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Childhood polybrominated diphenyl ether (PBDE) exposure and neurobehavior in children at 8 years

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Abstract

Background—Prenatal polybrominated diphenyl ether (PBDE) exposure has been associated with decrements in IQ and increased attention deficit/hyperactivity disorder related behaviors in children; however, data are limited for the role of postnatal exposures.

Objectives—We investigated the association between a series of childhood PBDE concentrations and Full-Scale Intelligence Quotient (FSIQ) and externalizing problems at 8 years.

Methods—We used data from 208 children in the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort. Child serum PBDEs were measured at 1, 2, 3, 5, and 8 years; missing serum PBDE concentrations were estimated via multiple imputation. The Wechsler Intelligence Scales for Children-IV and the Behavior Assessment System for Children-2 was used to assess intelligence and externalizing behavior, respectively, in children at 8 years. We used multiple informant models to estimate associations

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between repeated lipid-adjusted PBDEs and child neurobehavior and to test for windows of susceptibility.

Results—Postnatal exposure to PBDE congeners (-28, -47, -99, -100, and -153) at multiple ages was inversely associated with FSIQ at 8 years. For instance, a 10-fold increase in BDE-153 concentrations at 2, 3, 5, and 8 years were all related to lower FSIQ at age 8 (β for 3 years: −7.7-points, 95% CI −12.5, −2.9; β for 8 years: −5.6-points, 95% CI −10.8, −0.4). Multiple PBDE congeners at 8 years were associated with increased hyperactivity and aggressive behaviors at 8 years.

Conclusions—Postnatal PBDE exposure was associated with decrements in FSIQ and increases in hyperactivity and aggressive behaviors.

Keywords

Polybrominated diphenyl ether (PBDE); neurobehavior; postnatal; intelligence; externalizing behavior

1. Introduction

Commercial mixtures of polybrominated diphenyl ethers (PBDEs) were used extensively for decades as additive flame retardants in a multitude of consumer products, including polyurethane foams, carpet padding, furniture, and electronic devices to reduce fire incidence and the related economic costs. While PBDEs have been removed from the U.S. market, they remain ubiquitous environmental contaminants with detectable levels in air, dust, soil, wildlife, as well as in human biospecimens (Costa and Giordano, 2007). Infants and children have several fold higher serum PBDE concentrations on a lipid basis than adults due to placental and lactational transfers and child-specific behaviors, such as frequent hand-to-mouth actions and crawling on the floor (Schecter et al., 2005; Toms et al., 2008; Toms et al., 2009).

Evidence from several epidemiological studies indicates that PBDEs are neurotoxic when exposure occurs during fetal development, with reports of decrements in Full Scale IQ (FSIQ), impaired executive function, lower reading and language abilities, and increased attention deficit/hyperactivity disorder (ADHD) related behaviors (Chen et al., 2014; Cowell et al., 2015; Ding et al., 2015; Eskenazi et al., 2013; Herbstman et al., 2010; Shy et al., 2011; Vuong et al., 2016; Zhang et al., 2016). Postulated mechanisms by which PBDEs may exert neurotoxic effects include indirectly affecting brain development through thyroid hormone disruption or directly acting on brain cells by causing oxidative stress, interfering with signal transduction, altering cholinergic system responses, inducing neuronal apoptosis, and altering neurotransmitter release and function (Costa et al., 2014; Costa and Giordano, 2011; Dingemans et al., 2011).

PBDEs may continue to adversely affect neurobehavioral domains even after birth as rapid brain growth continues until two years of age. In addition, neural development, including synaptogenesis and myelination, extends through puberty (Rice and Barone, 2000). However, it is uncertain whether childhood PBDE exposures are adversely associated with neurobehavior, as few studies have examined early childhood as a vulnerable window of

susceptibility to PBDE neurotoxicity. Only four papers have investigated childhood serum PBDEs and neurobehavior; half observed adverse associations with FSIQ and ADHD-related behaviors (Eskenazi et al., 2013; Gascon et al., 2011; Przybyla et al., 2016; Sagiv et al., 2015). Given that PBDE concentrations are higher in children than the developing fetus and the lack of studies that identified windows of susceptibility for PBDE neurotoxicity in childhood, we examined the association between childhood PBDEs measured at 1–8 years and FSIQ and externalizing behaviors at 8 years.

2. Methods

2.1 Study Participants and Design

The study consisted of participants enrolled in the Health Outcomes and Measures of the Environment (HOME) Study, an ongoing prospective pregnancy and birth cohort established in the Greater Cincinnati area (Ohio, USA). Detailed information on enrollment, inclusion criteria, and neurobehavioral assessments are described by Braun et al. (2016). The HOME Study included 390 singleton births at delivery and completed multiple postnatal follow-up visits up to age 8 years. The present study included 208 singleton children with at least one serum PBDE measure between 1–8 years and a neurobehavior assessment at 8 years. The study protocol was approved by the Institutional Review Boards at the Cincinnati Children's Hospital Medical Center and the Centers for Disease Control and Prevention (CDC).

