Hormones and Behavior xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review article

Exposure to polybrominated diphenyl ethers (PBDEs) and child behavior: Current findings and future directions

Ann M. Vuong[a,*], Kimberly Yolton[b], Kim N. Dietrich[a], Joseph M. Braun[c], Bruce P. Lanphear[d], Aimin Chen[a]

[a] Division of Epidemiology, Department of Environmental Health, University of Cincinnati College of Medicine, P.O. Box 670056, Cincinnati, OH 45267, USA
[b] Division of General and Community Pediatrics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 7035, Cincinnati, OH 45229, USA
[c] Department of Epidemiology, Brown University School of Public Health, 121 South Main St, Box G-S121-2, Providence, RI 02912, USA
[d] BC Children's Hospital Research Institute, Faculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby, BC V5A 1S6, Canada

ARTICLE INFO

Keywords:
Polybrominated diphenyl ether (PBDE)
Behavior
Neurodevelopment
Externalizing behavior
Executive function
Attention
Internalizing behavior
Social behavior
Adaptive skills

ABSTRACT

Polybrominated diphenyl ethers (PBDEs) are recognized neurotoxicants, but the extent to which PBDEs influence various domains of behavior in children is not fully understood. As such, we reviewed epidemiologic studies published to date to provide an overview of the current state of knowledge on PBDEs' potential role in behavioral development. We identified 19 epidemiologic studies reporting on associations of prenatal and childhood concentrations of PBDEs with behaviors assessed in children from 1 to 12 years, including executive function, attention, externalizing and internalizing behaviors, adaptive skills, and social behaviors/Autism Spectrum Disorder (ASD). While the mechanisms of PBDE neurotoxicity in humans are still not clearly elucidated, findings from this review indicate that PBDE exposure during fetal development is associated with impairments in executive function and poorer attentional control in children. Results from large prospective cohorts demonstrate that prenatal and postnatal PBDE exposure adversely impacts externalizing behavior (*e.g.*, hyperactivity and conduct problems). Additional studies are needed to determine whether PBDEs are associated with internalizing problems, adaptive skills, and social behaviors/ASD in children. Future studies will help better understand the potential neurotoxic effects of PBDE exposures during adolescence, possible sex-dependent effects, and the impact of exposure to BDE-209 and alternative flame retardants. Future studies should also examine chemical mixtures to capture real-world exposures when examining PBDEs and their impact on various behavioral domains in the context of multiple chemical exposures.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a major class of synthetic flame retardants used in large quantities since the 1970s to reduce the risk of combustion. Commercially marketed as three mixtures - penta-, octa- and deca-brominated BDE - PBDEs were added to a variety of consumer products, including polyurethane foam, electrical equipment, textiles, and construction materials. PBDEs, which are not covalently bound to polymer matrices, readily leach from consumer products to the surrounding environment. PBDEs are ubiquitous in the environment due to their persistence and bioaccumulating properties; they are found in house dust, soil, sewage sludge, and wildlife (de Wit et al., 2006; Hale et al., 2003; Hites, 2004; Law et al., 2006; Muir et al., 2006).

Measurable PBDE levels have been detected in human serum, adipose and liver tissue, placenta, cord serum, and breastmilk in populations around the world (Frederiksen et al., 2009b). The body burden of PBDEs in Americans is at least one order of magnitude higher than those found in Europeans and Japanese (Frederiksen et al., 2009b; Inoue et al., 2006; Petreas et al., 2003; Schecter et al., 2005). Due to voluntary and regulatory measures in the US, penta- and octa-brominated formulations were phased out in 2004; the deca-brominated mixture was discontinued in 2013 (Linares et al., 2015). Other countries, including those in Europe and Japan, have also ceased production and use. However, PBDEs will persist in the environment for decades, because of their long half-lives (Geyer et al., 2004) and inability to easily degrade in the environment (Sjodin et al., 2004). Continued use of PBDE-laden products and eventual leaching from disposed products

* Corresponding author at: Division of Epidemiology, Department of Environmental Health, University of Cincinnati College of Medicine, P.O. Box 670056, Cincinnati, OH 45267-0056, USA.
E-mail address: ann.vuong@uc.edu (A.M. Vuong).

