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## **Prenatal PBDE and PCB Exposures and Reading, Cognition, and Externalizing Behavior in Children**

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**Running title:** Prenatal PBDE and PCB exposures and reading.

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### **Competing financial interest declaration**

Dr. Lanphear has served as an expert witness and a consultant to the California Attorney General's Office for the plaintiffs in a public nuisance case related to childhood lead poisoning, but he has not personally received any compensation for these services. Dr. Lanphear has also served as a paid consultant on a US Environmental Protection Agency research study related to childhood lead poisoning. Dr. Braun was financially compensated for conducting a re-analysis of a study of child lead exposure for the plaintiffs in a public nuisance case related to childhood lead poisoning. None of these activities are directly related to the present study. The other authors declare they have no actual or potential competing financial interests.

## Abstract

**Background:** Prenatal polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) exposures may influence children's neurodevelopment.

**Objective:** To examine the association of prenatal PBDE and PCB exposures with children's reading skills at ages 5 and 8 years, Full-Scale Intelligence Quotient (FSIQ) and Externalizing Problems at age 8 years.

**Methods:** From 239 mother-child pairs recruited (2003-2006) in Cincinnati, OH, we measured maternal serum PBDE and PCB concentrations, assessed child's reading skills using the Woodcock-Johnson Tests of Achievement III (WJ-III) at age 5 years and the Wide Range Achievement Test-4 (WRAT-4) at age 8 years, tested FSIQ using the Wechsler Intelligence Scale for Children-IV (WISC-IV), and Externalizing Problems using the Behavioral Assessment System for Children-2 (BASC-2) at age 8 years. We used multiple linear regression to examine the association of prenatal PBDE and PCB concentrations and reading, FSIQ and Externalizing Problems after adjustment for covariates.

**Results:** A 10-fold increase in Sum<sub>4</sub>PBDEs (BDE-47, -99, -100 and -153) was not significantly associated with reading scores at age 5 years at the p=0.05 level, but was inversely associated with Reading Composite scores ( $\beta$ : -6.2, 95% CI: -11.7, -0.6) and FSIQ ( $\beta$ : -5.3, 95% CI: -10.6, -0.02) at age 8 years; it was positively associated with Externalizing Problems score ( $\beta$ : 3.5, 95% CI: -0.1, 7.2) at age 8 years. Prenatal Sum<sub>4</sub>PCBs (PCB-118, -153, -138-158, and -180) was not significantly associated with child's reading skills, FSIQ and Externalizing Problems.

**Conclusion:** Prenatal PBDE concentration was inversely associated with reading skills and FSIQ, positively associated with Externalizing Problems at age 8 years. No significant associations were found in prenatal PCB concentration.

## **Introduction**

PBDEs were widely used as flame retardants in the manufacture of electronics, furniture, carpets and textiles, and are detectable in indoor dust, fish, birds, human serum and adipose tissue. The phase-out of PBDEs using in US consumer products began in 2004 (Penta- and Octa-PBDE) and 2013 (Deca-PBDE), PBDEs still exist in the environment and biological samples. PCBs, a group of structurally related organic compounds with inertness and thermal stability, were extensively used in various industrial products before 1979. Although PCBs' manufacture was banned in 1979 due to possible adverse effects in humans, PCBs still persist in the environment and accumulate through the food chain, and seafood consumption is currently the main exposure route in human (Thompson and Boekelheide 2013; Xue et al. 2014).

Several previous studies have focused on the association of prenatal PBDE and PCB exposures with child's overall cognition (Chen et al. 2014b; Stewart et al. 2008; Zhao et al. 2013), and our publication reported that prenatal exposure to PBDEs was associated with cognitive deficits and hyperactivity behaviors in children at age 5 years (Chen et al. 2014a). However, few studies have assessed the influence of those chemicals on specific cognitive domains, in particular, the language development and reading skills (Dzwilewski and Schantz 2015). The prenatal period is the most sensitive time window to the influence of environmental factors on cognitive development, when brain development involves neuronal proliferation, differentiation and migration (Kang et al. 2011; Stiles and Jernigan 2010). Reading ability is central to educational attainment and academic achievement, and is predominantly influenced by the development in the brain reading region (Houston et al. 2014). Studies have reported that child's reading ability was impaired by prenatal maternal smoking exposure (Cho et al. 2013). Externalizing problems are symptoms or signs of neurodevelopment, including hyperactivity,

oppositional and aggressive behavior, as well as conduct problems. The purpose of this study was to test the hypothesis that prenatal exposures to PBDEs and PCBs are associated with the poorer reading abilities, lower intelligence and more externalizing problems in children.

