clearly, studies investigating the relationship between body burden of PBDEs and child development are needed, in order to validate the animal findings.

The USEPA had derived chronic oral references doses (RfD) for the commercial mixtures: penta (2 ug/kg/d), octa (3 ug/kg/d) and deca (10 ug/kg/d) (Jones-Otazo et al. 2005). However, these values were based on toxicological effects in the liver and not on developmental effects. Estimated exposure of an infant (through breast milk) is about 0.3 ug/kg/d (Table 4), with a range of 0.003 to 4.1 ug/kg/day, based on minimal and maximal concentrations of PBDEs in breast milk from Canada (Jones-Otazo et al. 2005). These values are within the current RfDs of most PBDEs. Recently, the USEPA has proposed RfD values for single congeners, based on developmental neurotoxicity (e.g. 100 ng/kg/day for BDE-47).

Overall perspective and research needs

Many issues need to be investigated before a clearer picture on possible risks of developmental neurotoxicity in children due to exposure to PBDEs can emerge. First, in this review, as in most of the literature, PBDEs are considered as a uniform class of chemicals, with possible toxicokinetic and relative potency differences, but sharing a common mechanism of action (which is still unknown). There is evidence for and against this concept. For example, all PBDEs tested so far, including higher brominated congeners, have been shown to produce alterations in locomotor behavior (Table 7). On the other hand, in vitro experiments suggest that octa-, nona-and deca-BDEs may have much lower biological activity (see Table 10). The Joint FAO/WHO Expert Committee on Food Additives stated in an evaluation of PBDEs that "data are inadequate to establish a common mechanism of action that would allow a single congener to be used as surrogate for total exposure or, alternatively, as the basis for establishing toxic equivalency factors" (JECFA, 2006).

A second issue, as pointed out by McDonald (2005), is that PBDEs may be converted to polybrominated dibenzo-*p*-dioxins (PBDDs) and dibenzofurans (PBDFs) when flame-retarded plastic material is subjected to thermal stress (Ebert and Bahadir, 2003). PBDDs and PBDFs have been found as impurities in commercial PBDE mixtures (Hanari et al. 2006), have been measured in adipose tissue (Choi et al. 2003), and share many of the toxicological characteristics of their chlorinated analogs (Birnbaum et al. 2003). High levels of PBDDs, exceeding those of chlorinated dioxins, have been found in fish and shellfish from the Baltic Sea, and their natural origin has been suggested (Haglund et al. 2007). Additionally, humans can also be directly exposed to hydroxylated BDEs, which are known to be a product of PBDE metabolism (Malmberg et al. 2005; Marsh et al. 2006). Hydroxylated PBDEs are found, for

example, in fish such as salmon (Marsh et al. 2004), and some may also have a natural origin. As said earlier, hydroxylated-PBDEs have a much greater affinity for TTR than PBDEs (Meerts et al. 2000).

A third important issue is that PBDEs cannot be considered in isolation, as if they were the only chemicals people are exposed to. For example, the structurally similar PCBs remain a widespread class of contaminants. Exposure to PCBs causes developmental neurotoxicity, as evidenced by animal studies and observations in humans (Seegal, 1996; Carpenter, 2006). PCBs have been shown to cause effects which are similar, albeit not identical, to those observed with PBDEs in many of the in vivo and in vitro experiments summarized in this review. Indeed in several cases, the effects of PBDEs were compared with those of PCBs, which were used as a sort of "positive" control. In a study in adult rats, Hallgren and Darnerud (2002) found that BDE-47 and Aroclor 1254 had at least an additive effect on serum T_4 levels. Exposure of neonatal mice to either BDE-99 or PCB-52 impaired spontaneous locomotor activity at 4 and 6 months of age (Eriksson et al. 2006). Of relevance is that while a low dose of each of these compounds did not produce any behavioral effect when given alone, upon co-exposure the same low doses of BDE-99 and PCB-52 produced significant behavioral alterations. These were equal, if not greater, than those caused by a high dose of each compound alone. This finding is suggestive of a strong synergistic effect. Verification of the potential interaction between PBDEs and PCBs is needed, before any conclusion can be drawn. Nevertheless, one should also consider that in addition to PBDEs and PCBs, exposure to several other developmental neurotoxicants (e.g. lead, methylmercury, perchlorate, dioxins etc.) can occur. The significance of these multiple co-exposures is still elusive, but their potential adverse effects on child neurodevelopment have been pointed out (Grandjean and Landrigan, 2006).

