Curr Envir Health Rpt (2014) 1:101–112
DOI 10.1007/s40572-014-0010-3

SYNTHETIC CHEMICALS AND HEALTH (M PORTA, SECTION EDITOR)

Developmental Exposure to Polybrominated Diphenyl Ethers and Neurodevelopment

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Published online: 24 April 2014

Abstract Exposure to polybrominated diphenyl ethers (PBDEs) during sensitive developmental windows can interfere with cognitive function and behavior, which are critical components of neurodevelopment. The association between developmental exposure to PBDEs and neurodevelopment has been extensively studied using animal models. In this review, we focus on the accumulating evidence in humans. Despite methodologic, geographic, and temporal differences between studies, the majority of the epidemiologic evidence supports that early-life exposure to PBDEs measured during pregnancy and/or during childhood is detrimental to child neurodevelopment in domains related to child behavior, cognition, and motor skills. While the precise mechanism of action of PBDEs on neurodevelopment is unknown, PBDE-induced neurotoxicity via thyroid hormone disruption and direct action of PBDEs on the developing brain have been proposed and tested. Additional studies are suggested to better understand how early-life and/or childhood PBDE exposures, including exposure to specific PBDE congeners, impact neurodevelopmental indices.

Keywords Polybrominated diphenyl ethers · Neurodevelopment · Epidemiology · Perinatal · Developmental exposure

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Introduction

Neurodevelopmental processes begin soon after conception and, in humans, continue through the first years of life, and through adolescence into early adulthood [1]. Neurodevelopment can be disrupted leading to neurodevelopmental disorders, which are a group of conditions associated with impaired learning, language, or behavior. One or more of these conditions affect 17 % of children under 18 years of age in the US [2]. In 2009, 19 % of US children between 4 and 17 years of age had a parental report of difficulties with a broad range of symptoms including control of emotions, concentration, behavior, or interacting with other people [3]. According to the National Health Interview Survey in 2010, 5 million US children aged 3–17 years (8 % of this age group) had ever received a diagnosis of attention-deficit/hyperactivity disorder (ADHD) [4]. ADHD is characterized by impulsive behavior and inattention and often affects cognitive abilities involved in executive function [5]. In the US, ADHD diagnoses have increased over time, and are now considered the most commonly diagnosed neurobehavioral disorders of childhood [6]. A diagnosis of ADHD often co-occurs with learning disabilities and other behavioral disorders such that 28 % of children diagnosed with either learning disabilities or ADHD reported having been diagnosed with both conditions [7]. It has also been estimated that approximately one third of childhood ADHD cases persist into adulthood [8]. Studies examining the economic impacts including costs related to healthcare, special education, parental work loss, disciplinary actions, and the juvenile justice system estimate that ADHD is associated with US$12,005 and US$17,458 per affected individual and US$42.5 billion annually (based on a conservative 5 % population prevalence in the US) [9].

Exposure to environmental chemicals occurring during sensitive development windows can interfere with cognitive function and behavior, both of which are critical components

of neurodevelopment. Polybrominated diphenyl ethers (PBDEs) are a group of 209 organohalogenated compounds ("congeners", numbered according to their degree of bromination and position of bromine atoms on the diphenyl ether backbone) that are produced as three commercial mixtures — penta-, octa-, and deca-brominated diphenyl ethers (BDEs) (Fig. 1). The penta-BDE mixture is 24–38 % BDE with four bromines (e.g., BDE-47), 50–60 % BDE with five bromines (e.g., BDE-99, 100), and 4–8 % BDE with six bromines (e.g., BDE-153, 154). Octa-BDE mixture is 10–12 % BDE with six bromines, 44 % BDE with seven bromines, 31–35 % with eight bromines, 10–11 % BDE with nine bromines, and <1 % fully brominated (BDE-209). The Deca-BDE mixture contains a small amount of BDE with eight bromines, <3 % of BDE with nine bromines, and >97 % BDE-209 [10•].

PBDEs have been among the most highly used chemical compounds for reducing flammability because of their low cost and availability [11, 12]. They have been added to a wide variety of consumer products including furniture, textiles, electronics, and construction materials to reduce product flammability and meet regulatory requirements. Because PBDEs are additive compounds and are not chemically bound to consumer products, they have the propensity to migrate into the external environment [13]. They are persistent, organic chemicals, are lipophilic, and can bioaccumulate in fatty tissues. Their estimated half-life is 1.6 years in sediment [14] and 1.8–6.5 years in humans [15]. Therefore, PBDEs have become ubiquitous contaminants, detectable in humans, in animals, and in all aspects of the environment [16•, 17].