## **Methods**

**Study subjects.** The Health Outcomes and Measures of the Environment (HOME) Study is a prospective birth cohort recruited between March 2003 and February 2006 in Cincinnati, OH, as previously described (Geraghty et al. 2008). The study enrolled 468 pregnant women at 16±3 weeks gestation, who were 18 years of age or older, living in Cincinnati, OH, not diagnosed with diabetes, hypertension or reported infection with Human Immunodeficiency Virus, and did not take medicine for seizures or thyroid disorders during pregnancy. Of the 468 women, 389 remained in the study and delivered live-born singletons. For the current study, we excluded infants with congenital malformations or genetic abnormalities (n=2), mothers with missing chemical measures in serum (n=15), and children lost to follow-up and those did not complete assessment at age 5 or 8 years (n=131). This led to a final sample of 239 mother-child pairs for the current analysis. The HOME Study was approved by the Institutional Review Boards at the Cincinnati Children's Hospital Medical Center (CCHMC) and the Centers for Disease Control and Prevention (CDC). All participants provided their written informed consents.

**Maternal serum chemicals measurement.** Maternal blood samples were obtained at 16±3 weeks of gestation, and sera were immediately isolated and stored at -80 °C until shipment on dry ice to the National Center for Environmental Health (NCEH) at CDC for analysis. Maternal sera were analyzed for 10 PBDE congeners (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, -183) and

36 PCB congeners (PCB-18, -28, -44, -49, -52, -66, -74, -87, -99, -101, -105, -110, -118, -128, -138-158, -146, -149, -151, -153, -156, -157, -167, -170, -172, -177, -178, -180,-183, -187, -189, -199, -196-203, -194, -195, -206, -209) using gas chromatography/isotope dilution high-resolution mass spectrometry (Sjodin et al. 2004). All analytic runs included blank and positive quality control samples. PBDEs and PCBs are expressed as nanogram per gram lipid (ng/g lipid) because they are lipophilic compounds. Serum lipid concentrations were calculated using the Phillips formula summing total cholesterol and triglycerides (Phillips et al. 1989). Values below the limit of detection (LOD) were replaced with the LOD divided by the square root of 2 (Hornung-RW and Reed-LD 1990).

**Reading ability assessments.** We assessed children's reading skills at age 5 years using the Woodcock-Johnson Tests of Achievement-III (WJ-III) (Woodcock et al. 2001). For these analyses, we focused on Basic Reading and Brief Reading scores. Basic Reading is a composite of Letter-Word Identification and Word Attack, and measures sight vocabulary, phonics, and structural analysis. Brief Reading is a composite of Letter-Word Identification and Passage Comprehension, and measures reading concepts and readiness. Letter-Word Identification measures the ability to identify letters and read individual words. Word Attack measures skills in applying phonic and structural analysis to the reading of unfamiliar words. Passage Comprehension tests the ability to match a symbol with an actual picture of the object, to point to the picture represented by a phrase, and to identify a missing key word within a passage based on contextual cues.

At age 8 years, we measured each child's basic academic skills to read words and comprehend sentences using the Wide Range Achievement Test 4 (WRAT-4) (Sayegh et al.

2014). Reading Composite score was assessed in the analysis, which was calculated from the Word Reading and Sentence Comprehension subtests. Word Reading measures letter and word reading, and Sentence Comprehension measures the skills to obtain meaning from words and comprehend ideas and information in sentences. Both WJ-III and WRAT-4 items have a population mean of 100 and a standard deviation of 15.

***Neurodevelopmental and behavioral assessments.*** At age 8 years, we administered the Wechsler Intelligence Scale for Children-IV (WISC-IV) to obtain Full scale IQ (FSIQ) (Wechsler 2003), and the Behavioral Assessment System for Children-2 (BASC-2) to obtain Externalizing Problems score (Reynolds and Kamphaus 2004). The FSIQ measures cognitive function and has a population mean of 100 and standard deviation of 15. Externalizing Problems offer an assessment of a child's adaptive and problem behaviors, which includes subscales of aggression and hyperactivity. The Externalizing Problems score has a population mean of 50 and a standard deviation of 10, for which higher score suggests non-optimal behavior. All clinical assessments were performed by HOME study staffs who were trained and certified by a developmental psychologist (KY). The assessors conducted the neurobehavioral assessments without knowledge of maternal serum PBDE and PCB concentrations.