A fourth aspect relates to the possible mechanism(s) of developmental neurotoxicity of PBDEs. As evidenced by the summary of existing data, two general, and not mutually exclusive, modes of action are emerging, one related to effects of PBDEs on T_4, and the other involving a direct effect of PBDEs on the developing brain. Whether the hypothesized mechanisms of PBDE-induced hypothyroxemia (induction of UDPGT and interference with TTR) are operational in humans remains to be determined. For example, as the major T_4 transporter in humans is believed to be a thyroid-binding globulin (TBG), followed by TTR and albumin (Schussler, 2000; Palha, 2002), the impact of PBDE binding to TTR may be lower in humans than in rodents. Furthermore, hydroxylated PCBs bind to TBG with much lower affinity than to TTR (Lans et al. 1994), and the same may be true for hydrolated PBDEs. TTR may still facilitate the transport of OH-PBDEs in the brain (Meerts et al. 2000), though it has been shown that TTR is not indispensable for T_4 entry into the brain (Palha, 2002). Biochemical studies on direct effects of PBDE on the developing brain have yet to provide convincing evidence of precise mechanisms, though some indications (e.g. interference with signaling pathways, oxidative stress) are beginning to emerge.

In conclusion, available evidence indicates a high body burden of PBDEs, particularly in the North America population, and particularly in infants and young children. Evidence is accumulating indicating that in animals PBDEs cause developmental neuroxicity, by still unknown mechanisms, at dose levels not much different from reported levels of exposure in humans. The earliest reports on PBDEs in the environment and on their health effects date back to the early 1980s (Carlson, 1980; Andersson and Blomkvist, 1981). Given that PCBs were first detected in environmental samples in 1966 (Jensen, 1966), and that they still represent a prominent health and environmental issue, increased efforts in investigating adverse health effects of PBDEs and their underlying mechanisms are a matter of great relevance and urgency.

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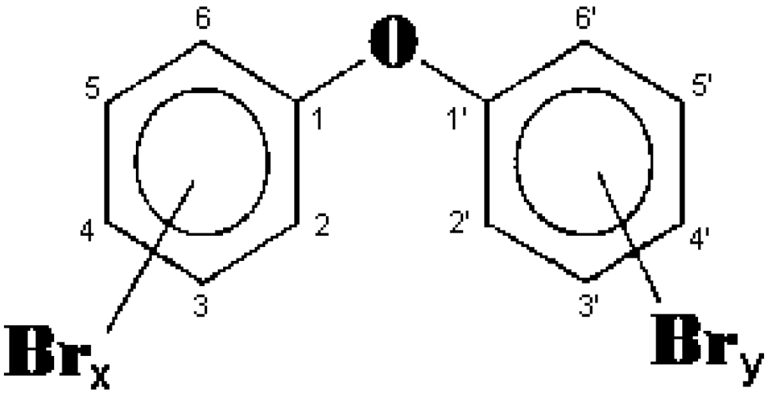

Fig. 1.
General chemical structure of PBDEs (x + y = 1 to 10).

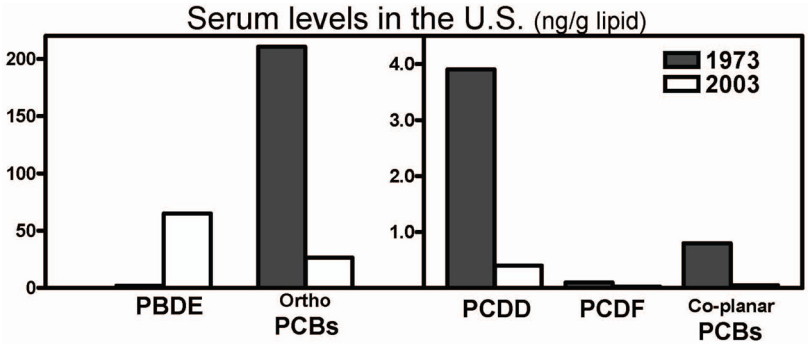

Fig. 2.

Serum levels (ng/g lipid) of polychlorinated dibenzodioxins (PCDD), polychlorinated dibenzo furans (PCDF), co-planar polychlorinated biphenyls (PCB), mono-ortho substitutes PCBs, and PBDEs in the U.S. population in 1973 and 2003. Data from Schecter et al. (2005).