2.2 Childhood serum PBDEs

Concentrations of BDEs-17, -28, -47, -66, -85, -99, -100, -153, -154, -183, and -209 were measured in children's serum samples collected at 1, 2, 3, 5, and 8 years, using gas chromatography/isotope dilution high-resolution mass spectrometry (Jones et al., 2012; Sjodin et al., 2004). Samples were processed in batches of twenty-four unknown, three quality control, and three method blank samples. PBDE concentrations <LOD (limit of detection) were substituted with LOD/√2 (Hornung and Reed, 1990). LOD was defined as three times the SD of the method blanks or the lowest calibration standard point 0.5 pg/μL corresponding to 5 pg per sample (in the absence of detectable blanks). We report PBDE concentrations as ng/g serum lipid. Serum lipid concentrations were calculated from concentrations of triglycerides and total cholesterol (Phillips et al., 1989). We analyzed individual PBDE congeners with detection frequencies ≥80%, which included BDE-28, -47, -99, -100, -153, and their sum (ΣPBDEs). Of the 208 children with neurobehavioral assessments at 8 years, PBDEs were available for 86 (41%), 69 (33%), 69 (33%), 141 (68%), and 192 (92%) at ages 1, 2, 3, 5, and 8 years, respectively.

Due to limited serum availability at 1–3 years required to meet the volume needed by the assays, PBDEs were unable to be measured in the majority of the children during early childhood. Thus, we estimated PBDE concentrations for children who had at least one PBDE measurement from 1–8 years, but were missing concentrations at other time points via multiple imputation using the Markov Chain Monte Carlo (MCMC) method, in which 100 imputations were produced (Bodner, 2008). This provides a set of 100 plausible PBDE estimates that also incorporates the uncertainty or error associated with the missing data (Rubin, 1987). Auxiliary variables in the imputation models were selected based on their

correlation with childhood PBDEs ($p<0.05$) and included maternal blood lead concentrations during pregnancy, household income, marital status, whether the child was breastfed, and Home Observation for Measurement of the Environment (HOME) Score. Maternal serum polychlorinated biphenyls (ΣPCBs) of 15 congeners during pregnancy were added to the imputation model due to its correlation with PBDEs at 2 years ($p=0.02$). Both $\log_{10}$-transformed prenatal and postnatal PBDEs were included, because of their long half-life and consideration of placental and lactational transfers (Toms et al., 2009). Lastly, FSIQ at 8 years was included as excluding the dependent variable would cause estimated associations to be biased toward the null (Enders, 2010). Convergence of imputation models were assessed using trace and auto-correlation plots.

2.3 Neurobehavior Assessments

Trained HOME Study staff, certified by a developmental psychologist, administered the Wechsler Intelligence Scale for Children-IV (WISC-IV) to children at age 8 years to measure FSIQ (Wechsler, 2003; Wechsler, 2004). To assess adaptive and behavioral problems in children, parents were requested to complete the Behavioral Assessment System for Children-2 (BASC-2) (Reynolds and Kamphaus, 2004). We focused on FSIQ and Externalizing Problems and its subscales (hyperactivity, aggression, conduct disorder), because prenatal PBDEs were significantly associated with FSIQ deficits and increased externalizing behavior in several epidemiologic studies (Chen et al., 2014; Cowell et al., 2015; Eskenazi et al., 2013; Roze et al., 2009; Zhang et al., 2016). The BASC-2 has a population mean of 50±10, with higher scores indicating increased problem behaviors. Neither HOME Study staff nor parents had knowledge of prenatal or childhood PBDE concentrations at the neurobehavioral assessment.

2.4 Statistical analyses

We investigated associations between $\log_{10}$-transformed child serum PBDEs and FSIQ and Externalizing Problems at 8 years with multiple informant models (Horton et al., 1999; Litman et al., 2007), which are non-standard versions of generalized estimating equations that allow for repeated environmental chemical measurements (Sanchez et al., 2011). This method allows us to identify windows of susceptibility for PBDE neurotoxicity by including interaction terms between child age and PBDE concentrations. We estimated βs and 95% confidence intervals (CIs) for BDE-28, -47, -99, -100, -153, and ΣPBDEs with separate multiple informant models for each of the 100 imputed datasets. Final estimates for PBDEs were an average of the 100 results from imputed datasets (Beunckens et al., 2008; Shen and Chen, 2013) and are presented for ages 1, 2, 3, 5, and 8 years, because several interaction terms between PBDEs (continuous) and age (categorical) were statistically significant ($p<0.10$).

Covariates in the final models, selected based on their relationship with FSIQ or Externalizing Problems ($p<0.10$), included maternal age, race/ethnicity, household income, maternal serum cotinine at 16±3 weeks (ng/mL, continuous), marital status, maternal IQ (continuous, assessed by Wechsler Abbreviated Scale of Intelligence) (Wechsler, 1999), maternal depression (assessed by Beck Depression Inventory II at enrollment) (Beck et al., 1996), HOME inventory score at the 1-year home visit (Caldwell and Bradley, 1984), and

child sex. Effect measure modification by child sex was examined using interaction terms between PBDEs (continuous), child sex (categorical), and child age (categorical), as well as all 2-way interactions (p<0.10).

In a sensitivity analysis, we performed non-imputation-based modeling to determine whether results differ between imputation-based and non-imputation-based models. We ran multiple informant models, as described above, using the original, non-imputed data to examine associations between childhood PBDEs and FSIQ and externalizing behaviors in children at 8 years. We also wanted to determine whether overall conclusions would differ had we used a traditional modeling method rather than multiple informant models. Using the original, non-imputed data, we performed separate multiple linear regression models to estimate βs and 95% CIs for individual PBDE congeners and ΣPBDEs measured during childhood in relation to our outcomes at 8 years. In another sensitivity analysis, we added blood lead levels at 8 years as a covariate to determine whether results are similar after adjustment for this known neurotoxicant. While peak exposure levels for lead occur at 18–30 months in the US, studies have reported that concurrent blood lead levels are associated with decreased IQ points (Chen et al., 2005; Lanphear et al., 2005). We also performed an adjustment for prenatal PBDEs, which have been found to neurotoxic in previous epidemiologic studies, and breastfeeding duration (months).