***Statistical analysis.*** We analyzed the associations between maternal serum PBDE or PCB concentrations and the outcome (reading ability, FSIQ or Externalizing Problems) scores using multiple linear regression. We separately used the following exposure variables in the analyses: 1) the sum of BDE-47, -99, -100, and -153 (Sum<sub>4</sub>PBDEs), the four congeners detected in 91% of the HOME study samples, 2) the sum of PCB-118, -153, -138/158, and -180 (Sum<sub>4</sub>PCBs), these

congeners were detected in 94% of the HOME study samples, and Sum<sub>4</sub>PCBs was frequently used in other US cohort studies (Alm et al. 2008; Boucher et al. 2009). Considering their right-skewed distributions and over 100-fold exposure ranges, log<sub>10</sub> transformed Sum<sub>4</sub>PBDE and Sum<sub>4</sub>PCB concentrations were used in this analysis. Covariates for adjustment were identified based on their significant relationship with chemical concentrations and outcome scores using analysis of variance (ANOVA) or t-test for continuous variables, and chi-square test for categorical variables. In the final models, we adjusted for maternal age, race, education, household-income, parity, marital status, smoking status, maternal fish consumption (times of fish-containing meals from baseline visit to child birth), maternal depression, maternal intelligence quotient (IQ), child sex, and the Home Observation for Measurement of the Environment (HOME) score (Totsika and Sylva 2004). Maternal IQ was assessed using the Wechsler Abbreviated Scale of Intelligence, maternal depression was measured using the Beck Depression Inventory-II (Beck et al. 1996) during pregnancy. When the child was 1 year old, study staff visited them and completed the HOME Inventory describing the nurturing environment in the home (Caldwell B and Bradley R 1984).

We used the trend test to test the each outcome's trend by using the median value of each quartile as the independent variable. We also used the Least Absolute Shrinkage and Selection Operator (LASSO) test to simultaneously perform model selection and parameter estimation of each PBDE and PCB congener's relative contribution to the outcome scores (Tibshirani 1996). To ensure the consistency of results, the analysis was repeatedly run with all available data and with data available at both ages of 5 and 8 years. The statistical analysis was completed with SAS 9.4 (SAS Institute Inc., NC, USA), the LASSO test were performed in R 2.11 (R Developmental Team) glmnet packages. We report the regression coefficients and 95%

confidential intervals (CI) from the multiple regression analyses. The statistical significance was set at a two-sided p value of 0.05.

## **Results**

This analysis was based on 239 mothers who were enrolled in the HOME study and provided biological samples for evaluating exposures, and their children who had outcomes of reading ability, FSIQ and Externalizing Problems at age 5 or 8 years. There were no significant difference in either maternal PBDE or PCB concentration measured during pregnancy or demographic characteristics between the 239 subjects included in this analysis and those not included (data not shown).

In the HOME study, maternal median Sum<sub>4</sub>PBDEs concentrations (35.65 ng/g lipid) were slightly lower, the median Sum<sub>4</sub>PCBs (31.30 ng/g lipid) was a little higher as compared to the median concentrations of the U.S. general pregnant women (NHANES, 2003-2004) (Sum<sub>4</sub>PBDEs: 43.2 ng/g lipid, Sum<sub>4</sub>PCBs: 26.8 ng/g lipid) (Woodruff et al. 2011) (Figure 1). Mothers were mainly 25-34 years of age (61%), non-Hispanic White (62%) and married or living with a partner (76%), with college education or above (74%), middle or high level of household income (>\$40,000/y, 76%); most of them did not drink alcohol (56%) and did not smoke tobacco (85%) during pregnancy. Babies were born at a mean gestational age of 39 ± 5.4 weeks. Mothers who were younger than 25 years of age at enrollment, non-white, with a high school or less education, household-income less than \$40,000/y, not married or living alone, were smokers or had higher depression symptom scores (>19), had higher prenatal PBDE and lower PCB concentrations. Additionally, prenatal concentrations of Sum<sub>4</sub>PBDE and Sum<sub>4</sub>PCB were comparable for boys and girls (Table 1).

Children's scores of reading, FSIQ and Externalizing Problems were normally distributed. Reading subset items were highly correlated with each other ( $r=0.58$  for composite measures,  $p<0.001$ ). Reading Composite score was positively correlated with FSIQ ( $r=0.75$ ,  $p<0.0001$ ), and not correlated with Externalizing Problems score ( $r=-0.05$ ,  $p=0.43$ ) at age 8 years. Reading Composite score and FSIQ were positively associated with maternal age, education, household-income, and inversely associated with maternal depression and HOME scores (Supplement material, Figure S1). Externalizing Problems score was negatively associated with maternal education and household-income, and positively associated with maternal depression and HOME.