PBDE exposure varies geographically, with age, and over time [16•]. While concentrations measured in food from Europe, Asia, and the US are similar, household dust concentrations in the US greatly exceed measurements from Europe and most Asian countries [18–21]. In humans, PBDE body burdens are approximately an order of magnitude higher in US individuals compared with Europeans and Asians [16•], implicating dust as the principal exposure pathway [22]. In cross-sectional studies, children have, on average, 2- to10-fold higher PBDE concentrations than adults [23–25]. This is concerning because neonates and children have rapidly developing nervous systems and reduced abilities to metabolize and excrete environmental contaminants they encounter [26].

In response to their ubiquity and concern over associated health effects, Europe banned penta- and octa-BDEs outright in 2004 and prohibited the use of deca-BDEs in electronics and electrical equipment in 2006 [27]. In 2004, there was a voluntary phase-out of penta- and octa-BDEs in the US. This voluntary phase-out followed a series of US states, including

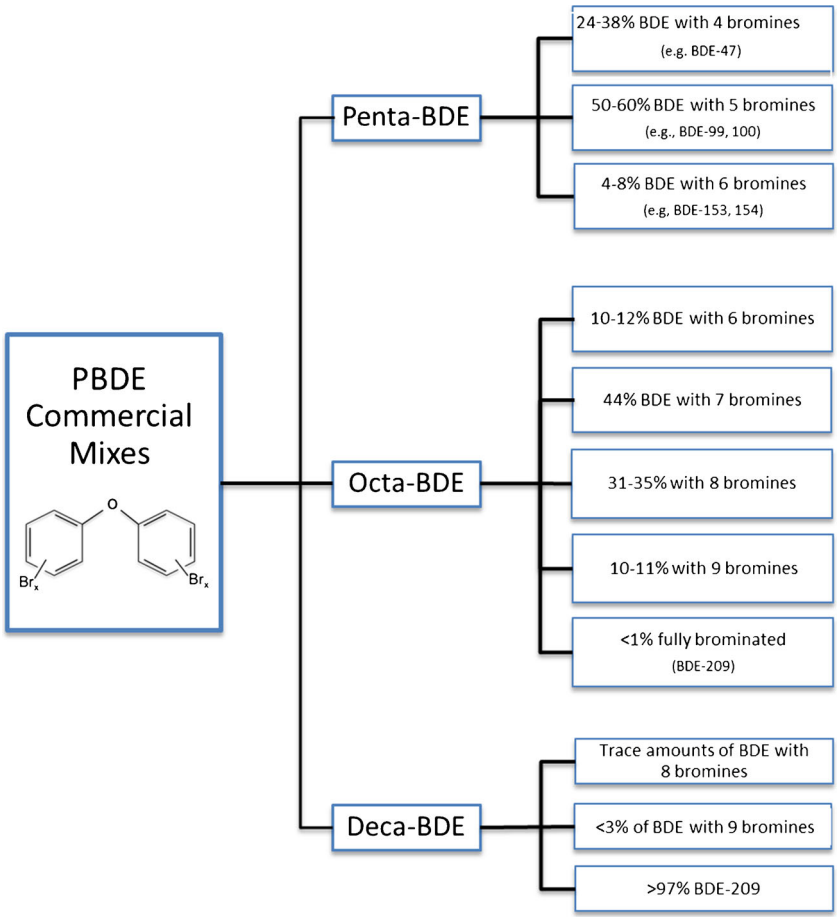

Fig. 1 PBDE commercial mixtures. (Adapted from: Birnbaum LS, Staskal DF (2004) Brominated flame retardants: cause for concern? Environmental health perspectives 112: 9–17) [10•]. *PBDE* polybrominated diphenyl ether, *BDE* brominated diphenyl ether

California, banning penta- and octa-BDEs. Interestingly, California's state-level flammability standard (TB-117) was one of the original driving forces behind the widespread use of PBDEs in upholstered furniture. Shortly after the removal of penta- and octa-BDEa, deca-BDE was also phased out of production over the course of 3 years beginning in 2009 [28•]. In Asia, China is the major producer of PBDEs. However, the production has decreased in recent years because of concerns about dioxin production when materials containing deca-BDEs are burned and the availability of other non-PBDE flame-retardant compounds [29]. Despite the worldwide reduction in production and use, it is widely believed that like other persistent organic pollutants, long-term exposure will continue long after PBDE production has ceased. This will occur through both direct exposure to emissions from PBDE-containing products that remain in use and by indirect dietary exposure occurring as a consequence of these emissions escaping into the outdoor environment and biomagnifying in the food chain [30].