3. Results

3.1 PBDE concentrations

The geometric mean (GM) of PBDEs at 2 and 3 years in the imputed datasets were slightly higher than the original dataset, while concentrations at 1, 5, and 8 years were more comparable to the original dataset (see Table S1). Imputed ΣPBDE concentrations in the datasets peaked at 2 years (127.7±2.5 ng/g lipid) and gradually decreased as children aged (Table 1). The most abundant congener was BDE-47, with GMs of 58.5±2.6, 66.2±2.9, 47.3±2.8, 30.8±2.6, and 20.3±2.5 ng/g lipid at 1, 2, 3, 5, and 8 years, respectively (see Table S1). PBDE congeners were positively correlated with each other during childhood, with high correlation coefficients at 1 year (r_p=0.64–0.95, p<0.0001), 2 years (r_p=0.60–0.95, p<0.0001), 3 years (r_p=0.48–0.97, p<0.001), 5 years (r_p=0.49–0.95, p<0.0001), and 8 years (r_p=0.43–0.94, p<0.0001) (see Table S2).

3.2 Participant characteristics

Overall, childhood ΣPBDEs were significantly higher among children whose mothers identified as non-Hispanic black or other race/ethnicities, were younger, were experiencing moderate to severe depression, and were single or living alone. Children from homes with a household income <$40,000 and who had lower HOME scores were more likely to have higher ΣPBDE concentrations. Child FSIQ at age 8 years was higher among those with mothers who were older, non-Hispanic white, of higher income, married/living with a partner, minimally/mildly depressed, and who had a higher HOME score. Scores for Externalizing Problems were significantly higher in males and children of mothers experiencing moderate to severe depression. Children included in our study (n=208) were more likely to have mothers who were not married or living alone than those excluded due to

loss of follow-up, inability to complete a blood draw, or missing neurobehavioral assessments at age 8 years (n=182) (see Table S3). However, children excluded from the present study due to missing information were comparable on all other sociodemographic characteristics, maternal characteristics (e.g., depression, IQ), home environment, and child sex. Maternal IQ was inversely correlated with ΣPBDEs at 2 and 3 years and positively correlated with child FSIQ (Table 2). Maternal serum cotinine was positively correlated with ΣPBDEs at 2 and 3 years and inversely correlated with child FSIQ.

3.3 Postnatal PBDEs and FSIQ

We observed an overall pattern of an inverse association between $\log_{10}$-transformed childhood PBDEs and FSIQ at age 8 years (Figure 1). A 10-fold increase in BDE-28 at 3 years was associated with a 7.9-point decrease (95% CI: −13.6, −2.3) in FSIQ. Ten-fold higher BDE-153 at ages 2, 3, 5, and 8 years were significantly associated with FSIQ decrements of 5.4-points (95% CI: −10.8, −0.1), 7.7-points (95% CI: −12.5, −2.9), 8.2-points (95% CI: −13.4, −3.0), and 5.6-points (95% CI: −10.8, −0.4), respectively. Ten-fold ΣPBDE increases at ages 3 and 5 years were associated with lower FSIQ at 8 years (β=−4.8, 95% CI: −10.2, 0.5 and β=−4.5, 95% CI: −9.6, 0.6, respectively), with borderline significance (p<0.10).

3.4 Postnatal PBDEs and externalizing behaviors

Several PBDE congeners at 8 years were associated with higher concurrent Externalizing Problems scores, including BDE-28 (β=4.7, 95% CI: 0.8, 8.6), BDE-47 (β=3.4, 95% CI: 0.004, 6.8), BDE-153 (β=4.2, 95% CI: 0.4, 8.0), and ΣPBDEs (β=4.3, 95% CI: 0.4, 8.2); estimates were all for a 10-fold concentration increase (Figure 2). Hyperactivity and Aggression scores were higher among children with increased PBDE concentrations at age 8 years, with statistical significance for BDE-28 and -153 in relation to Hyperactivity and BDE-28, -47, -99, and ΣPBDEs in relation to Aggression. For earlier ages of PBDE exposures, only BDE-153 at 1 year was associated with Externalizing Problems (β=3.7, 95% CI: 0.1, 7.2) and Aggression (β=3.4, 95% CI: 0.1, 6.8). We did not observe any association between childhood PBDEs and Conduct Disorder scores (results not shown).

3.5 Child sex differences

We observed effect modification by child sex between several PBDE congeners at 8 years and FSIQ (see Table S4). Concurrent BDE-47 and ΣPBDEs were associated with lower FSIQ scores in males (β=−5.6, 95% CI: −11.0, −0.2 and β=−7.4, 95% CI: −13.2, −1.6), but no associations in females. This pattern was also noted with BDE-99 and -100 at 8 years. For Externalizing Problems, a 10-fold increase in BDE-153 at 8 years was associated with a 7.2-point increase (95% CI: 2.9, 11.5) in males, but no associations in females.

3.6 Sensitivity analyses

Results from our non-imputation-based multiple informant models were similar to findings from imputation-based analyses despite a smaller sample size. Significant decreases in FSIQ were observed with 10-fold increases in BDE-28 at 3 years (β=−12.3, 95% CI: −23.6, −1.1) and BDE-153 at 5 years (β=−8.1, 95% CI: −14.0, −2.2) in our non-imputation-based

modeling (Table 3). Several PBDEs at 8 years remained positively associated with externalizing behaviors, hyperactivity, and aggression. In addition, linear regression models using the original, non-imputed data yielded similar results, with statistically significant positive associations noted between concurrent PBDEs and externalizing behaviors, hyperactivity, and aggression (see Table S5). Decrements in FSIQ were again observed with increased BDE-153 concentrations at 5 years. However, previous inverse associations between BDE-153 at other years during childhood as well as BDE-28 at 3 years failed to reach statistical significance. Lastly, adjusting for blood lead at age 8 years, prenatal PBDEs, and breastfeeding duration did not appreciably change our results (results not shown).