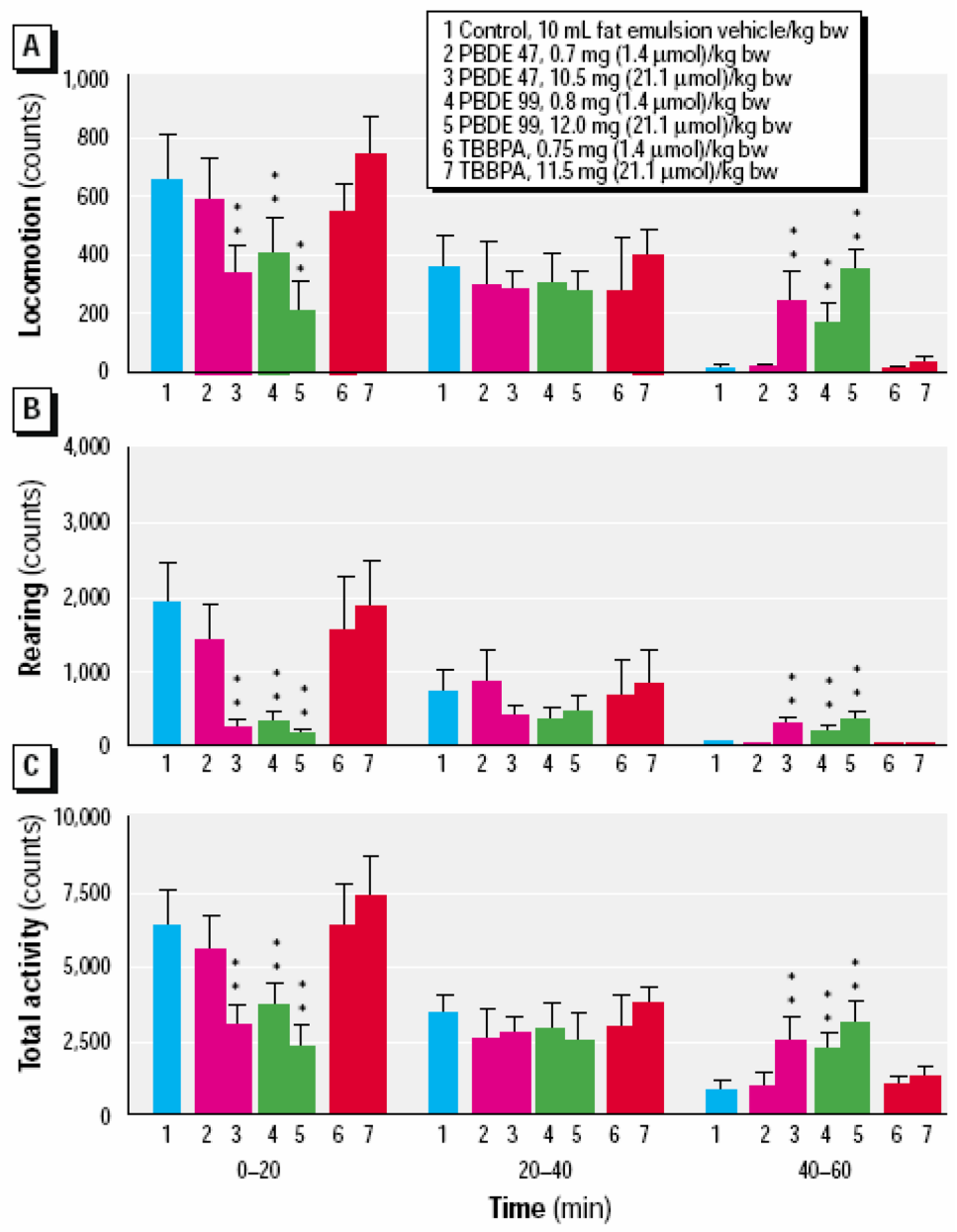

Fig. 3.

Spontaneous behavior in 4 month-old NMRI mice exposed to a single oral dose of BDE-47, BDE-99 and TBBPA (tetrabromo-bis-phenol A) on PND 10. From Eriksson et al. (2001) with permission.

