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Childhood polybrominated diphenyl ether (PBDE) exposure and executive function in children in the HOME Study

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ABSTRACT

Prenatal exposure to polybrominated diphenyl ethers (PBDEs) have been reported to impair executive function in children, but little is known whether childhood PBDE exposures play a role. Using the Health Outcomes and Measures of the Environment (HOME) Study, a prospective birth cohort in the greater Cincinnati area, we investigated the association between repeated measures of PBDEs during childhood and executive function at 8 years in 208 children and whether effect modification by child sex was present. We used child serum collected at 1, 2, 3, 5, and 8 years to measure PBDEs. The Behavior Rating Inventory of Executive Function was completed by parents to assess executive function at 8 years. We used multiple informant models to examine childhood PBDEs during several exposure windows. Null associations were observed between early childhood PBDEs and executive function. However, we observed significant adverse associations between a 10-fold increase in concurrent concentrations of BDE-28 (β = 4.6, 95% CI 0.5, 8.7) and BDE-153 (β = 4.8, 95% CI 0.8, 8.8) with behavioral regulation. In addition, PBDEs at 8 years were significantly associated with poorer emotional and impulse control. No associations were noted between childhood PBDEs and metacognition or global executive function. However, child sex significantly modified the associations, with significantly poorer executive function among males with higher concurrent BDE-153, and null associations in females. Our study findings suggest that concurrent PBDE exposures during childhood may be associated with poorer executive function, specifically behavior regulation. Males may also be more sensitive to adverse associations of concurrent PBDEs on executive function.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are persistent chemicals that were introduced in the late 1970s to retard fire in commercial polymer-based products, including furniture and electronics. In the 2000s, restrictions on the use of PBDEs were made in Europe, the US, and other countries in light of the potential adverse health effects of PBDEs and their persistence in the environment, biota, and in humans (Siddiqi et al., 2003). Several epidemiologic studies have reported that higher PBDE concentrations during fetal development were associated with decreased full scale intelligence quotient (FSIQ) scores, diminished language and reading abilities, increased problems with hyperactivity and attention, and poorer executive function in children (Braun et al., 2017b; Chen et al., 2014; Cowell et al., 2015; Ding et al., 2015;

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CHAMACOS Study, Center for the Health Assessment of Mothers and Children of Salinas; FSIQ, full scale intelligence quotient; GAM, generalized additive model; GEE, generalized estimating equations; GM, geometric mean; GSD, geometric standard deviation; HOME Study, Health Outcomes and Measures of the Environment study; MCMC, Markov Chain Monte Carlo; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; OR, odds ratio; SD, standard deviation; TTR, transthyretin

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Eskenazi et al., 2013; Gascon et al., 2011; Herbstman et al., 2010; Roze et al., 2009; Sagiv et al., 2015; Shy et al., 2011; Vuong et al., 2016; Zhang et al., 2017).

One study has examined childhood PBDEs and executive function (Sagiv et al., 2015). While no associations were reported between Σ_4PBDEs (BDE-47, -99, -100, and -153) at 9 years and executive function at 9 and 12 years, Sagiv et al. (2015) observed poorer parent-reported executive function in females with higher Σ_4PBDE concentrations, but not in males. Executive function reflects prefrontal cortex activities and encompasses distinct and inter-related components, including attentional control, cognitive flexibility, goal setting, and information processing, that are necessary for complex activities, academic achievement, as well as daily behavioral and social interactions. PBDE exposures that occur during infancy and childhood may impair brain maturation, particularly with respect to executive function, as it has been shown to have a continued developmental course through adolescence (Anderson et al., 2001a). While various executive function domains have heterogeneous developmental trajectories, rapid incremental advances in executive function parallel the major periods of growth of the frontal lobes, which occur from birth to 2 years, 7–9 years, and 16–19 years (Anderson et al., 2001a; Anderson et al., 2001b). Further, PBDE concentrations are higher among infants, toddlers, and children compared to the adult population (Costa and Giordano, 2007; Schecter et al., 2005; Toms et al., 2008; Toms et al., 2009). The objective of the present study was to investigate the relationship between PBDE concentrations during childhood (1–8 years) and executive function at 8 years and to examine effect modification by child sex.

2. Materials and methods

2.1. Study participants

This study included children from the Health Outcomes and Measures of the Environment (HOME) Study, a well-characterized, ongoing prospective pregnancy and birth cohort in Cincinnati, OH, USA. Details regarding recruitment, eligibility criteria, biospecimen collection, environmental samples, neurobehavioral assessments, as well as follow-up visits are described in detail by Braun et al. (2017a). Briefly, 468 pregnant women at 16 ± 3 weeks of gestation were enrolled during 2003–2006 from nine prenatal clinics and 390 remained to deliver live singleton infants. To be included in the present study, children had to have had at least one PBDE measure during childhood and an assessment of executive function at 8 years. The institutional review boards at the Cincinnati Children's Hospital Medical Center and the Centers for Disease Control and Prevention (CDC) approved this study.