4. Discussion

Our findings suggest that childhood PBDEs are associated with lower FSIQ in children. Specifically, each 10-fold increase in BDE-28 at 3 years and BDE-153 at 2–8 years were significantly associated with >5-point decrements in FSIQ at 8 years. Our results align with findings from the U.S. CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) Study that examined PBDEs and FSIQ, both assessed at 7 years of age (−5.6-point decrease [95% CI: −10.8, −0.3] with a 10-fold increase in Σ_4PBDEs [BDEs 47, 99, 100, and 153]) (Eskenazi et al., 2013). However, null associations were reported between 4-year BDE-47 and cognition scores in a cohort in Menorca, Spain (Gascon et al., 2011). No other study outside of these has examined child serum PBDEs and FSIQ. Studies examining PBDEs in breastmilk and cognition have yielded conflicting results. In a Taiwanese study, Σ_{14}PBDEs in breastmilk was not correlated with scores on cognition or language at 8–12 months (Chao et al., 2011). In contrast, improvements in cognition were reported in children at 36 months with higher breastmilk BDE-153 in the North Carolina PIN (Pregnancy, Infection, and Nutrition) Babies Study (Adgent et al., 2014).

We found consistent evidence suggesting PBDE concentrations at age 8 years were associated with externalizing behaviors measured concurrently, including hyperactivity and aggression. Further, increased risk of having a score ≥60 in Hyperactivity or Aggression was also observed with higher BDE-28, -47, -153, and ΣPBDEs. Previously, BDE-47, -99, and -100 concentrations in breastmilk were associated with increased externalizing behaviors at 30 months of age (Hoffman et al., 2012). Findings from our study also corroborate those of the CHAMACOS Study, which reported increased attention and hyperactivity problems in children with higher Σ_4PBDEs concentrations at 7 years (Eskenazi et al., 2013). However, null associations were reported within the same cohort between Σ_4PBDEs at 9 years and hyperactivity and attention problems at 9–12 years, though sex-specific impairments in executive function were observed among females (Sagiv et al., 2015). Gascon et al. (2011) reported increased risk of attention deficit symptoms at 4 years with higher concurrent BDE-47, though no association was observed with hyperactivity. Additionally, no association was reported between PBDEs in children 12–15 years and self-reported ADHD in the U.S. National Health and Nutrition Examination Survey (NHANES) (Przybyla et al., 2016).

Epidemiologic studies examining postnatal PBDEs and neurobehavior are limited and inconsistent. Contradictory conclusions may be due to the timing and matrices in which

PBDEs were quantified. Only three studies measured PBDEs in child serum: CHAMACOS, Spain, and the NHANES (Eskenazi et al., 2013; Gascon et al., 2011; Przybyla et al., 2016; Sagiv et al., 2015), as we did; while others assessed concentrations in breastmilk, which only partially indicate first year exposure levels for breastfed infants without incorporating placenta transfer or postnatal dust ingestion (Adgent et al., 2014; Chao et al., 2011; Hoffman et al., 2012). Secondly, our study is a prospective birth cohort with multiple prospective PBDE measurements, while Gascon et al. (2011) and Przybyla et al.'s (2016) were cross-sectional. Third, contrasting neurobehavioral domains, neurodevelopmental batteries, and age at assessment may also contribute to discordant findings. Only two studies (PIN and CHAMACOS) utilized the same assessments we used (WISC-IV, BASC-2) (Adgent et al., 2014; Eskenazi et al., 2013; Sagiv et al., 2015), and the CHAMACOS Study assessed neurobehavior at 7–12 years, whereas Adgent et al. (2014) examined children at 36 months. Fourth, PBDE concentrations varied between cohorts. The GM of BDE-47 in HOME Study children at age 8 years was 20.3 ng/g lipid, while the CHAMACOS Study had lower concentrations at 7 years (15.8 ng/g lipid) and higher concentrations at 9 years (35.2 ng/g lipid) (Eskenazi et al., 2013; Sagiv et al., 2015). Further, median serum concentrations of BDE-47 at 4 years in the Menorca cohort were very low (0.12 ng/g lipid) (Gascon et al., 2011).

We did not observe sexually dimorphic relationships for our main findings between PBDEs and FSIQ (BDE-28 at 3 years; BDE-153 at 2, 3, 5, and 8 years) and Externalizing Problems (BDE-28, -47, and ΣPBDEs at 8 years; BDE-153 at 1 year). Although, effect measure modification by child sex was found among associations that were not significant in our main analyses (FSIQ: BDE-47, -100, and ΣPBDEs at 8 years), with male-specific deficits in FSIQ. While it is unclear whether the associations between childhood PBDEs and FSIQ are modified by child sex, Leonetti et al (2016) have reported higher concentrations of PBDEs in the placentas of male infants than females. In addition, PBDEs were observed to alter thyroid hormone function in a sex-specific manner. However, the CHAMACOS Study reported no sex differences between Σ_4PBDEs and FSIQ at 7 years (Eskenazi et al., 2013). In contrast, Sagiv et al. (2015) observed females in the same cohort were more sensitive to Σ_4PBDEs at 9 years for attention and hyperactivity at 9–12 years of age. It is possible that sexually dimorphic relationships exist between PBDEs and neurobehavior at some combination of congeners and age points. However, the main findings from the HOME and CHAMACOS Studies suggest postnatal PBDEs are neurotoxic to both sexes.