Table 1

Major PBDE congeners or mixtures

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
DE-71[a]	PentaBDE technical mixture (BDE-99, 44%; BDE-47, 32%; BDE-100, 9%; BDE-153, 4 %)
DE-79[b]	OctaBDE technical mixture (BDE-183, 37%; BDE-197, 22%; BDE-207, 14%; BDE-196, 9%)

[a]Composition of DE-71 is from Wellington Laboratories (Guelph, ON, Canada). An analysis by La Guardia et al. (2006) similarly indicated the following congeners as the most abundant in DE-71: BDE-99 (49%), BDE-47 (38%), BDE-100 (13%), BDE-153 (5.5%). The European pentaBDE formulation Bromkal 70-5DE had a similar composition (Sjodin et al. 1998).

[b]Composition of DE-79 is from Wellington Laboratories (Guelph, ON, Canada). BDE-183 is a heptaBDE; BDE-197 and BDE-196 are octaBDEs; BDE-207 is a nonaBDE.

Table 2

Concentrations of ΣPBDEs in human milk (ng/g lipid)

Country	Year	N	Median	Range	Most prominent BDE congeners	Reference
U.S.A.	2001–04	59	30.1	6.2–418	BDE-47 BDE-153	Schecter et al. 2005a
U.S.A. (Boston)	2004–05	46	28	4–263	BDE-47 BDE-153	Wu et al. 2005
U.S.A. (Texas)	2002	47	34.0	6.1–419	BDE-47 BDE-99	Schecter et al. 2003
U.S.A. (Texas)	2004	25	43.0	8.9–246	ND	Ryan et al. 2006
U.S.A/Canada (Pacific Northwest)	2003	40	50.0	6–321	BDE-47 BDE-153	She et al. 2007
Canada	2001–02	92	22.1	0.84–956	BDE-47 BDE-99	Gill et al. 2004
Canada	2005	34	20	3.7–580	ND	Ryan et al. 2006
Sweden (Uppsala)	1996–99	93	3.15	0.91–28.2	BDE-47 BDE-153	Lind et al. 2003
Sweden (Uppsala)	2000–01	31	2.90	1.20–8.07	BDE-47 BDE-153	Lind et al. 2003
Sweden (Uppsala)	ND	39	3.37	1.14–28.2	BDE-47 BDE-153	Atuma et al. 2001
Sweden (Stockholm)	2000–01	15	2.14	0.56–7.72	BDE-47 BDE-153	Meironyte Guvenius et al. 2003
Norway	ND	151	2.34	0.95–21.05	BDE-47 BDE-153	Thomsen et al. 2005
Finland	1994–98	11	2.25	0.88–5.89	BDE-47 BDE-99	Strandman et al. 2000
Faroe Islands	1999	9	5.8	4.7–13	BDE-153 BDE-47	Fangstrom et al. 2005
Russia	2000	25	0.81	0.51–3.62	BDE-47 BDE-153	Polder et al. 2006
Russia	2003–04	10	0.96	0.46–1.7	BDE-153 BDE-47	Tsydenova et al. 2007
Poland	2004	22	2.0	0.8–8.4	BDE-47 BDE-153	Jaraczewska et al. 2006
Czech Republic	2003	103	0.61*	0.30–1.43*	BDE-47*	Kazda et al. 2004
Germany	2001–03	93	1.78	ND	BDE-47 BDE-153	Vieth et al. 2004
Germany	2002	79	3.02	0.85–24.6	BDE-47 BDE-153	Furst, 2006
United Kingdom	2001–03	54	6.3	0.3–69	BDE-47 BDE-153	Kalantzi et al. 2004
France	2005	23	2.65	1.39–11.63	BDE-47 BDE-99	Antignac et al. 2006
Italy	1998–01	39	ND	1.6–4.1	BDE-47 BDE-99	Ingelido et al. 2007
Turkey	2004	37	ND	0.0–0.4	BDE-47 BDE-99	Erdogrul et al. 2004
Japan	1999	13	~1.3	0.56–291	BDE-47 BDE-28	Akutsu et al. 2003
Japan	2003–04	105	1.28	0.01–23	BDE-47 BDE-99	Eslami et al. 2006
Japan	ND	12	ND	0.67–2.84	BDE-47 BDE-153	Ohta et al. 2002
Japan	ND	89	1.54	0.49–4.55	BDE-47 BDE-153	Inoue et al. 2006