After adjusting for covariates, each 10-fold increase in Sum<sub>4</sub>PBDEs concentration was significantly associated with a 6.6-point decrement in Sentence Comprehension score ( $p=0.038$ ), a 6.2-point decrement in Reading Composite score ( $p=0.029$ ), and a 5.3-point decrease in FSIQ score ( $p=0.049$ ). It was marginally associated with a 3.5-point increase in Externalizing Problems score ( $p=0.057$ ) at 8 years of age (Table 2). Sum<sub>4</sub>PCBs concentration as a continuous variable was positively associated with children's reading scores, FSIQ and Externalizing Problems at age 8 years, but none of them was statistically significant (Table 2). The Sum<sub>4</sub>PCBs concentration was correlated with maternal fish consumption during pregnancy ( $r=0.38$ ,  $p<0.0001$ ) whereas the Sum<sub>4</sub>PBDEs concentration was not ( $r=0.05$ ,  $p=0.38$ ). Non-significant interaction was found between the fish consumption and serum Sum<sub>4</sub>PCBs on child's reading abilities, FSIQ and Externalizing Problems in the HOME study (Data not shown).

Trend tests based on quartiles indicated that as the median Sum<sub>4</sub>PBDEs increased in the quartiles, Reading Composite score was significantly decreased ( $p=0.04$ ), Externalizing Problems score was statistically increased ( $p=0.03$ ). No significant trend was found in Brief

Reading score and FSIQ with Sum<sub>4</sub>PBDEs; Neither trend nor association was significant between Sum<sub>4</sub>PCBs quartiles and reading scores at ages 5 and 8 years, FSIQ and Externalizing Problems scores at age 8 years (Figure 2).

The specific analysis for each PBDE or PCB congener demonstrated that a 10-fold increase of BDE-99 was marginally associated with a 5.1-point decrease (95% CI: -10.3, 0.2) in FSIQ at age 8 years ( $p=0.058$ ). A 10-fold increase of BDE-100 was significantly associated with a 6.0-point decrease (95% CI: -11.8, -0.3) in Sentence Comprehension score ( $p=0.039$ ), and a 5.7-point decrease (95% CI: -10.8, -0.6) in Reading Composite score ( $p=0.028$ ) at age 8 years. A 10-fold increase of BDE-153 was significantly associated with a 6.3-point decrease (95% CI: -11.6, -0.9) in Sentence Comprehension score ( $p=0.022$ ), a 5.4-point decrease (95% CI: -10.1, -0.7) in Reading Composite score ( $p=0.026$ ), and a 3.9-point increase (95% CI: 0.8, 6.9) in Externalizing Problems score ( $p=0.014$ ) at age 8 years. No significant associations were found between PCB congeners and children's reading abilities, FSIQ and Externalizing Problems (Table 3). The results were similar when we ran the analysis with all available data and data available at both 5 and 8 years of age. The findings of the LASSO analysis were consistent with the results of the multiple linear regression, and are seen in Table S1.

## **Discussion**

In this study, we comprehensively assessed child's various aspects of neurodevelopment, including reading abilities, intelligence and behavior, and highlighted that the reading ability was an important aspect of neurodevelopment, which was influenced by prenatal chemical exposure. After adjustment, prenatal PBDE concentration was inversely associated with reading skills and FSIQ, and positively associated with externalizing problems in children at age 8 years. Prenatal

PBDE concentration was not associated with reading skills at age 5 years; Prenatal PCB concentration was not statistically associated with reading abilities, FSIQ and externalizing problems in children at age 5 or 8 years. Prenatal PBDE and PCB concentrations were measured in maternal serum samples at approximately 16 weeks of gestation, when blood volume expansion and hyperlipidemia status have not been established (Bloom et al. 2007; Faupel-Badger et al. 2007), thus the impact of physiological variation during pregnancy on prenatal serum PBDE and PCB concentrations is less important in this study.