The association between developmental exposure to PBDEs and neurodevelopment has been extensively studied using animal models. In this review, we highlight key animal studies but focus on the accumulating evidence in humans. PubMed and Google Scholar searches were performed in November 2013 with the search terms Polybrominated Diphenyl Ethers OR PBDE OR BDE AND neurodevelopment. We included all full-text articles in English published prior to November 2013. References of all articles were reviewed to identify additional matching articles.

Toxicology

Detailed reviews of animal evidence on the effects of developmental exposure to PBDEs on neurodevelopment are available [31•, 32, 33]. In brief, Eriksson and colleagues conducted a series of experiments exposing neonatal mice to individual PBDEs (including BDE-47, BDE-99, BDE-153, BDE-183, BDE-203, BDE-206, and BDE-209) on either postnatal day 3, 10, or 19. They observed that with some variation between congeners, exposure was associated with changes in spontaneous behavior (increased locomotor activity consistent with hyperactivity), habituation, learning, and memory functions [34–38]. The neurodevelopmental effects were apparent when exposure occurred within the period of rapid brain growth corresponding to the first 2 weeks after birth (analogous to the human perinatal period beginning during the third trimester and continuing through the first 2 years of life) [35, 39]. Effects did not vary by sex or mouse strain [40] and appeared to worsen with age, such that PBDE-related effects on altered spontaneous behavior and reduced habituation capabilities were more pronounced as the animals aged [34, 36–38]. Effects on neurodevelopment were corroborated by other investigators who found that in mice, perinatal PBDE exposure was associated with impaired learning and poorer functioning on memory tasks [41–44], altered locomotor activity, increased hyperactivity [45–49], and increased impulsivity, particularly in adult animals [50]. In rats, similar detrimental effects on attention and learning were also observed [43, 51].

Epidemiology: Summary of the Evidence

Only a small number of studies have examined the relationship between prenatal and childhood PBDE exposure and neurodevelopment in humans (Table 1). Among the eight studies identified, three are from Europe (one from the Netherlands and two from Spain) [52••, 53••, 54••], three are from the US (New York, California, and North Carolina) [55••, 56••, 57••], and two are from Asia (Taiwan) [58••, 59••]. The studies examining the impact of prenatal PBDEs and neurodevelopment during childhood are necessarily longitudinal while those examining the impact of childhood exposure on neurodevelopmental indices are cross-sectional. The prospective studies identified had a size range of 36–288 participants.

In the Netherlands, Roze and colleagues measured five BDE congeners (not including BDE-209, the fully brominated congener that is the predominant component of the decaBDE formulation) in 62 maternal blood samples collected from women during pregnancies occurring in 2001 and 2002 [54••]. PBDE concentrations in maternal blood are highly correlated with cord blood concentrations [60]. They compared PBDE concentrations in maternal blood to a large battery of motor, cognitive, and behavioral tests in children aged 5–6 years. They reported significant correlations between some individual BDE congeners and impaired fine manipulative abilities (BDE-154) and sustained attention (BDE-47, −99, −100), but also significant correlations between selective BDE congeners and improved selective attention and internalizing behavior. The number of comparisons conducted and the limited adjustment for relevant confounders are important limitations of this analysis.

In Spain, Gascon and colleagues measured 19 BDE congeners (not including BDE-209) in cord and peripheral blood from 88 children born in 1997–1998 and in peripheral blood samples from 156 additional children at age 4 years [53••]. They evaluated the association with motor, cognitive, and behavioral outcomes at age 4 years. They analyzed only BDE-47 (as a dichotomous measure) because it was the dominant congener and the only one detected in over 50 % of samples. Detectable levels of childhood BDE-47 exposure were associated with increased risk of attention (but not hyperactivity) symptoms and poorer social competency scores. Detectable levels of prenatal and childhood BDE-47 were both associated with lower cognitive and motor function,