Country	Year	N	Median	Range	Most prominent BDE congeners	Reference
South China	ND	27	3.5	1.5–17	BDE-47 BDE-153	Bi et al. 2006
Taiwan	2000–01	20	3.65	ND	BDE-47 BDE-153	Chao et al. 2007
Indonesia	2001–03	30	1.5	0.49–13	BDE-47 BDE-153	Sudaryanto et al. 2007
Vietnam	2000	10	1.1	ND	BDE-153 BDE-47	Sudaryanto et al. 2005
Cambodia	2000	11	1.7	ND	BDE-47 BDE-99	Sudaryanto et al. 2005
Korea	2004	9	2.6	ND	BDE-47 BDE-153	Sudaryanto et al. 2005
Australia	2002–03	157	11.0	6.1–18.7	BDE-47 BDE-99	Toms et al. 2007

* Values are for BDE-47 only. ND, not determined.

Table 3

Time-related trend of PBDE levels in human milk (ng/g lipid)

Country	ΣPBDE (year)	ΣPBDE (year)	Fold increase	Reference
Japan	Not detected (1973)	1.39 (2000)	N.M.	Akutsu et. al. 2003
Sweden	0.07 (1973)	4.02 (1997)	57	Meironyte et al. 1999
Germany	1.87 (1992)	3.75 (2002)	2	Furst, 2006
Faroe Islands	1.9 (1987)	8.2 (1999)	4	Fangstrom et al. 2005
Canada	3.0 (1992)	22.0 (2002)	7	Ryan et al. 2002

N.M. = not meaningful

Table 4

Estimated exposure of North America population to PBDEs

Infant	Child (1–5)	Child (6–11)	Adolescent (12–19)	Adult	Reference
ND	49.3	14.4	9.1	7.7	Lorber et al. 2007
ND	ND	ND	ND	16	McDonald, 2005
ND	12–38	ND	ND	0.75–4.5	Wilford et al. 2005
280	20	ND	ND	2.2	Jones-Otazo et al. 2005
306*	2.6*	1.7*	1.4*	1.0*	Schecter et al. 2006a

Data are in ng/kg body weight/day.

*Exposure through diet only. ND, not determined.

Table 5

Serum levels of PBDEs in a family from Northern California in 2004

Family member	Age	Σ(5)PBDEs*	BDE-47	BDE-99	BDE-153	BDE-209
Father	35	64	32	4	19	23
Mother	36	106	60	10	22	14
Female child	5	247	137	28	49	143
Male toddler	1.5	418	245	37	75	233

PBDE levels are expressed as ng/g lipid weight.

*Sum of five BDEs (BDE-47, BDE-99, BDE-100, BDE-153, BDE-154). Adapted from Fischer et al. (2006).

Table 6

PBDE levels in maternal and fetal blood

Country	Year	N	Maternal blood	Fetal blood	Most prominent BDE congener	Reference
U.S.A.	1997–99	50	<10–511 (10)	ND	*	Petreas et al. 2003
U.S.A.	1999–01	24	5.3–320 (21)	ND	BDE-47	Bradman et al. 2007
U.S.A.	2001	15	15–580 (580)	14–460 (39)	BDE-47	Mazdai et al. 2003
Sweden	2000–01	15	0.71–8.39 (2.07)	0.46–4.28 (1.69)	BDE-47	Meironyte Guvenius et al. 2003
France	2005	26	0.21–1.91 (0.69)	0.14–1.08 (0.41)	**	Antignac et al. 2006
Japan	ND	89	0.74–21.19 (2.99)	ND	BDE-209	Inoue et al. 2006
China	ND	21	1.6–17 (4.4)	1.5–12 (3.9)	BDE-47 BDE-153 (fetus)	Bi et al. 2006

Values of ΣPBDE levels are expressed as ng/g lipid. Results indicate range and median (in parenthesis).

* BDE-47 only;