No evidence is reported on the association of prenatal PBDE and PCB concentrations with child's reading ability so far. This study highlights reading ability as a key outcome, and found that prenatal PBDE concentration was inversely associated with child's reading ability at age 8 years after adjustment for covariates, but was not associated with reading ability at age 5 years. Reading ability is an aspect of neurodevelopment, which was significantly influenced by the neurodevelopment maturity, such as brain area and volume (Spann et al. 2014), the ratio of neuron to glial cells, cell integrity and inter-neuronal communication underlying the frontal and temporal cortices (O'Muirheartaigh et al. 2014). The results in the HOME study showing the association of prenatal PBDE with decrements in FSIQ and increment in externalizing problems were remarkably consistent with previous studies. In the HOME study, the decrement in FSIQ (-5.3 [95% CI: -10.6, -0.1]) and increment in externalizing problems (3.5 points [95% CI: -0.1, 7.2]) at age 8 years with a 10-fold increase in maternal serum Sum<sub>4</sub>PBDEs concentration are consistent with our previous report for FSIQ ( $\beta$ : -4.5, 95% CI: -8.8, -0.1) and externalizing behavior problems ( $\beta$ : 2.6, 95% CI: -0.4, 5.5) at age 5 years with maternal serum BDE-47 concentration (Chen et al. 2014a), and are also consistent with other two reports [California farming community cohort: FSIQ ( $\beta$ : -4.7, 95% CI: -9.4, 0.1) and Attention Deficit/Hyperactivity

Disorder (ADHD) index ( $\beta$ : 2.9, 95% CI: -0.7, 5.2) at age 7 years with maternal Sum<sub>4</sub>PBDEs; World Trade Center cohort: FSIQ ( $\beta$ : -5.5, 95% CI: -10.8, -0.2) at age 4 years related to cord BDE-47 (derived from original estimate of natural log BDE-47)] (Eskenazi et al. 2013; Herbstman et al. 2010). Maternal serum PBDE concentration was associated with more externalizing problems (BDE-100,  $\beta$ : 0.31), worse fine manipulative abilities (BDE-154,  $\beta$ : -0.30) in 62 healthy Dutch children aged 5-6 years (Roze et al. 2009).

Several mechanisms underlying PBDE-mediated developmental neurotoxicity have been suggested in rats and mice neonatal exposure to PBDE (Johansson et al. 2008; Viberg et al. 2003, 2005, 2007; Zhang et al. 2013). BDE-47 and BDE-153 changed hippocampus morphology and ultra structure in rats (He et al. 2009; Zhang et al. 2013). BDE-47 and BDE-99 damaged rats or mice's neuron cytoskeletal formation and neuronal maturation by affecting Ca<sup>2+</sup>/calmodulin-dependent protein kinase II, synaptophysin and cytoskeletal protein expression, decreasing expressions of brain-derived neurotrophic factor and anti-apoptotic bcl-2 mRNA and protein (Alm et al. 2008; Blanco et al. 2011; Viberg 2009). PBDEs induced oxidative stress, DNA damage and apoptosis (He et al. 2008; Tagliaferri et al. 2010), disrupted intercellular Ca<sup>2+</sup> homeostasis (Gassmann et al. 2014), affected neuron cell signal transduction (Fan et al. 2010) and voltage-gated sodium channels *ex vivo* (Xing et al. 2010). Moreover, PBDEs suppressed thyroid receptor-mediated transcription (Ibhazehiebo et al. 2011), impair rats' synaptic plasticity (Xing et al. 2009), inhibited human neural progenitor cells migration and differentiation into neurons and oligodendrocytes (Schreiber et al. 2010). All of the above provided potential mechanisms underlying PBDE-mediated developmental neurotoxicity.

PCBs are among the most well-studied endocrine-disrupting chemicals, and can cause rat pups' hyperactivity (Lesmana et al. 2014), induce oxidative stress and increase apoptosis in the

developing rat brain (Yang and Lein 2010). In the HOME study, prenatal Sum<sub>4</sub>PCBs concentration (median: 31.30 ng/g lipid) was not associated with reading skills, FSIQ and externalizing problems in children at age 8 years after adjusting for maternal fish consumption and other covariates. This findings was inconsistent with the Oswego cohort study showing an inverse association between placenta Sum<sub>4</sub>PCBs concentration (1.5 ng/g wet) and FSIQ ( $\beta=-0.167$ ,  $p=0.021$ ) and Verbal IQ ( $\beta=-0.213$ ,  $p=0.003$ ) in 9-year-old children (Stewart et al. 2008). The LASSO test revealed positive associations of Sum<sub>4</sub>PCBs or some PCB congeners with child's neurodevelopment as well in this study. Consumption of contaminated fish and other food is the main source of human exposure to PCBs (Braun et al. 2014). Fish contains beneficial nutrients for fetal development and maternal health, including polyunsaturated fatty acids (PUFAs) and others, but also may contain harmful contaminants such as PCBs and methylmercury (MeHg). In the HOME study, maternal serum PCB concentrations were positively correlated with fish consumption, yet non-significant interaction was found between maternal serum Sum<sub>4</sub>PCBs and fish consumption on outcomes.

