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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 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.

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, 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. (2017). 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 and 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 / $\sqrt{2}$ (Hornung and Reed, 1990). LOD was defined as three times the standard deviation 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 to 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, 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,