** BDE-153 only. ND = not determined.

Table 7

Neurobehavioral effects of developmental PBDE exposure

PBDE	Species	Treatment	Effect	Reference
BDE-47	NMRI mice	0.7, 10.5 mg/kg oral in el/po on PND10	Decreased habituation at 2, 4 mo. (high dose only)	Eriksson et al. 2001
BDE-47	Wistar rats	0.14, 0.7 mg/kg, oral, in po, GD6	Increased locomotor activity on PND35 and 70 (0.7 mg/kg). Decreased thigmotaxis	Kuriyama et al. 2004a
BDE-99	NMRI mice	0.2, 0.4, 12.0 mg/kg, oral, in el/po, PND10	Decreased habituation at 4 mo. (high dose only)	Viberg et al. 2004b
BDE-99	NMRI mice	8 mg/kg, oral, in el/po, PND3 or 10 or 19	Decreased habituation at 4 mo. Only if treated on PND 3 or 10	Eriksson et al. 2002
BDE-99	NMRI mice	8 mg/kg, oral, in el/po, PND10	Decreased habituation at 2 mo. Altered response to nicotine at 2 mo.	Viberg et al. 2002
BDE-99	C57/BI mice	0.4, 0.8, 4.0, 8.0, 16.0 mg/kg, oral in el/po, PND10	Decreased habituation at 2 mo at 8.0 and 16.0 mg/kg. No gender differences	Viberg et al. 2004a
BDE-99	Wistar rats	0.06, 0.3 mg/kg, oral, in po, GD6	Hyperactivity (0.3 mg/kg) on PND36, and at both doses on PND71. No effect on male sexual behavior	Kuriyama et al. 2005
BDE-99	Long Evans rats	1, 10 mg/kg, sc, in olive oil, GD10- GD18	Increased sweet preference in males on PND120 (10 mg/kg only)	Lilienthal et al. 2006
BDE-99	Long Evans rats	1, 10 mg/kg, sc in olive oil, GD10–18	Decreased sexual behavior in females	Lichtensteiger et al. 2004
BDE-99	CD-1 Swiss mice	0.6, 6.0, 30.0 mg/kg, oral, in co, GD6-PND21	Hyperactivity on PND22 and 60, not on PND120. Decreased thigmotaxis at 2 mo	Branchi et al. 2002
BDE-99	CD-1 Swiss mice	18 mg/kg, oral, in co, by self administration, GD6-PND21	Hyperactivity on PND34, not at PND60, 90, 120	Branchi et al. 2005
BDE-99	NMRI mice	0.8, 12.0 mg/kg, oral, in el/po, PND10	Decreased habituation at 2 and 4 mo at both doses. Decreased performance in Morris swim maze at 5 mo.	Eriksson et al. 2001
BDE-153	NMRI mice	0.45, 0.9, 9.0 mg/kg, oral, in el/po, PND10	Decreased habituation at 2, 4, 6 mo at the two higher doses. Effect increases with age. Decreased performance in Morris swim maze at 6 mo. (0.9 and 9.0 mg/kg)	Viberg et al. 2003a
BDE-183	NMRI mice	15.2 mg/kg, oral, el/po, PND3 or 10	Decreased habituation at 2 mo. (PND3 only)	Viberg et al. 2006
BDE-203	NMRI mice	16.8 mg/kg, oral, in el/po, PND3 or 10	Decreased habituation at 2 mo. Decreased performance in the Morris swim maze (PND10 only)	Viberg et al. 2006
BDE-206	NMRI mice	18.5 mg/kg, oral, in el/po PND3 or 10	Decreased habituation at 2 mo (PND10 only)	Viberg et al. 2006
BDE-209	NMRI mice	2.22, 20.1 mg/kg, oral, in el/po, on PND3 or 10 or 19	Decreased habituation at 2,4, 6 mo. at the high dose, only if exposed on PND3	Viberg et al. 2003b
BDE-209	Sprague Dawley rats	6.7, 20.1 mg/kg, oral, in el/po, PND3	Decreased habituation at 2 mo with both doses. Altered response to nicotine at 2 mo (high dose only)	Viberg et al. 2007a
BDE-209	C57BL6/J mice	6, 20 mg/kg, oral, in el/po, PND2–15	Developmental delay in palpebral reflex. Hyperactivity in males (20 mg/kg) at PND70, not at 1 year	Rice et al. 2007
DE-71	Long Evans rats	5, 30, 100 mg/kg, oral, in co, GD6- PND21	No effect on motor activity	MacPhail et al. 2003 (abstract)
DE-71	Rats	1, 5, 30, 100 mg/kg, oral, in co, GD6-PND21	No effect on startle reflex. Decreased fear conditioning in adult males	Taylor et al. 2003 (abstract)
DE-71	Long Evans rats	30 mg/kg, oral, in co, PND6–12	Impaired learning in a visual discrimination task on PND30–70. No effect on attention. Subsensitivity to scopolamine effect on attention	Dufault et al. 2005
DE-71	Killifish (*Fundulus heteroclitus*)	0.001–100 ug/L in embryos	Hyperactivity (from 0.001 dose level). Decreased predation avoidance (from 0.01 dose level)	Timme-Laragy et al. 2006

Abbreviations: co, corn oil; el/po, egg lecithin/peanut oil.