Our findings provide evidence to support PBDEs' neurotoxicity during childhood. Deficits in FSIQ at age 8 were observed across several PBDE congeners as well as the sum of the congeners. We observed statistically significant associations with BDE-153, which is more difficult to metabolize and excrete and has a higher fat deposition than other PBDE congeners (Staskal et al., 2006). We found that PBDEs at multiple time points during childhood were associated with FSIQ decrements at age 8, but most significant associations with externalizing behaviors were with concurrent PBDE concentrations at 8 years. It is possible that PBDEs are neurotoxic; however, windows of susceptibility may depend on the neurodevelopmental domain. Both the CHAMACOS and HOME Study report decrements in FSIQ and increased externalizing problems with increased prenatal PBDEs and postnatal PBDEs measured in children up to 8 years.

This study has several methodological strengths, including its prospective study design and long follow-up period. We also had comprehensive measures of childhood serum PBDEs at multiple time points that allowed us to estimate associations for different exposure windows. By utilizing multiple informant models, we were able to conduct a comprehensive investigation of childhood PBDEs to identify windows of susceptibility to postnatal PBDE neurotoxicity, which has not been done in previous epidemiologic studies. Third, we estimated missing PBDEs using multiple imputation to minimize a loss in power. While imputing PBDE estimates are likely to result in some degree of random error, multiple imputation yielded GMs that were similar to the original, non-imputed PBDE measurements, with only slightly higher GMs for PBDEs at 2 and 3 years. In addition, study findings did not differ when we only examined non-imputed data, providing further assurance of the imputation-based modeling. Further, the main findings from our study were between PBDEs at 5 and 8 years and decrements in FSIQ and increased externalizing problems. PBDE concentrations were only imputed in 32% and 8% of HOME Study children at 5 and 8 years, respectively. Additional analyses examining this research question using the original, non-imputed data with a traditional modeling approach of multiple linear regression yielded similar conclusions. As such, concerns regarding the study's findings based on imputed data are alleviated. Fourth, PBDE concentrations in the HOME Study are similar to levels in other U.S. cohorts (Eskenazi et al., 2013). Further, PBDE concentrations in HOME Study mothers (GM=21.7 ng/g lipid) are representative of pregnant women in US population (GM=23.9 ng/g lipid) (Woodruff et al., 2011). Lastly, we were able to adjust for an extensive array of confounders, including sociodemographics, the home environment, and maternal IQ and depressive symptoms.

Nevertheless, our findings are subject to some limitations, including selection bias. However, despite sample attrition, children included in the present study were similar to those excluded due to missing PBDEs and/or neurobehavior measures with regard to prenatal BDE-47 concentrations, sociodemographics, home environment, sex, and maternal characteristics (except marital status). Multiple comparisons is also a concern; however, we used multiple informant models to incorporate all PBDE measures in the same model, thereby reducing the total number of models. Of the 24 models in the present study, we would expect to see one statistically significant association based on chance alone. However, we observed 10 statistically significant findings. Further, our sensitivity analyses of the 24 models resulted in 12 statistically significant associations. In addition, we acknowledge that separating congener-specific associations is difficult due to the high correlations between congeners. Residual confounding by socioeconomic status may also be a concern as effect estimates were greatly attenuated by the inclusion of household income. Finally, our study cannot address the discrepancies that were observed in the CHAMACOS Study with regard to postnatal PBDEs and externalizing behaviors. In that study, despite reporting increased hyperactivity problems in children at 7 years with increased concurrent PBDE concentrations, non-significant findings were observed between PBDE concentrations at 9 years and hyperactivity at 9–12 years. These conflicting results may be due to the nonlinear continuity of externalizing problems, which decreases from early childhood to preadolescence and increases during adolescence before declining once more as adolescents reach adulthood (Petersen et al., 2015). Further, the cohort profile of the CHAMACOS

Study changed with the second child recruitment wave at age 9 years. The examination of childhood PBDEs and attention and executive function were limited to 9 year concentrations due to unmeasured PBDE estimates earlier in childhood in the newly enrolled children.

5. Conclusion

These findings suggest that PBDE exposure during childhood may be associated with decrements in child IQ and increases in externalizing behaviors. Given that the increases in PBDE concentrations after birth coincide with ongoing brain development, it is paramount that additional studies examine PBDEs' potential neurotoxicity during childhood taking into account mixtures of multiple environmental pollutants and in adolescence when children are encountering academic challenges and new social patterns. Finally, this study highlights the need to further reduce exposures to PBDEs in childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADHD	Attention deficit/hyperactivity disorder
BASC-2	Behavioral Assessment System for Children-2
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CHAMACOS Study	Center for the Health Assessment of Mothers and Children of Salinas Study
FSIQ	Full Scale IQ
GM	Geometric mean
HOME Score	Home Observation for Measurement of the Environment Score
HOME Study	Health Outcomes and Measures of the Environment Study
LOD	Limit of detection
NHANES	National Health and Nutrition Examination Survey

PBDEs	Polybrominated diphenyl ethers
PCBs	Polychlorinated biphenyls
PIN Babies Study	Pregnancy, Infection, and Nutrition Babies Study
WISC-IV	Wechsler Intelligence Scale for Children-IV

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Highlights

- Childhood PBDEs are associated with decrements in FSIQ at 8 years
- BDE-28 at 3 years and BDE-153 at 2–8 years significantly reduced FSIQ by >5 points.
- Several PBDEs at 8 years were positively associated with externalizing behaviors
- Concurrent PBDEs were associated with increased hyperactivity and aggression scores