Table 1 Summary of epidemiologic evidence

Author/Year [Location]	Exposure Information	Outcome Information (age at assessment)	Key Findings
Roze et al. 2009 [54] [Netherlands]	Matrix: maternal blood during 35th wk of pregnancy (n=62) Collection: 2001-2002 PBDEs measured: 47, 99, 100, 153, 154	Movement ABC (5-6)[a]	--
		Touwen's age-specific neurologic examination (5-6)[a]	correlation with worsening fine manipulative ability (BDE-154)
		Developmental Coordination Disorder Questionnaire, DCD-Q (5-6)[a]	--
		Wechsler Preschool and Primary Scale of Intelligence, revised, WPPSI-R (5-6)[b]	--
		Neuropsychological Assessment--2nd ed., NEPSY-II (5-6)[b]	--
		Rey's Auditory Verbal Learning Test, AVLT (5-6)[b]	correlation w/ worse verbal memory (BDE-153); correlation w/ worse sustained attention (BDE-47); correlation w/ worse sustained attention (BDE-47, 99, 100), correlation with better selective attention (BDE-47)
		Child Behavior Checklist, CBCL (5-6)[c]	correlation w/ fewer total and internalizing behavior problems (BDE-99, 100)
		CBCL Teacher's Report Form (5-6)[c]	correlation w/ fewer internalizing behavior problems (BDE-47, 99, 100)
		ADHD questionnaire by Scholte et al. 2004 (5-6)[c]	--
		McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population (4)[c]	--
		The California Preschool Social Competence Scale (4)[c]	correlation with worsening fine manipulative ability (BDE-154)
		ADHD Criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th Ed (4)[c]	--
Gascon et al. 2011 [53] [Spain]	Matrix: cord blood (n=88); peripheral blood at 4 yrs (n=288) Collection: 1997-1998 PBDEs measured: 12–13, 32, 17, 28–33,47, 100, 119, 99, 116, 85, 126, 155, 153, 183, 66, 71, 154, 138, and 190	McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population (4)[a,b]	--
		The California Preschool Social Competence Scale (4)[c]	association w/poor social competence (BDE-47 at age 4)
		ADHD Criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th Ed (4)[c]	association w/ attention deficit symptoms (BDE-47 at age 4)
Gascon et al. 2012 [52] [Spain]	Matrix: breast milk (n=209) Collection: 2004-2008 *PBDEs measured: 17, 28, 47, 66, 71, 85, 99, 100, 138, 153, 154, 183, 190, 209	Bayley Scales (1-1.5)[a,b]	association w/ lower mental developmental index (BDE-209)
Herbstman et al. 2012 [56] [NY, USA]	Matrix: cord blood (n=210) Collection: 2001-2002 PBDEs measured: 47, 85, 99, 100, 153, 154, and 183	Bayley Scales--2nd Ed. (1,2,3)[a,b]	association w/ lower psychomotor at 1yr (BDE-100), w/ mental developmental index scores at 2yrs (BDE-47, 99, 100) and 3yrs (BDE-100)
		Wechsler Preschool and Primary Scale of Intelligence, revised, WPPSI-R (4, 6)[b]	association w/ lower full scale IQ at 4yrs (BDE-47, 99, 100) and lower verbal IQ at 4yrs (BDE-47, 99)