Table 8

Effect of developmental exposure to PBDEs on plasma T_4 levels

PBDE	Species	Treatment	Effect	Reference
BDE-47	Wistar rats	0.14, 0.7 mg/kg, oral, in po, GD6	Decrease in females on PND14, not on PND1, 22. Decrease in dams on PND1, not on PND22	Talsness et al. 2004; Kuriyama et al. 2004b
BDE-99	CD-1 Swiss mice	18 mg/kg, oral, in co, GD6- PND21, by self administration	N.S. decrease on PND22	Branchi et al. 2005
BDE-99	NMRI mice	80 umol/kg, oral, in co, every 3 days, GD4- PND17	No effect	Skarman et al. 2005
BDE-209	C57BL6/J mice	6, 20 mg/kg, oral, in el/po, PND2–15	Decrease in males on PND21 (20 mg/kg)	Rice et al. 2007
DE-71	Long Evans rat	0.3, 1, 3, 10, 30, 100, 300 mg/kg, oral in co, PND28–31 (female only)	Decrease on PND32. No effects on T_3	Zhou et al. 2001
DE-71	Long Evans rats	1, 10, 30 mg/kg, oral, in co, GD6-PND21	Decrease on GD20 (fetus), PND4, 22 (10,30 mg/kg) Recovery by PND36	Zhou et al. 2002
DE-71	Sprague Dawley rats	18 mg/kg, oral in co, GD6- PND18	Decrease on PND18. Recovery by PND31	Ellis-Hutchings et al. 2006
DE-71	Rats	1, 5, 30, 100 mg/kg, oral, in co, GD6-PND21	Decrease on PND5, 14 (5–100 mg/kg)	Taylor et al. 2003 (abstract)
DE-71	Ranch mink (*Mustela vison*)	1, 5, 10 ppm in feed for 11 wks from weaning	Decrease at 5, 10 ppm. Decrease of T_3	Martin et al. 2004
Bromkal- 705DE	NMRI mice	80 umol/kg, oral, in co, every 3 days GD4-PND17	Decrease on PND11. Recovery by PND18	Skarman et al. 2005
DE-79	Long Evans rats	0.3, 1, 3, 10, 30, 60, 100 mg/kg, oral in co, PND28–31 (female only)	Decrease on PND32. No effect on T_3	Zhou et al. 2001
DE-83R	Long Evans rats	0.3, 1, 3, 10, 30, 60, 100 mg/kg, oral in co, PND28–31 (female only)	No effect	Zhou et al. 2001

Abbreviations: co, corn oil; el/po, egg lecithin/peanut oil; N.S., not significant.

DE-83R is a >98% decaPBDE mixture.

Table 9

Neurochemical effects of developmental exposure to PBDEs

PBDE	Species	Treatment	Effect	Reference
BDE-47	C57BI/6 mice	6.8 mg/kg, oral in el/po, on PND10	Decrease GluR subunits NR2B, GluR1, CaMKII	Dingemans et al. 2007
BDE-99	NMRI mice	0.2,0.4,12.0 mg/kg oral, in el/po, on PND10	Decreased NR in hippocampus at 4 mo., only at 12 mg/kg	Viberg et al. 2004b
BDE-99	NMRI mice	12 mg/kg, oral in el/po, on PND10	On PND12 changes in a number of proteins in hippocampus, striatum (proteomics analysis)	Alm et al. 2006
BDE-99	Wistar rats	30 mg/kg, sc, in olive oil, GD2–9	Increase in cGMP, NMDA-stimulated cGMP, calmodulin , soluble GC alpha subunit. No change in nNOS	Llansola et al. 2007
BDE-153	NMRI mice	0.45, 0.9, 9.0 mg/kg, oral, in el/po, on PND10	Decreased NR in hippocampus on PND180 (9.0 mg/kg only)	Viberg et al. 2003a
BDE-209	NMRI mice	20.1 mg/kg, oral, in el/po, on PND3	Decreased BDNF, Gap-43, CaMKII at PND10, not at PND4	Viberg et al. 2007b (abstract)
DE-71	Ranch mink	0.01, 0.05, 0.25 mg/kg, in feed, GD0-PND42 (weaning)	No effects on MR, NR, AChE, ACh levels (PND 42, 190)	Bull et al. 2007

Abbreviations: el/po, egg lecithin/peanut oil; ACh, acetylcholine; AChE, acetylcholinesterase; MR, muscarinic receptors; NR, nicotinic receptors; GC, guanylate cyclase; nNOS, neuronal nitric oxide synthase.