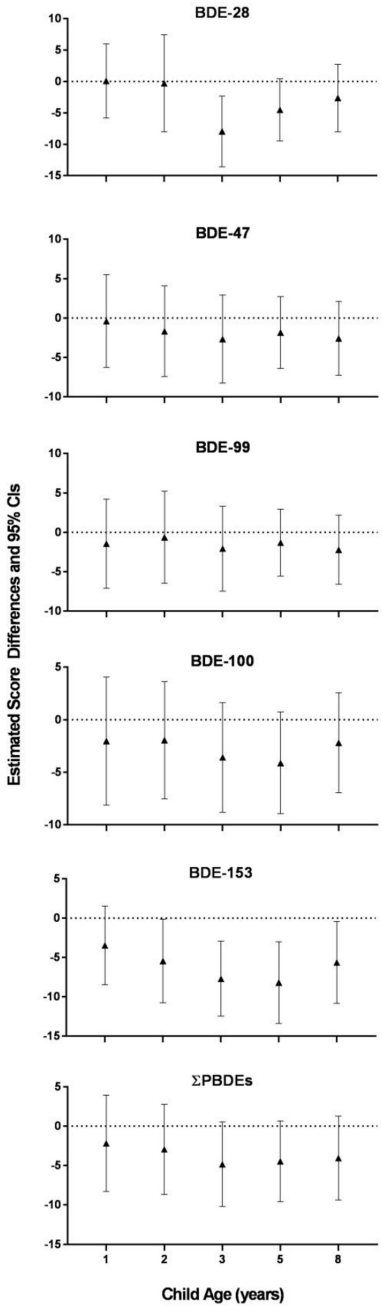

Figure 1.

Estimated score differences and 95% CIs in WISC FSIQ at 8 years by a 10-fold increase in childhood PBDE concentrations in each exposure window, HOME Study. Adjusted by maternal age, race, marital status, maternal serum cotinine, maternal IQ, child sex, maternal depression, household income, and HOME Score.

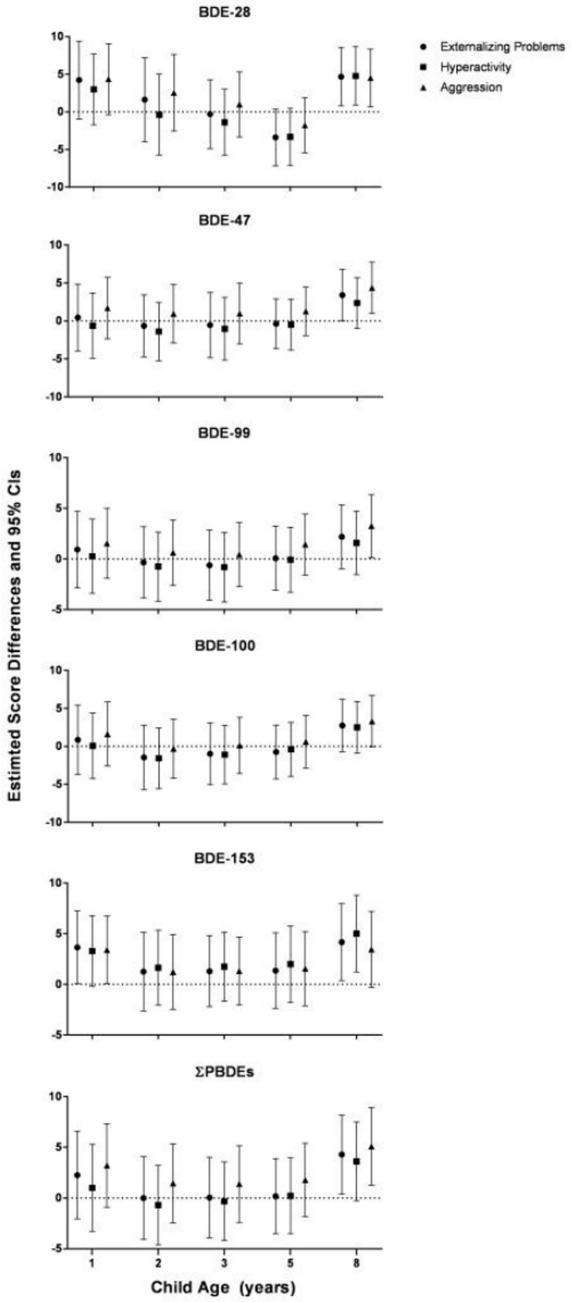

Figure 2.

Estimated score differences and 95% CIs in BASC-2 Externalizing Problems and its subscales by a 10-fold increase in childhood PBDE concentrations, HOME Study. Adjusted by maternal age, race, marital status, maternal serum cotinine, maternal IQ, child sex, maternal depression, household income, and HOME score.

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Table 1

Childhood serum concentrations of ΣPBDEs (ng/g lipid) and neurobehavior at 8 years by maternal and child characteristics, HOME Study