Shy et al. 2011 [59] [Taiwan]	Matrix: cord blood (n=36) Collection: 2007-2008 PBDEs measured: 15, 28, 47, 49, 99, 100, 153, 154, 183,196, and 197	Bayley Scales--3rd Ed (8mo-1 yr)[a,b]	association w/ higher cognitive scores (BDE-15, 99, 197, and sum of congeners)
		Bayley Scales--Parent-report questionnaires (8mo-1yr)[c]	association w/ worse adaptive behavior (BDE-28, 99, 154, 183 and sum of congeners)
Hoffman et al. 2012 [57] [NC, USA]	Matrix: breast milk (n=222) Collection: 2001-2005 PBDEs measured: 28, 47, 99, 100, and 153	Infant–Toddler Social and Emotional Assessment (1-2)[c]	association w/ more externalizing problems (BDE-99, 100), w/ worse activity/impulsivity scores (BDE-28, 47, 99, 100, and sum)
Chao et al. 2011 [58] [Taiwan]	Matrix: breast milk (n=70) Collection: 2007-2010 *PBDEs measured: 28, 47, 99, 100, 153, 154, 183, 196,197, 203, 206, 207, 208, and 209	Bayley Scales--3rd Ed (8mo-1 y)[a,b]	association w/worse cognitive scores (BDE-209); association w/improved language (BDE-196)
		Bayley Scales--Parent-report questionnaires (8mo-1yr)[c]	--
Eskanazi et al. 2013 [55] [CA, USA]	Matrix: maternal blood during pregnancy or at delivery (n=279); peripheral blood at age 7 yrs (n=272) Collection: 1999-2000 (cord) PBDEs measured: 17, 28, 47, 66, 85, 99, 100, 153, 154, and 183	Child Behavior Checklist, CBCL (5)[c]	--
		Conners' Kiddie Continuous Performance Test (5)[c]	association w/ more errors of omission and ADHD confidence index (sum of maternal 47, 99, 100, and 153)
		Conners' ADHD/DSM-IV Scales, maternal report (7)[c]	association w/ADHD index and DSM-IV total (sum of maternal 47, 99, 100, and 153)
		Conners' ADHD/DSM-IV Scales, teacher report (7)[c]	association w/ADHD index, DSM-IV total, inattentive subscale (sum of all child 47, 99, 100 ,and 153)
		Behavior Assessment System for Children, 2nd edition (7)[c]	association w/hyperactivity and attention problems (sum of child 47, 99, 100 ,and 153)
		McCarthy Scales of Children's Abilities (5)[a]	association w/ worse pegboard performance (non-dominant hand), worse finger tap (dominant hand) (sum of maternal 47, 99, 100, and 153)
		McCarthy Scales of Children's Abilities (7)[a]	association w/ worse pegboard performance (non-dominant hand) (sum of maternal 47, 99, 100, and 153)
		Peabody Picture Vocabulary Test (5)[b]	--
		Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (5)[b]	--
		Wechsler Intelligence Scale for Children–Fourth Edition (7)[b]	association w/ lower verbal comprehension IQ (sum of maternal 47, 99, 100, and 153); full scale IQ and processing speed (sum of child 47, 99, 100, 153)

[a]Motor domain

[b]Cognitive domain

[c]Behavioral domain

*Deca-BDE measured

although the associations were not statistically significant. In a follow-up study conducted in 2004–2008, the same group measured seven BDE concentrations including BDE-209 in colostrum from 290 women just after delivery and assessed neurodevelopment at 14 months (on average) using the Bayley Scales [52••]. Individual BDE congeners as well as the sum of the seven BDEs were associated with worse scores on the mental developmental index but not with the psychomotor developmental index. The effects were strongest for BDE-209, which is often not measured or detectable in biologic matrices with lower lipid concentrations (e.g., blood).

In New York City, where exposures are, on average, an order of magnitude higher than those reported in the Netherlands [54••] and Spain [52••, 53••], Herbstman et al. measured seven BDEs (not including BDE-209) in cord blood collected in 2001–2002 [56••]. They evaluated the association between prenatal PBDEs and neurodevelopment among 152 children at age 1–4 years and at age 6 years. In this lower Manhattan-based cohort, exposure to individual BDE congeners was negatively associated with various indices of mental and psychomotor development assessed from 1 to 3 years, as well as with full-scale, verbal, and performance intelligence quotient (IQ) assessed at 4 and 6 years.

In a small study, Shy et al. measured 11 PBDEs (not including BDE-209) in cord blood from 36 neonates in Taiwan [59••]. They reported associations between exposure to the sum of 11 BDEs and higher cognitive scores and worse adaptive behavior measured by the Bayley Scales at age 8 months to 1 year; however, their small sample size warrants a cautious interpretation.

In a study in North Carolina, Hoffman et al. measured BDE-47, −99, and −100 concentrations in postpartum breast milk collected between 2001 and 2005 and social and emotional development in 222 children at age 2 years [57••]. They observed a positive dose-dependent relationship between the sum of PBDE concentrations and increased externalizing behavior problems, specifically activity and impulsivity behavior. While this study examined children who were too young for a clinical diagnosis, similar activity and impulsivity behaviors displayed in later childhood would be expected among children with an established ADHD diagnosis [61].

Chao et al. investigated PBDE exposure in postpartum breast milk [58••]. This study of mothers and infants in southern Taiwan enrolled between 2000 and 2001, noted a significant correlation with BDE-209 body concentrations and worse cognitive abilities in infants at age 1 year as measured using the Bayley-III. In addition, this study described a significant correlation between BDE-100 and better language skills at age 1 year as measured on the Bayley-III.