https://doi.org/10.1016/j.yhbeh.2017.11.008
Received 27 July 2017; Received in revised form 19 October 2017; Accepted 10 November 2017

provide ongoing sources of global redistribution through environmental circulation patterns (Hale et al., 2003). In addition, the debromination of higher PBDEs in the biota contribute to the environmental presence of lower brominated PBDEs as it has been reported that Deca-BDE metabolizes *via* a reductive debromination process to lower brominated congeners (de Wit, 2002). Biomonitoring data has shown progressive decreases in serum PBDEs among Californian women since the PBDE phase out (Zota et al., 2013). However, recent temporal trends indicate that these declines may have plateaued and could be on the rise (Hurley et al., 2017).

The bioaccumulation of PBDEs in humans is of substantial concern, particularly for the developing nervous system. Neurodevelopment begins early in the embryonic period with neurulation and extends through puberty and early adulthood with synaptogenesis and myelination (Rice and Barone, 2000). Experimental studies, in both *in vitro* and in animal models, have extensively documented PBDE neurotoxicity and long-lasting behavioral alterations with prenatal and postnatal exposures (Birnbaum and Staskal, 2004; Branchi et al., 2003; Costa and Giordano, 2007, 2011; Williams and DeSesso, 2010). Prenatal exposure to PBDEs in humans occurs *via* transplacental transfer from mother to fetus during gestational development and through breastmilk during infancy. Ingestion of household dust from frequent hand-to-mouth behaviors and crawling on household surfaces additionally contribute to infants and children having the highest body burden of PBDEs on a lipid basis (Fischer et al., 2006; Lunder et al., 2010; Schecter et al., 2003; Toms et al., 2008; Toms et al., 2009). Given that several vulnerable periods of neurodevelopment coincide with periods of highest exposure to PBDEs, epidemiologic studies have investigated the relationship between PBDEs and neurodevelopmental domains in children, including cognition, motor function, and behavior. Evidence from epidemiological studies strongly supports that PBDE exposure is associated with deficits in IQ in children and has been reviewed by Herbstman and Mall (2014) and in a meta-analysis by Lam et al. (2017). Thus, the aims of this review are to summarize the available epidemiologic evidence of PBDEs and behavioral development and identify future directions for research to enhance our understanding of the neurotoxicity of PBDEs in children.

2. Potential mechanisms of action

The underlying mechanism of PBDE neurotoxicity is not clear. Two general modes of action, though not mutually exclusive, have been identified. First, PBDEs may directly act on the developing brain. PBDEs cross the blood-brain barrier and accumulate in the central nervous system of wildlife (Naert et al., 2007; Zhao et al., 2016). In the hippocampus of mice, PBDEs altered cholinergic nicotinic receptors, and *in vivo* exposure to BDE-47 reduced long-term potentiation and decreased levels of postsynaptic proteins, which play a vital role in glutamate receptor signaling (Dingemans et al., 2007; Eriksson et al., 2002; Viberg et al., 2003). *In vitro* studies have found interference with signal transduction pathways. In particular, PBDE mixture DE-71 was observed to stimulate arachidonic acid release, inhibit calcium signaling and uptake, and alter protein kinase C translocation (Kodavanti and Derr-Yellin, 2002; Kodavanti and Ward, 2005; Madia et al., 2004).

PBDEs may also affect cell viability; DE-71 was observed to cause apoptotic cell death at low concentrations of ~7 μM (Reistad et al., 2006; Reistad et al., 2007). In addition, PBDE exposure increased production of reactive oxygen species, resulting in oxidative stress in human cells (Hu et al., 2007; Reistad and Mariussen, 2005; Zhang et al., 2007). In an *in vitro* study of human neuroprogenitor cells, PBDEs induced a concentration-dependent decrease in the migration and differentiation of cells into oligodendrocytes and neurons (Schreiber et al., 2010). PBDEs could also have a potential neuroendocrine effect, altering neurotransmitter uptake and release (Coburn et al., 2007; Llansola et al., 2007; Mariussen and Fonnum, 2003). Lastly, epigenetic effects from PBDE exposure have been proposed. In mice perinatally exposed to low doses of BDE-47, there was a reduction in global DNA methylation in the cerebral cortex and decreased expression of genes involved in DNA methylation and histone modification (Suvorov and Takser, 2010; Woods et al., 2012).