	ΣPBDEs - 1 year		2 years		3 years		5 years		8 years		WISC FSIQ		BASC Externalizing Problems	
	n	GM±GSD	n	GM±GSD	n	GM±GSD	n	GM±GSD	n	GM±GSD	n	Mean±SD	n	Mean±SD
All participants	208	118.1±2.3	208	127.7±2.5	208	100.5±2.5	208	64.6±2.2	208	43.6±2.2	204	101.7±15.8	208	49.6±9.7
Age at delivery, years[b,e,f]														
<25	59	100.7±2.1	59	173.4±2.1	59	113.3±2.2	59	63.0±2.3	59	39.3±2.2	56	93.2±16.3	59	49.3±10.8
25–34	117	130.0±2.4	117	129.4±2.5	117	103.7±2.5	117	66.1±2.2	117	49.0±2.1	116	103.3±14.3	117	49.8±9.4
≥35	31	112.9±2.2	31	68.4±2.3	31	71.6±2.5	31	61.8±2.3	31	34.2±2.3	31	110.7± 13.0	31	50.0±8.5
Race/ethnicity[b,c,f]														
Non-Hispanic White	122	117.7±2.2	122	99.0±2.3	122	82.3±2.3	122	60.2±2.2	122	44.0±2.2	120	107.7±12.8	122	49.6±8.7
Non-Hispanic Black and Others	85	115.7±2.4	85	184.6±2.5	85	134.2±2.6	85	71.4±2.3	85	43.0±2.2	83	93.0±15.6	85	49.9±10.9
Family Income[a,b,c,d,f]														
<$40,000	89	130.6±2.2	89	198.3±2.3	89	136.4±2.5	89	73.8±2.3	89	45.8±2.2	87	94.0±15.4	89	50.9±11.1
$40,000–$79,999	65	144.5±2.1	65	122.0±2.3	65	100.7±2.3	65	65.7±2.1	65	44.3±2.2	64	103.5±13.4	65	48.6±8.7
≥$80,000	53	78.4±2.4	53	64.8±2.0	53	60.4±2.1	53	50.4±2.2	53	39.4±2.2	52	112.2±12.1	53	49.1±8.0
Maternal Depression[b,f,g]														
Minimal/mild	185	116.1±2.2	185	121.1±2.4	185	97.3±2.4	185	65.2±2.2	185	44.6±2.1	182	102.6±15.5	185	49.1±9.4
Moderate/severe	20	138.2±2.8	20	204.1±3.1	20	135.5±3.5	20	61.3±2.9	20	36.0±2.7	19	95.0±15.5	20	55.9±10.7
HOME score[b,c,f]														
≥40	118	106.8±2.4	118	99.4±2.3	118	86.6±2.3	118	59.7±2.1	118	43.4±2.2	115	107.7±13.7	118	48.9±8.8
35–39	40	128.3±2.3	40	188.2±2.7	40	136.1±3.0	40	77.7±2.7	40	48.4±2.5	40	96.0±16.4	40	51.8±12.0
<35	34	147.0±2.1	34	178.8±2.3	34	115.5±2.4	34	74.6±2.2	34	42.9±1.8	33	92.6±13.8	34	50.4±8.5
Marital status[a,b,c,d,f]														
Married/living with partner	151	107.0±2.3	151	100.3±2.2	151	80.9±2.2	151	57.3±2.1	151	43.2±2.1	148	105.4±14.3	151	49.3±8.7
Not married, living alone	56	155.2±2.1	56	245.8±2.3	56	181.2±2.5	56	88.8±2.4	56	44.6±2.3	55	91.7±15.2	56	50.9±11.9
Child Sex[g]														
Male	93	124.2±2.2	93	129.4±2.2	93	99.5±2.4	93	62.4±2.3	93	44.0±2.3	92	101.1±15.5	93	51.8±9.9
Female	115	113.4±2.3	115	126.4±2.7	115	101.3±2.5	115	66.4±2.2	115	43.3±2.1	112	102.2±16.0	115	47.9±9.2
n Pearson r														

	ΣPBDEs - 1 year		2 years		3 years		5 years		8 years		WISC FSIQ		BASC Externalizing Problems	
Maternal IQ[b,c,f]														
(Mean±SD 105.6±15.6)	197	−0.11	197	−0.35	197	−0.28	197	−0.13	197	−0.04	193	0.51	197	0.01
Maternal cotinine[b,c,f]														
(GM±GSD 0.07±22.8 ng/mL)	203	0.10	203	0.31	203	0.24	203	0.08	203	−0.08	199	−0.31	203	0.06

Abbreviations: GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.

$p < 0.05$ for ΣPBDEs at:

[a] 1 year,

[b] 2 years,

[c] 3 years,

[d] 5 years,

[e] 8 years; $p < 0.05$ for:

[f] WISC FSIQ and

[g] BASC Externalizing Problems (two-sided p values using ANOVA

Table 2

Pearson correlation coefficients for maternal characteristics with concentrations of ΣPBDEs (ng/g lipid) and neurobehavior at 8 years, HOME Study

	ΣPBDEs - 1 year		2 years		3 years		5 years		8 years		WISC FSIQ		BASC Externalizing Problems	
	n	**Pearson r**	**n**	**Pearson r**	**n**	**Pearson r**	**n**	**Pearson r**	**n**	**Pearson r**	**n**	**Pearson r**	**n**	**Pearson r**
Maternal IQ[b,c,f]														
(Mean±SD 105.6±15.6)	197	−0.11	197	−0.35*	197	−0.28*	197	−0.13	197	−0.04	193	0.51*	197	0.01
Maternal cotinine[b,c,f]														
(GM±GSD 0.07±22.8 ng/mL)	203	0.10	203	0.31*	203	0.24*	203	0.08	203	−0.08	199	−0.31*	203	0.06

Abbreviations: GM, geometric mean; GSD, geometric standard deviation; SD, standard deviation.