In a recent study of California children, Eskenazi and colleagues reported associations between both prenatal and childhood PBDE exposure with neurodevelopmental deficits, specifically in areas of cognition, attention, and motor function [55••]. The study measured PBDEs in maternal serum before birth or at delivery between October 1999 and October 2000, as well as in children's serum at age 7 years. This cohort study used the sum of the levels of BDE-47, −99, −100, and −153 as the measure of exposure. Children's neurodevelopment skills were analyzed at age 5 years and at age 7 years using a number of neurodevelopmental tests. They found that both the 5- and 7-year-old age groups demonstrated impaired attention and exhibited poorer fine motor coordination in association with maternal and childhood PBDE exposure; only the 7-year-old age group exhibited significant decrements in verbal and full-scale IQ with increasing maternal and childhood PBDE exposure. Interestingly, developmental and behavioral associations between cognition, motor function, and attention with both maternal and child PBDE exposures were found, even though only weak correlations existed between maternal serum PBDE concentrations and corresponding child serum PBDE concentrations.

Epidemiology: Interpretation of the Evidence

The majority of the epidemiologic studies published to date report associations between early-life concentrations of PBDEs (prenatal, at birth, or during early childhood) and worse neurodevelopmental outcomes (both cognitive and behavioral). However, among the published studies, there are a number of inter-related, non-mutually exclusive, methodological discrepancies enumerated below. In addition, when evaluating the weight of the evidence from the scientific literature, publication bias cannot be ruled out, as "positive" findings are more likely to be published than "negative" findings [62].

First, PBDE exposure is known to differ geographically, such that body concentrations in North America are, on average, an order of magnitude higher than those reported in Europe or Asia [16•]. This geographic difference is likely the result of differing product marketing histories, product usage, and regulatory policies regarding flame retardants [18]. Therefore, neonates with "high" exposure in a European-based study are likely to have equivalent concentrations of PBDEs as those who are classified as having "low" exposure in a North American-based study. Even within North America, large inter-individual differences in body concentrations are observed. For example, using the National Health and Nutrition Examination Survey (NHANES), Zota et al. examined serum PBDE concentrations by US region and observed a wide range of exposure within and across regions, with higher concentrations of PBDE among Californians in comparison with other US regions [21]. They speculate that this is because of the California-based TB-117 regulation, which is a 1975 performance-based furniture flammability standard. However, it is not clear that manufacturers make products for California consumption different than products

for use throughout the rest of the country. Formal analyses of geographic differences are scarce.

Second, PBDE exposure likely differed temporally in different world areas. For example, from 1986 to 2006, PBDEs detected in falcon eggs collected in California increased [63]. In addition, a meta-analysis of human exposure to PBDEs demonstrates a marked increase in PBDEs measured in human blood, milk, and tissue from 1970 to 2004 [16•]. It is also possible that after a phase-out, a decrease in PBDE exposure will be observed. This was observed in Sweden where PBDEs measured in breast milk increased from 1996 to 1998 and then decreased from 1998 to 2001 following the phase-out of PBDEs in the EU in 1997 [64]. In the US, this relationship was examined using PBDEs measured in serum from three NHANES survey periods: 2003/04, 2005/06, and 2007/08 [65•]. Sjodin et al. found that overall, lower PBDE concentrations were observed in 2007/08 compared with 2003/04, although these differences were not statistically different. They speculate that this may be because not enough time has passed since the phase-out and many US households likely still possess furniture and other PBDE-containing products.

Third, a critical difference between studies concerns the congeners measured. Because BDE-209 is ubiquitous in dust, it was not detectable in study samples over 'background' laboratory exposure in earlier studies. New laboratory methods have been developed to minimize contamination by 'background' BDE exposure, enabling better quantification (with lower limits of detection) of BDE-209 in biological samples [66, 67]. Different congeners (specifically BDE-209 in comparison with the lower brominated congeners that are associated with the penta- and octa-BDE mixtures) may elicit different neurodevelopmental effects. The direct comparison of studies that have and have not included the measurement of BDE-209 is difficult.

Fourth, differences in the ages to which the children were followed and/or tested as well as the neurodevelopmental indices used to measure either cognition or specific domains of child behavior may account for some discrepancies between reports. There are neurodevelopmental tests that are not translated into the languages required for use in the different international settings. The majority of the tests cited above are available in English with validated translations in Spanish. More language options, especially tests with Asian language options need to be available for comparability in the future. It is also worth noting that some translations are region specific. For example, the Wechsler Intelligence Scale for Children, Fourth Edition has been translated and validated for US Spanish, which, in some cases, may or may not be appropriate for Spanish spoken in other countries [68]. In addition, different versions of the same instrument may or may not provide equivalent information. An example of this incongruity occurred with Bayley version II and Bayley version III for which scores of the two tests are not directly comparable. Finally, the Bayley instrument used in children aged 12 months may not be sensitive enough to detect PBDE-associated neurodevelopmental deficits.