Second, PBDEs may indirectly impact the developing brain by altering thyroid hormone homeostasis. Thyroid hormones, which control cell growth and metabolism, are essential for the normal development of the central nervous system (Bernal, 2000). In particular, the maturation of the cerebral cortex is exceedingly sensitive to thyroid hormones. Insufficient thyroid hormones, or hypothyroidism, have been observed to result in irreversible damage, including reduced neuronal migration, disrupted cortical layering, altered circuitry, and differentiation defects in rodents (Berbel et al., 2014; Guadano Ferraz et al., 1994). Even subtle deficiencies of thyroid hormones have resulted in impaired cognitive and motor development in children (de Escobar et al., 2008; Haddow et al., 1999; Zoeller, 2003). Significant decreases in circulating thyroid hormones and altered thyroid hormone homeostasis have been reported in rats with perinatal exposure to PBDEs (Bowers et al., 2015; Szabo et al., 2009; Zhou et al., 2002). Epidemiologic studies have also shown that PBDEs disrupt thyroid hormone regulation, but the results are inconsistent in pregnant women. Some studies have reported increases in maternal thyroid hormone levels with PBDE exposure whereas others have observed decreased levels (Abdelouahab et al., 2013; Chevrier et al., 2010; Lignell et al., 2016; Mazdai et al., 2003; Stapleton et al., 2011; Vuong et al., 2015; Zhang et al., 2010; Zota et al., 2011).

Transplacental transfer of maternal thyroid hormones are critical during gestational development since fetal synthesis of thyroid hormones does not begin until approximately 18–22 weeks of gestation; even after this time the fetus will continue to rely on maternal input for thyroid hormone stabilization in cases in which the fetus is unable to produce sufficient thyroid hormones (Ahmed et al., 2008; Morreale de Escobar et al., 2000). PBDEs and their metabolites, hydroxylated-PBDEs (OH-PBDEs), bear structural similarities to thyroid hormones and may alter levels and downstream effects on hormone action (Richardson et al., 2008). Disruption of thyroid hormone homeostasis may be through competitive binding to thyroid transport proteins thyroxin-binding globulin (TBG) and transthyretin (TTR), increasing thyroid hormone excretion and metabolism, altering thyroid hormone receptor activity, and interfering with deiodinase activity (Cao et al., 2010; Hamers et al., 2006; Hamers et al., 2008; Ibhazehiebo et al., 2011; Kojima et al., 2009; Li et al., 2010; Marchesini et al., 2008; Meerts et al., 2000; Noyes et al., 2010; Ren et al., 2013; Szabo et al., 2009; Zhou et al., 2002). Thus, thyroid disruption may be a mediating pathway for PBDE neurotoxicity.

3. Description of the state of knowledge

The impact of prenatal and postnatal PBDE exposures on child behavior has been investigated by a number of epidemiologic studies (Table 1). Aside from two cross-sectional studies and one case-control study in the United States (Gump et al., 2014; Przybyla et al., 2016), a majority (n = 16) of the 19 identified studies were conducted using prospective cohorts located in the United States (California, New York, North Carolina, and Ohio) (Adgent et al., 2014; Braun et al., 2014, 2017; Chen et al., 2014; Cowell et al., 2015; Eskenazi et al., 2013; Hoffman et al., 2012; Sagiv et al., 2015; Vuong et al., 2017a; Vuong et al., 2016; Vuong et al., 2017b; Zhang et al., 2017), while the remaining were conducted using cohorts from the Netherlands (Roze et al., 2009), Spain (Gascon et al., 2011), Taiwan (Shy et al., 2011), and China (Ding et al., 2015). PBDE exposure was assessed at various time points during development, including gestation (maternal and cord sera), infancy (breastmilk), and childhood (child serum). Neurobehavioral batteries were completed in children ranging from 1 to 12 years of age to assess attention, executive function, and behavioral problems, such as externalizing, internalizing, adaptive, and social behaviors/