Environment International 118 (2018) 9–16

Contents lists available at ScienceDirect

Environment International

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

Associations between prenatal and childhood PBDE exposure and early adolescent visual, verbal and working memory

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ARTICLE INFO

Keywords:
PBDE
Flame retardant
Prenatal
Trajectory
Childhood
Memory

ABSTRACT

Background: Prenatal and childhood exposure to polybrominated diphenyl ether (PBDE) flame retardants has been inversely associated with cognitive performance, however, few studies have measured PBDE concentrations in samples collected during both prenatal and postnatal periods.

Methods: We examined prenatal (cord) and childhood (ages 2, 3, 5, 7 and 9 years) plasma PBDE concentrations in relation to memory outcomes assessed between the ages of 9 and 14 years. The study sample includes a subset (n = 212) of the African American and Dominican children enrolled in the Columbia Center for Children's Environmental Health Mothers and Newborns birth cohort. We used multivariable linear regression to examine associations between continuous $\log_{10}$-transformed PBDE concentrations and performance on tests of visual, verbal and working memory in age-stratified models. We additionally used latent class growth analysis to estimate trajectories of exposure across early life, which we analyzed as a categorical variable in relation to memory outcomes. We examined interactions between PBDE exposure and sex using cross-product terms.

Results: Associations between prenatal exposure and working memory significantly varied by sex (p-*interaction* = 0.02), with inverse relations observed only among girls (i.e. $\beta_{BDE\text{-}47}$ = −7.55, 95% CI: −13.84, −1.24). Children with sustained high concentrations of BDEs-47, 99 or 100 across childhood scored approximately 5–8 standard score points lower on tests of visual memory. Children with PBDE plasma concentrations that peaked during toddler years performed better on verbal domains, however, these associations were not statistically significant.

Conclusions: Exposure to PBDEs during both prenatal and postnatal periods may disrupt memory domains in early adolescence. These findings contribute to a substantial body of evidence supporting the developmental neurotoxicity of PBDEs and underscore the need to reduce exposure among pregnant women and children.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of organohalogenated flame retardant chemicals that were used extensively in furniture and furnishings to meet United States fire safety standards until their phase-out between 2004 and 2013 (Abbasi et al., 2015). Exposure to PBDEs occurs primarily through incidental ingestion of dust (EPA, 2010) and owing to their lipophilicity, PBDEs readily cross the placenta (Leonetti et al., 2016) and partition into breastmilk (Carrizo et al., 2007).

Mounting evidence supports an association between prenatal exposure to PBDEs and reduced cognitive abilities in children (Lam et al., 2017; Roth and Wilks, 2014). Importantly, the brain continues to develop postnatally, remaining vulnerable to insult by environmental toxicants throughout childhood (Grandjean and Landrigan, 2014). Additionally, research indicates PBDE exposure may peak during childhood due to breastfeeding, as well as increased ingestion of dust from close proximity to the floor and frequent hand to mouth behavior (Fromme et al., 2016). Despite these factors, limited research has examined health effects associated with PBDE concentrations measured

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https://doi.org/10.1016/j.envint.2018.05.004
Received 8 January 2018; Received in revised form 12 April 2018; Accepted 1 May 2018

during both prenatal and postnatal periods (Eskenazi et al., 2013; Gascon et al., 2011; Vuong et al., 2017).

In the present study, we examined associations between plasma PBDE concentrations measured repeatedly throughout the early life-course (birth through age 9 years) in relation to several subdomains of memory measured during early adolescence. We selected memory outcomes based on the results of animal research demonstrating inverse associations between PBDEs and performance on tests of memory and learning (Driscoll et al., 2009; Dufault et al., 2005; Viberg et al., 2003; Viberg et al., 2006), as well as findings from human studies demonstrating inverse associations between PBDEs and cognitive performance (Eskenazi et al., 2013; Herbstman et al., 2010).

2. Methods

2.1. Study design and participants

The Columbia Center for Children's Environmental Health (CCCEH) Mothers and Newborns study is a longitudinal birth cohort of African American and Dominican mother-child pairs recruited from Northern Manhattan and the South Bronx. Additional details describing the study design have been previously published (Perera et al., 2006). Eligible (healthy, 18–35 year old women free of tobacco and illicit drug use who initiated prenatal care by the 20th week of gestation) participants were recruited between 1998 and 2006 from two prenatal clinics. At the time of delivery, 727 mother-child pairs remained eligible and were fully enrolled into the cohort.

Bilingual research staff conducted structured participant interviews during the prenatal period, after delivery, and repeatedly during childhood (3 months, 6 months, 1, 2, 3, 5, 7, 9, 11, and 14 years) to collect information on demographic and lifestyle factors. As previously described (Rauh et al., 2004), prenatal exposure to environmental tobacco smoke was assessed using a combination of questions about smokers in the home and validated by blood cotinine concentrations. Maternal distress was evaluated using the Psychiatric Epidemiology Research Instrument-Demoralization (PERI-D) scale (Dohrenwend et al., 1981) and material hardship was indexed using a series of questions about access to basic needs (food, housing and clothing) (Mayer and Jencks, 1988). At the 3-year follow-up visit, maternal non-verbal intelligence was assessed using the Test of Nonverbal Intelligence, 2nd Edition (TONI-II) (Brown et al., 1997) and the child's living environment was evaluated using the Home Observation for Measurement of the Environment (HOME) Early Childhood Inventory, which was completed during a visit to the family's home (Caldwell and Bradley, 2003). The HOME inventory is designed to evaluate stimulation and support available to children within their family surroundings and includes 8 areas of emphasis, including academic stimulation. Information on birthweight and gestational age was abstracted from medical records.