2.2. Assessment of childhood PBDEs

Postnatal PBDEs were measured from blood samples collected at 1, 2, 3, 5, and 8 years using gas chromatography/isotope dilution high-resolution mass spectrometry. Information regarding postnatal PBDE measurement procedures (e.g., quality assurance, lipid adjustment) have been described previously (Vuong et al., 2017). PBDE measurements less than the limit of detection (LOD) were replaced with the following: LOD/√2. Detection frequencies of select PBDE congeners (-28, −47, −99, −100, and −153) examined in this study are listed in Supplemental Table S1. A total of 208 children with an assessment of executive function at 8 years had PBDE concentrations measured at least once during childhood. However, only 49 (24%), 77 (37%), 18 (9%), 20 (10%), and 44 (21%) children had 1, 2, 3, 4, and 5 PBDE measures during childhood, respectively. Due to limited serum availability from ages 1–3, only a subset of the children who came for follow-up had sufficient serum for PBDE measurements. Thus, we were missing 122 (59%), 139 (67%), 139 (67%), 67 (32%), and 16 (8%) of the 208 children with PBDE measurements at ages 1, 2, 3, 5, and 8 years, respectively. Multiple imputation using the Markov Chain Monte Carlo (MCMC) method was utilized to estimate missing PBDE concentrations for children who had at least one PBDE measurement during childhood. Detailed procedures to produce 100 imputed datasets using multiple imputation models can be found elsewhere (Vuong et al., 2017).

2.3. Behavior Rating Inventory of Executive Function (BRIEF)

To assess executive function at 8 years, the BRIEF, a valid and reliable questionnaire (Gioia et al., 2000a,b; Skogerbo et al., 2012), was completed by a parent who had extensive contact with the child within the past 6 months. The BRIEF comprises of 86 items and is designed to assess executive function abilities during everyday activities at home, school, and community settings. Behaviors are rated as either: never, sometimes, or often a problem. Raw scores were converted to standardized *T*-scores based on sex-specific norms for the age as described in the BRIEF manual. Questionnaire responses were used to derive a summary measure from eight clinical scales, referred to as the global executive composite. These clinical scales also yield two broad indexes: 1) behavioral regulation index (scales: inhibit + shift + emotional control); and 2) metacognition index (scales: initiation + working memory + plan/organize + organization of materials + monitor). BRIEF *T*-scores have a mean of 50 ± 10, with higher scores indicating poorer performance. While scores 1.5 SDs (standard deviation) above the mean are clinically significant (Gioia et al., 2000a), we defined BRIEF scores 1 SD above the mean (≥60) as "at risk" of a clinically relevant executive function problem due to our modest sample size (Supplemental Table S2).

2.4. Statistical analyses

To examine PBDE neurotoxicity at different exposure windows during childhood, we used multiple informant models to estimate βs and 95% confidence intervals (CIs) between repeated measures of $\log_{10}$-transformed lipid-adjusted PBDE concentrations (BDE-28, -47, -99, -100, -153, and their sum [ΣPBDEs]) with BRIEF scores at 8 years using the imputed datasets (Horton et al., 1999; Litman et al., 2007). Multiple informant models uses a non-standard version of generalized estimating equation that allows for repeated measures of PBDEs during childhood. Details regarding multiple informant models have been described by Sanchez et al. (2011). We modeled each PBDE congener individually, including all five windows of exposure (1, 2, 3, 5, and 8 years). Statistically significant interaction terms between child age and PBDEs indicate a potential window of vulnerability to PBDE neurotoxicity. We report β estimates for each exposure time, because several interaction terms (PBDEs × age) had a $p < 0.10$. We also investigated whether childhood PBDEs are associated with having an "at risk" BRIEF score (≥60) using multiple informant models to generate odds ratios (ORs) and 95% CIs. To determine whether effect measure modification by child sex was present between childhood PBDE concentrations and executive function, we included interaction terms between PBDEs (continuous), child sex (binary), and child age (categorical), as well as all 2-way interactions. We also examined non-linear exposure response using separate generalized additive models (GAMs) for each window of exposure for childhood PBDEs and executive function. All models included the following covariates based on bivariate analysis with executive function ($p < 0.10$) (as categorized in Table 1): maternal age, race/ethnicity, household income, child sex, maternal blood lead level, maternal depression (Beck et al., 1996), prenatal vitamin use, maternal IQ (Wechsler, 1999), marital status, and Home Observation for Measurement of the Environment score.

We performed a sensitivity analysis to re-examine research questions using the original, non-imputed data to alleviate the concerns of imputed exposures mostly in early childhood (1–3 years). In other