This study has notable strengths and limitations. We comprehensively focused on children's reading abilities, an often overlooked facet of neurodevelopment, and FSIQ and externalizing problems, in a prospective birth cohort, and assessed chemical exposure during the sensitive prenatal period using maternal serum chemical concentrations, and successfully followed up children into school age when neurodevelopment measures stabilize. We tested the trend of outcome with maternal serum PBDE and PCB concentrations in quartile analysis. One limitation is that we did not have the measurements of serum PUFAs, the omega-3 docosahexaenoic acid, and MeHg in this analysis. These may be correlated with co-exposure to PCBs through fish consumption and neurodevelopmental outcomes and outcomes and thus may confound our

analysis. Another limitation is that possible random finding in multiple comparisons without corrections, which cannot be entirely ruled here. While there are statistical methods such as Bonferroni correction to control for multiple comparisons, they tend to be stringent and neglect the correlation between neurodevelopmental outcomes. Finally, we had limited sample size at ages 5 and 8 years, thus limiting our statistical power and precision.

In conclusion, prenatal PBDE concentration was inversely associated with children's reading abilities and FSIQ at age 8 years, positively associated with externalizing problems at age 8 years. Prenatal PCB concentration was not significantly associated with child's reading abilities, FSIQ and externalizing behavior problem. These findings highlight the importance of understanding the potential impact that being exposed to persistent organic chemicals during pregnancy can have on children's neurodevelopment during early childhood, alert people to protect child' neurodevelopment from environmental exposure during the entire gestation by minimizing exposure to persistent organic chemicals. Additionally, reading ability is an aspect of neurodevelopment and should be assessed in further studies.

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Table 1 Participant's demographic characteristics, maternal serum PBDE and PCB concentrations, and child's scores of reading, FSIQ and Externalizing Problems [mean  $\pm$  SD or n (%)]

Maternal and Child's Characteristics	N (%)	Log <sub>10</sub> Sum <sub>4</sub> PBDEs	Log <sub>10</sub> Sum <sub>4</sub> PCBs
Maternal age (yrs)	28.38 $\pm$ 5.75		
<25 yrs	57 (23.55)	1.64 $\pm$ 0.31	1.28 $\pm$ 0.24
25-34 yrs	150 (61.98)	1.59 $\pm$ 0.46	1.53 $\pm$ 0.24
$\geq$ 35 yrs	35 (14.46)	1.40 $\pm$ 0.34	1.75 $\pm$ 0.21
Maternal education			
High school or less	61 (25.21)	1.72 $\pm$ 0.38	1.38 $\pm$ 0.32
Some college or 2 year degree	62 (25.62)	1.58 $\pm$ 0.33	1.47 $\pm$ 0.20
Bachelor's	74 (30.58)	1.50 $\pm$ 0.44	1.56 $\pm$ 0.25
Graduate or professional	45 (18.60)	1.51 $\pm$ 0.52	1.63 $\pm$ 0.27
Maternal race			
Non-Hispanic White	150 (61.98)	1.52 $\pm$ 0.42	1.55 $\pm$ 0.24
Non-Hispanic Black and Others	92 (38.02)	1.68 $\pm$ 0.41	1.43 $\pm$ 0.32
Maternal parity			
Nulliparous	111 (45.87)	1.53 $\pm$ 0.43	1.54 $\pm$ 0.31
Parity=1	71 (29.34)	1.56 $\pm$ 0.38	1.49 $\pm$ 0.24
Parity>1	60 (24.79)	1.66 $\pm$ 0.45	1.49 $\pm$ 0.23
Marital status			
Married or living with partner	184 (76.03)	1.53 $\pm$ 0.43	1.55 $\pm$ 0.25
Not married, living alone	58 (23.97)	1.72 $\pm$ 0.36	1.38 $\pm$ 0.31
Household income			
<\$40,000/y	58 (23.97)	1.73 $\pm$ 0.35	1.35 $\pm$ 0.29
\$40,000-79,999/y	121 (50.00)	1.57 $\pm$ 0.44	1.55 $\pm$ 0.25
$\geq$ \$80,000/y	63 (26.03)	1.42 $\pm$ 0.39	1.58 $\pm$ 0.26
Maternal alcohol drinking			
Never drinking	136 (56.20)	1.56 $\pm$ 0.43	1.48 $\pm$ 0.26
<1/month drinking	75 (30.99)	1.59 $\pm$ 0.41	1.54 $\pm$ 0.24
>1/month or binge	31 (12.81)	1.59 $\pm$ 0.43	1.60 $\pm$ 0.37
Maternal smoking			
Non smoking (serum cotinine < 1 ng/ml)	206 (85.12)	1.55 $\pm$ 0.42	1.52 $\pm$ 0.27
Secondhand tobacco smoking (1 ng/ml= $\leq$ serum cotinine < 10ng/ml)	19 (7.85)	1.63 $\pm$ 0.32	1.32 $\pm$ 0.21
Active smoking (serum cotinine $\geq$ 10 ng/ml)	17 (7.02)	1.91 $\pm$ 0.43	1.58 $\pm$ 0.28
HOME inventory score at 1 year home visit	39.14 $\pm$ 5.44		
$\geq$ 40	146 (64.60)	1.50 $\pm$ 0.43	1.57 $\pm$ 0.26