* $p < 0.05$

Table 3

Estimated score differences and 95% CIs in WISC FSIQ and BASC-2 Externalizing Problems and its subscales at 8 years by a 10-fold increase in childhood polybrominated diphenyl ether concentrations in the non-imputation-based analysis, HOME Study[a]

PBDEs	FSIQ	Externalizing Problems[b]	Hyperactivity	Aggression
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
BDE-28				
1 year	4.0 (−5.7, 13.8)	1.6 (−4.7, 8.0)	−0.6 (−7.4, 6.2)	3.8 (−2.6, 10.1)
2 years	−4.2 (−17.8, 9.4)	−3.4 (−10.8, 3.9)	−6.6 (−13.9, 0.7)	−0.6 (−8.8, 7.6)
3 years	−12.3 (−23.6, −1.1)	−2.0 (−11.3, 7.2)	−3.6 (−12.0, 4.8)	−1.2 (−9.0, 6.6)
5 years	−2.4 (−9.5, 4.8)	−3.6 (−7.8, 0.5)	−4.3 (−9.7, 1.2)	−0.9 (−4.5, 2.7)
8 years	−2.3 (−7.8, 3.3)	4.8 (1.6, 8.0)	5.0 (0.8, 9.2)	4.6 (1.4, 7.7)
BDE-47				
1 year	−1.5 (−7.3, 4.2)	−0.8 (−5.2, 3.6)	−2.4 (−6.7, 1.8)	1.4 (−2.7, 5.6)
2 years	−3.9 (−11.7, 3.9)	−2.3 (−8.2, 3.5)	−3.5 (−9.3, 2.2)	0.2 (−5.8, 6.2)
3 years	−4.7 (−12.6, 3.2)	−1.8 (−7.1, 3.5)	−2.7 (−8.2, 2.7)	0.2 (−4.9, 5.2)
5 years	−1.6 (−7.4, 4.1)	−0.8 (−3.8, 2.3)	−1.0 (−4.7, 2.8)	1.4 (−1.6, 4.4)
8 years	−1.3 (−6.5, 3.9)	3.4 (0.2, 6.5)	2.0 (−1.9, 5.8)	4.7 (1.7, 7.7)
BDE-99				
1 year	−2.8 (−7.9, 2.3)	−0.3 (−4.3, 3.8)	−1.3 (−5.1, 2.5)	1.2 (−2.6, 5.0)
2 years	−2.4 (−10.1, 5.2)	−1.4 (−6.6, 3.8)	−1.7 (−6.6, 3.2)	−0.01 (−5.7, 5.7)
3 years	−3.5 (−10.7, 3.7)	−1.2 (−5.9, 3.5)	−1.4 (−6.2, 3.4)	0.1 (−4.5, 4.6)
5 years	−1.8 (−7.3, 3.7)	−0.4 (−3.2, 2.5)	−0.6 (−4.0, 2.8)	1.5 (−1.3, 4.3)
8 years	−1.1 (−6.1, 3.8)	2.1 (−1.2, 5.4)	1.0 (−3.0, 4.9)	3.6 (0.5, 6.7)
BDE-100				
1 year	−3.0 (−8.9, 3.0)	−1.6 (−6.0, 2.8)	−2.8 (−7.0, 1.4)	0.3 (−3.7, 4.4)
2 years	−3.6 (−12.0, 4.8)	−3.5 (−8.9, 2.0)	−3.6 (−8.9, 1.7)	−2.0 (−7.9, 4.0)
3 years	−6.3 (−14.7, 2.1)	−3.0 (−8.3, 2.4)	−3.4 (−8.8, 2.0)	1.4 (−6.6, 3.8)
5 years	−4.5 (−10.4, 1.3)	−1.2 (−4.6, 2.1)	−0.9 (−4.8, 3.0)	0.7 (−2.6, 4.0)
8 years	−0.8 (−6.5, 4.9)	2.2 (−1.2, 5.7)	1.8 (−2.3, 5.9)	3.2 (−0.2, 6.6)
BDE-153				
1 year	−2.8 (−8.2, 2.6)	0.7 (−3.7, 5.1)	0.7 (−3.1, 4.6)	0.9 (−3.0, 4.8)
2 years	−4.1 (−11.5, 3.2)	−1.1 (−5.8, 3.5)	0.4 (−3.8, 4.5)	−2.1 (−6.9, 2.8)
3 years	−7.1 (−14.4, 0.2)	−1.1 (−6.7, 4.6)	0.3 (−4.7, 5.3)	−2.0 (−7.4, 3.4)
5 years	−8.1 (−14.0, −2.2)	−1.4 (−6.5, 3.6)	−0.4 (−5.5, 4.7)	0.1 (−4.8, 5.0)
8 years	−3.8 (−9.4, 1.8)	4.0 (0.2, 7.8)	4.7 (0.7, 8.6)	3.4 (−0.8, 7.6)
ΣPBDEs				
1 year	−1.3 (−9.2, 6.6)	0.3 (−5.0, 5.6)	−0.7 (−6.2, 4.9)	1.6 (−3.6, 6.8)
2 years	−6.2 (−19.7, 7.4)	−3.0 (−8.8, 2.7)	−5.0 (−11.0, 1.0)	−1.2 (−8.3, 5.9)
3 years	−11.1 (−23.9, 1.6)	−1.6 (−10.3, 7.2)	−1.3 (−10.3, 7.7)	−3.4 (−11.2, 4.3)
5 years	−2.7 (−10.0, 4.7)	−1.7 (−5.6, 2.2)	−1.7 (−6.7, 3.3)	0.5 (−3.1, 4.0)

PBDEs	FSIQ	Externalizing Problems[b]	Hyperactivity	Aggression
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
8 years	−2.5 (−8.7, 3.7)	3.9 (0.4, 7.5)	2.9 (−1.6, 7.4)	4.9 (1.4, 8.5)

[a]Adjusted by maternal age, race/ethnicity, marital status, maternal serum cotinine, maternal IQ, child sex, maternal depression, household income, and HOME Score.

[b]Externalizing Problems: Hyperactivity + Aggression + Conduct Disorder