Furthermore, the proper adjustment for confounders may be critical to demonstrate effects of PBDE exposure on neurodevelopment. Studies have measured different potential confounding factors and/or treated them differently in their analyses. Moreover, smaller studies have less statistical power precluding the inclusion of many confounders in their multivariate models. Finally, the choice of statistical model (which may, in part, be related to sample size/power) may impact the comparability of the studies. For example, Roze et al. present correlation coefficients adjusted for sex, socioeconomic status, and score on the Home Observation for Measurement of the Environment (HOME) questionnaire [54••]. In comparison, Eskenazi et al. present estimates and confidence intervals from multiple linear regression analyses adjusted for child's age, sex, HOME score, father living with family, handedness, location of testing, whether the child attended preschool, and maternal years in the US before giving birth [55••].

Despite these differences between studies, the preponderance of the evidence supports that early-life exposure to PBDEs is detrimental to child neurodevelopment.

Possible Mechanisms

While the precise mechanism of action of PBDEs on neurodevelopment is not known, at least two, non-mutually exclusive, mechanisms of action have been proposed. PBDE-induced neurotoxicity via thyroid hormone disruption has been studied in both laboratory and epidemiologic settings. This mechanism has been proposed, in part because of the structural similarity between PBDEs and thyroxine (T4). T4 and related thyroid hormones are critical for normal brain development, thereby providing a reasonable link between PBDE exposure and neurotoxicity. In addition, there may be a direct effect of PBDEs on glial and neuronal cells in the brain. Animal data suggest that deficits in thyroid hormones result in abnormal proliferation of axons and dendrites, synapse formation, gliogenesis and myelination in the cerebrum and cerebellum, and abnormal cellular proliferation in the cerebellum [69]. In humans, deprivation of thyroid hormone either in utero or during the perinatal period result in deficits in cognitive and motor function [70]. However, brain development does not stop at birth, but likely continues through the first two decades of postnatal life. This developmental period involves reorganization in the human cortex [71]. Although this reorganization begins prenatally, continued dendritic and axonal growth, synapse production, neuronal and synaptic pruning, and changes in neurotransmitter sensitivity continue to occur after birth [72]. Both thyroid hormone excesses and

deficiencies are thought to be detrimental throughout this developmental window [73]. Despite the clear evidence that thyroid hormones are critical for brain development, the mode of action of thyroid hormones on cellular and molecular targets within the central nervous system is still largely unknown [74].

Thyroid Function

Because of its structural similarity to the thyroid hormone T4, PBDE exposure likely disrupts thyroid hormones. In vitro models have shown that PBDE congeners, as well as their hydroxylated metabolites have the potential to bind to thyroid hormone receptors [75, 76] and animal models indicate that PBDEs may have a direct effect on the thyroid gland [44, 77].

There is much interest in thyroid hormone disruption following neonatal PBDE exposure because of the brain's dependence on carefully regulated levels of thyroid hormones for normal development. In studies where rodents were exposed perinatally to specific PBDE congeners or the PBDE commercial mixture DE-71, most identified a negative relationship between exposure and circulating levels of T4 [51, 78–83] and triiodothyronine (T3), the biologically active form of T4 [80, 81, 84] but little evidence of an effect on thyroid-stimulating hormone (TSH), which regulates the production of T4. Because of the similarity in the physiology of gestation between sheep and humans, a recent study examined the effects of lambs exposed prenatally to PBDEs and also found inverse associations with both T4 and T3 [85]. In humans, the number of studies is small and the evidence is inconsistent. Some studies have observed no association between indicators of prenatal PBDE exposure and thyroid hormones [84, 86, 87], some found some evidence of an inverse association [85, 88, 89], and one study observed a positive association [54••]. Differences in PBDE exposure levels and the timing and type of thyroid hormones measured may account for some of these differences; however, the full explanation for the discrepancies between human studies and between observations in animal models and humans is largely unknown.