35-39	41 (18.14)	1.74±0.39	1.46±0.22
<35	39 (17.26)	1.69±0.40	1.33±0.28
Maternal Full Scale IQ	105.98 ± 15.28		
Maternal depressive symptoms at 1 year home visit	9.92 ± 6.67		
Minimal or mild	221 (91.70)	1.55±0.42	1.53±0.27
Moderate or severe	20 (8.30)	1.81±0.40	1.37±0.23
Child sex			
Male	109 (45.04)	1.53±0.42	1.52±0.26
Female	133 (54.96)	1.61±0.42	1.50±0.28
Reading Scores			
WJ-III Score at age 5 years (n=203)			
Basic Reading (a+c)	109.94 ± 17.64		
Brief Reading (a+b)	104.44 ± 16.83		
a. Letter Word	106.12 ± 15.57		
b. Passage Comprehension	100.66 ± 11.07		
c. Word Attack	118.97 ± 13.28		
WRAT-4 Score at age 8 years (n=232)			
Reading Composite (d+e)	108.27 ± 15.40		
d. Word Reading	107.63 ± 14.24		
e. Sentence Comprehension	107.63 ± 17.88		
FSIQ at age 8 years (n=231)	102.10 ± 15.71		
Externalizing Problems at age 8 years (n=239)	49.54 ± 9.40		

Table 2 Adjusted  $\beta$  coefficients (95% CIs) in the multiple linear regressions of child's reading scores, FSIQ and Externalizing Problems score with prenatal serum Sum<sub>4</sub>PBDEs and Sum<sub>4</sub>PCBs concentrations (ng/g lipid)

Chemicals	WJ-III Score (n=203) at age 5 years		WRAT-4 Score (n=232) at age 8 years	WISC-IV (n=231) at age 8 years	BASC-2 (n=239) at age 8 years
	Basic Reading	Brief Reading	Reading Composite	FSIQ	Externalizing Problems
Log <sub>10</sub> Sum <sub>4</sub> PBDEs	-3.1 (-10.1, 3.9)	-2.8 (-9.9, 4.3)	-6.2 (-11.7, -0.6)*	-5.3 (-10.6, -0.1)*	3.5 (-0.1, 7.2) <sup>#</sup>
Log <sub>10</sub> Sum <sub>4</sub> PCBs	6.7 (-4.8, 18.3)	6.5 (-5.2, 18.2)	7.0 (-2.2, 16.2)	1.1 (-7.9, 10.0)	0.5 (-5.7, 6.7)

^: Adjusted for maternal age, education, race, IQ, household-income, parity, marital status, maternal smoking (serum cotinine concentrations), depression, fish consumption, child sex, and HOME score. CIs: confidential intervals; “\*”:  $p < 0.05$ , “#”:  $p < 0.10$ .