Table 10

In vitro effects of PBDEs in neuronal or astroglial cells

PBDE	Cell type	Concentration	Effect	Reference
BDE-47	CGN rat	10–50 uM	Increased PBDU binding (10 uM). Increased LDH release (100 uM)	Kodavanti et al. 2005
BDE-47	PC12 cells	2, 20 uM	Increased Ca^{++} and increased vesicular release of catecholamines (both at 20 uM)	Dingemans et al. 2007
BDE-47	SON tissue punches from LE and SD rats	5, 15 uM	Decreased vasopressin release at both concentrations	Coburn et al. 2007
BDE-47	SH-SY5Y (human neuroblastoma)	4–16 uM	Increased levels of ROS and lipid peroxidation. Increased apoptotic cell death	Zhang et al. 2007
BDE-77	CGN rat	10–50 uM	Increased PBDU binding at 30 uM	Kodavanti et al. 2005
BDE-77	SON tissue punches from LE and SD rats	15 uM	Decreased vasopressin release	Coburn et al. 2007
BDE-99	CGN Wistar rat	0.1, 0.3, 1.0 uM	Increased cGMP, NMDA- stimulated cGMP, calmodulin, soluble GC	Llansola et al. 2007
BDE-99	1321N1 cells (human astrocytoma)	1–100 uM	Decreased cell viability (MTT, IC50=47 uM). Increased translocation of PKC,(100 uM). Increased apoptosis and p53 (50, 100 uM). No increase in LDH release.	Madia et al. 2004
BDE-99	PC12 cells, rat astrocytes	?uM	Increased Ca^{++}	Smolnikar et al. 2001 (abstract)
BDE-99	CGN rat	10–50 uM	Increased PDBU binding (10 uM)	Kodavanti et al. 2005
BDE-100	CGN rat	10–50 uM	Increased PBDU binding (10 uM)	Kodavanti et al. 2005
BDE-153	CGN rat	10–50 uM	Increased PBDU binding (10 uM)	Kodavanti et al. 2005
DE-71	Rat brain synaptosomes	2–20 uM	Inhibition of vesicular dopamine uptake (5 uM). No effect on synaptosomal uptake of dopamine, GABA, glutamate	Mariussen and Fonnum, 2003
DE-71	CGN rat	2–100 uM	Increased arachidonic acid release (10 ug/ml)	Kodavanti and Derr-Yellin, 2002
DE-71	CGN rat	6–60 uM	Increased PBDU binding. No LDH release up to 50 ug/ml	Kodavanti and Ward, 2005
DE-71	Microsomes and mitochondria from rat brain areas	6–60 uM	Decreased microsomal and mitochondrial Ca^{++} uptake (>3 ug/ml).	Kodavanti and Ward, 2005
DE-71	CGN rat	2–20 uM	Increased apoptotic cell death. Prevented by Vit. E but no increase in ROS. No increase in Ca^{++} influx	Reistad et al. 2006
DE-71	SON tissue punches from LE and SD rats	10, 30 uM	Decreased vasopressin release (30 uM)	Coburn et al. 2007
DE-71	Rat cortical neurons	1–30 uM	Increased MAPK phosphorylation	Mundy et al. 2002
DE-71	CGN mouse	1–50 uM	Increased levels of ROS. Increased apoptotic cell death	Costa et al. 2007
DE-79	CGN rat	2–100 uM	No effect on arachidonic acid release	Kodavanti and Derr-Yellin, 2002
DE-79	CGN rat	6–60 uM	No effect on PBDU binding, microsomial and mitochondrial Ca^{++} uptake	Kodavanti and Ward, 2005
DE-79	Rat brain synaptosomes	2–20 uM	No effect on neurotransmitter uptake	Mariussen and Fonnum, 2003
DE-83R	Rat brain synaptosomes	2–20 uM	No effect on neurotransmitter uptake	Mariussen and Fonnum, 2003

Abbreviations: CGN, cerebellar granule neurons; SON, supraoptic nerve; LE, SD rats, Long-Evans, Sprague Dawley rats ; GC, guanylate cyclase.