Before each visit, mothers signed a letter of informed consent and children ≥7 years additionally signed a letter of informed assent. Study procedures were approved by the Institutional Review Boards of Columbia University Medical Center and the New York State Psychiatric Institute. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects' research.

2.2. Memory assessment

Trained research staff administered the Children's Memory Scale (CMS) to children between the ages of 9 and 14 years (mean ± SD: 11.1 ± 1.1); all tests were administered in English. The CMS is designed to measure memory and learning across three domains (attention-concentration, visual/non-verbal, and auditory/verbal) in children and adolescents (Cohen, 1997). We examined scores from the Attention-Concentration, Immediate (i.e. short-term recall) Visual Memory and Immediate Verbal Memory indices, which are age-scaled and standardized against a normative sample to reflect a mean ± SD of 100 ± 15 and range from 50 to 150. The visual ('dot locations' and 'faces') and verbal ('stories' and 'word pairs') indices are each comprised of two subtests which require the child to recall previously seen or heard information and reflect the ability to process, organize and hold material in short term visual and verbal memory. The Attention-Concentration Index is comprised of scores on two core subtests ('numbers' and 'sequences'), which require the participant to recall, manipulate and repeat sequences of numbers, letters, or categories, and thus places a heavy demand on auditory working memory (Cohen, 1997). Additional information describing each subtest is provided in the Supplemental material (Table S1). Sixteen children were excluded from models examining the Attention-Concentration Index scale because they were not administered one of the two core subtests due to factors unrelated to the child. At the time of CMS testing, child anxiety was ascertained using the Revised Children's Manifest Anxiety Scale (RCMAS), which is a brief self-report inventory designed to measure the degree and nature of anxiety (Reynolds and Richond, 1985).

2.3. PBDE exposure assessment

We measured PBDE concentrations in 903 stored plasma samples collected from 334 children between birth and age 9 years (N_{cord} = 327, $N_{2\text{-years}}$ = 56, $N_{3\text{-years}}$ = 115, $N_{5\text{-years}}$ = 42, $N_{7\text{-years}}$ = 203, and $N_{9\text{-years}}$ = 160). Details pertaining to sample collection and analysis of PBDE concentrations in this cohort have been previously published (Cowell et al., 2018a). Briefly, hospital staff collected umbilical cord blood at the child's delivery and a pediatric phlebotomist collected child venous blood at 2, 3, 5, 7 and 9-year follow-up visits. All samples were immediately transported to the CCCEH laboratory, processed and stored in multiple aliquots at −70 °C.

Plasma PBDE concentrations were measured by the CDC using gas chromatography isotope dilution high-resolution mass spectrometry on a DFS instrument (ThermoFisher, Bremen, Germany) (Jones et al., 2012; Sjodin et al., 2004). Before final analytic determinations were made, samples were fortified with internal standards and extracted using a Gilson 215 liquid handler (Gilson Inc., Middleton, WI). Blanks (n = 3) were processed with every 30 samples and the median blank value was subtracted from the final result. Lipids were co-extracted using a Rapid Trace modular SPE work station (Biotage, Uppsala, Sweden) and total cholesterol and triglycerides were measured using commercially available test kits (Roche Diagnostics, Indianapolis, IN). We estimated total cord blood lipids using a recently developed cord blood-specific formula [total cord blood lipids = 2.66 × total cord blood cholesterol + cord blood triglycerides + 0.268, in g lipids/L plasma] (Sjodin A, unpublished data) and child blood lipids using the short formula described by Phillips et al. (1989).

The limits of detection (LODs) for BDE-47 ranged from 0.69 to 11.59 ng/g lipid for cord plasma samples and 1.10 to 20.20 for child plasma samples. For the other three congeners investigated (BDEs-99, 100 and 153), LODs ranged from 0.29 to 5.46 ng/g lipid for cord plasma and 0.45 to 6.40 ng/g lipid for child plasma. As previously described (Cowell et al., 2018a), we replaced concentrations less than the LOD with values drawn at random from a sample-specific normal probability distribution with the same mean and variance of the natural-log transformed detected concentrations with an equal or lower LOD. To incorporate uncertainty introduced by imputation, we repeated this procedure 10 times. Given variation in PBDE detection frequencies for cord (BDE-47: 80%, BDE-99: 51%, BDE-100: 42%, BDE-153: 38%) versus child (across ages 2–9 years: BDE-47: 100%, BDE-99: 80–98%, BDE-100: 90–100%, BDE-153: 90–98%) plasma samples, we performed multiple imputation on cord plasma and child plasma samples separately (i.e. only cord plasma samples were used to impute non-detectable cord plasma concentrations and only child plasma samples were used to impute non-detectable child plasma concentrations).