While most studies of developmental PBDE exposure focused on the prenatal and early postnatal periods, PBDE exposure during childhood may also influence thyroid hormones. Gascon and colleagues investigated the association between PBDE exposure measured at age 4 years and thyroid hormones and identified a positive association with T3 [53••]. Both animal and human studies have found that adults are also susceptible to thyroid dysregulation following PBDE exposure; however, the direction of these effects varies by study. In adult mice, PBDE exposure is most often associated with lower T4 and no effect on TSH [90–92]. In humans, some studies of adults report that PBDEs are associated with higher levels of T4, T3, and/or TSH [93–95] and others report no observed effects [96, 97]. Pregnant women are a subgroup of adults that may have distinct susceptibility to thyroid disruption from PBDE exposure. This is because of the increased demand that pregnancy places on the thyroid hormone system, as mothers are the sole provider of thyroid hormone to the fetus before gestational week 16 when the fetal hypothalamic-pituitary axis matures [98]. In pregnant sheep, there was no reported association between PBDE exposure and thyroid hormones [99]. In humans, however, the results are inconsistent, with one study of PBDEs in pregnant women reporting lower TSH [100] and another reporting no association with TSH [85], one reporting higher T4 and T3 [101] and another reporting lower T3 and T4 [85] and yet another reporting no association with T4 [100].

Direct Effects on Brain Cells

As reviewed previously [31•, 32], there are three proposed mechanisms by which PBDE exposure may result in direct effects on brain cells, specifically neuronal and glial cells. Oxidative stress in response to PBDE exposure has been observed to cause neuronal death owing to apoptosis [32, 44, 102–104]. Additionally, PBDEs and PBDE metabolites have been shown to disrupt vital intracellular and extracellular signaling mechanisms in the brain including calcium homeostasis and protein kinase C [105]. Calcium levels require exquisite regulation and balance in the brain because calcium is essential in early brain development and influences almost every biochemical and physiologic process of the neuron [106]. In particular, calcium is involved in the opposing processes of brain growth and degeneration through the mechanisms of synaptic plasticity, cell excitability, and synaptic transmission [106]. It is therefore logical that even the smallest deviations in timing of calcium release and calcium level in response to PBDE exposure may result in substantial neurodevelopmental changes. Finally, Schreiber and colleagues found that exposing human neuroprogenitor cells to PBDEs affected cell migration and differentiation into neurons and oligodendrocytes [107]. Because cell migration and neurogenesis occur mainly during the prenatal period and oligodendrogenesis occurs postnatally, the authors provide evidence that both pre- and postnatal PBDE exposures may influence neurodevelopment.

Future Directions for Research and Conclusions

Longitudinal cohort studies are the "gold standard" in environmental epidemiology, where randomized clinical trials are not often possible and/or ethical. There have been a number of

longitudinal birth cohort studies that have demonstrated neurodevelopmental effects of early-life PBDE exposure [52••, 53••, 54••, 55••, 56••, 57••, 58••, 59••]. However, these studies are time consuming and expensive and many are relatively small in size. This limits the types of statistical analyses possible and also the strength of the conclusions that can be drawn from the results. Therefore, additional larger scale longitudinal studies would be informative and could fill in the data gaps and alleviate uncertainty surrounding this association. In addition, more studies measuring BDE-209 would be helpful to discriminate across congeners (assuming that there are some that may be less toxic than others). Finally, studies that examine the impact of the hydroxylated metabolites of PBDEs may be informative, as evidence suggests that the neurotoxic potential is higher for the hydroxylated metabolites than for the parent compounds [105]. While inroads have been made to identify the mechanism of action and a number of potential mechanisms have been tested, it is not clear how these mechanisms interact with one another and whether or not observations in animals are also operating in humans. As such, questions still remain as to exactly how early-life or childhood PBDE exposure may impact neurodevelopmental indices. A complete understanding of whether and how the various BDE congeners and hydroxylated metabolites elicit neurotoxic effects can be informative in terms of developing strategies to mitigate their impact.

By the end of 2013, the companies that produced penta-, hexa-, octa-, and deca-BDEs have either agreed to discontinue the use of these compounds (North America and Europe) [28•] or have reduced their production (China) [29]. However, PBDE exposure will likely continue well into the future, as PBDE-containing products are infrequently replaced [65•]. In addition, other substitute compounds are now being used to meet regulatory fire standards. Whether and how exposure to these replacement compounds in new products interacts with PBDEs in products currently in use has not been examined. Further, as PBDE-containing products are discarded or recycled over time, the post-consumer impact on the environment and ultimately human health is not well understood. Outside of these uncertainties, the weight of the epidemiologic evidence published to date supports that early-life exposure to PBDEs is detrimental to child neurodevelopment.

Compliance with Ethics Guidelines

Conflict of Interest Julie B. Herbstman and Jennifer K. Mall declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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