Table 3 Adjusted  $\beta$  coefficients (95% CIs) in the multiple linear regressions of child's reading scores, FSIQ and Externalizing Problems score with prenatal serum concentrations of PBDE and PCB congeners (ng/g lipid)

Chemicals	WJ-III score (n=203) at age 5 years		WRAT-4 score (n=232) at age 8 years	WISC-IV score (n=231) at age 8 years	BASC-2 score (n=239) at age 8 years
	Basic Reading	Brief Reading	Reading Composite	FSIQ	Externalizing Problems
Log <sub>10</sub>	-1.2	-0.9	-4.8	3.7	2.1
BDE-47	(-8.0, 5.6)	(-7.7, 6.0)	(-10.1, 0.6)	(-8.8, 1.5)	(-1.4, 5.6)
Log <sub>10</sub>	-3.8	-3.2	-4.2	-5.1	2.8
BDE-99	(-10.6, 3.0)	(-10.0, 3.7)	(-9.7, 1.3)	(-10.3, 0.2) <sup>#</sup>	(-0.8, 6.4)
Log <sub>10</sub>	-3.1	-3.1	-5.7	-4.6	2.6
BDE-100	(-9.7, 3.4)	(-9.7, 3.5)	(-10.8, -0.6)*	(-9.5, 0.2) <sup>#</sup>	(-0.7, 6.0)
Log <sub>10</sub>	-4.8	-4.7	-5.4	-3.6	3.9
BDE-153	(-10.5, 1.0)	(-10.6, 1.1)	(-10.1, -0.7)*	(-8.2, 0.9)	(0.8, 6.9)*
Log <sub>10</sub> PCB-118	2.0	1.2	3.8	-0.5	-1.2
	(-7.8, 11.7)	(-8.7, 11.1)	(-4.2, 11.8)	(-8.2, 7.2)	(-6.6, 4.1)
Log <sub>10</sub> PCB-153	6.3	7.1	6.3	-0.1	0.8
	(-4.8, 17.4)	(-4.1, 18.4)	(-2.5, 15.1)	(-8.7, 8.5)	(-5.1, 6.7)
Log <sub>10</sub> PCB-138-158	6.2	5.5	3.5	0.6	0.9
	(-4.5, 16.8)	(-5.3, 16.3)	(-5.1, 12.0)	(-7.7, 8.9)	(-4.8, 6.7)
Log <sub>10</sub> PCB-180	4.4	6.0	6.8	0.7	0.8
	(-6.3, 15.2)	(-4.8, 16.8)	(-1.6, 15.2)	(-7.5, 8.9)	(-4.9, 9.4)

^: Adjusted for maternal age, education, race, IQ, household-income, parity, marital status, maternal smoking (serum cotinine concentrations), depression, fish consumption, child sex, and HOME score. CI: confidential intervals; “\*”:  $p < 0.05$ , “#”:  $p < 0.10$ .

## Figure legends:

Figure 1. Concentrations of PBDE and PCB congeners in the pregnant women of HOME Study and NHANES (2003-2004) (Median and interquartile range).

^: Bars present the interquartile range (IQR) of chemical concentrations in the HOME Study. Medians of chemical concentrations in the NHANES pregnant women (2003-2004) were referenced, which did not provide the IQR or p25 and p75 percentiles (Woodruff et al. 2011).

National Health and Nutrition Examination Survey; BDE-47, -99, 100 and -153 are the congeners of polybrominated diphenyl ethers (PBDEs); PCB-118, -153, -138-158, -180 are the congeners of polychlorinated biphenyls (PCBs). Limit of detection (LOD) for NHANES pregnant women (2003-2004) is 4.2, 5.0, 1.4 and 2.2 ng/g lipid for BDE-47, -99, 100, and -153; 0.6 and 1.1 ng/g lipid for PCB-118, -153, 0.4 ng/g lipid for PCB-180, PCB-138-158.

Figure 2 Trend and association of child's reading scores, FSIQ and Externalizing Problems scores with prenatal Sum<sub>4</sub>PBDEs and Sum<sub>4</sub>PCBs concentrations quartiles

^: Adjusted for maternal age, education, race, IQ, home income, parity, married status, smoking (maternal serum cotinine), fish consumption, depression, and child sex and HOME score. a: The trend and association of child's reading scores, FSIQ and Externalizing Problems scores with prenatal Sum<sub>4</sub>PBDEs; b: The trend and association of child's reading scores, FSIQ and Externalizing Problems scores with prenatal Sum<sub>4</sub>PCBs. The quartile cutoffs were < 20.70, 20.70-35.64, 35.65-76.00, and ≥ 76.00 ng/g lipid for Sum<sub>4</sub>PBDEs, and <21.50, 21.50-31.29, 31.30-42.80, and ≥ 42.80 ng/g for Sum<sub>4</sub>PCBs, respectively. The score in the 1<sup>st</sup> quartile is the reference. “\*”:  $p < 0.05$ , “#”:  $p < 0.10$ .

Figure 1.

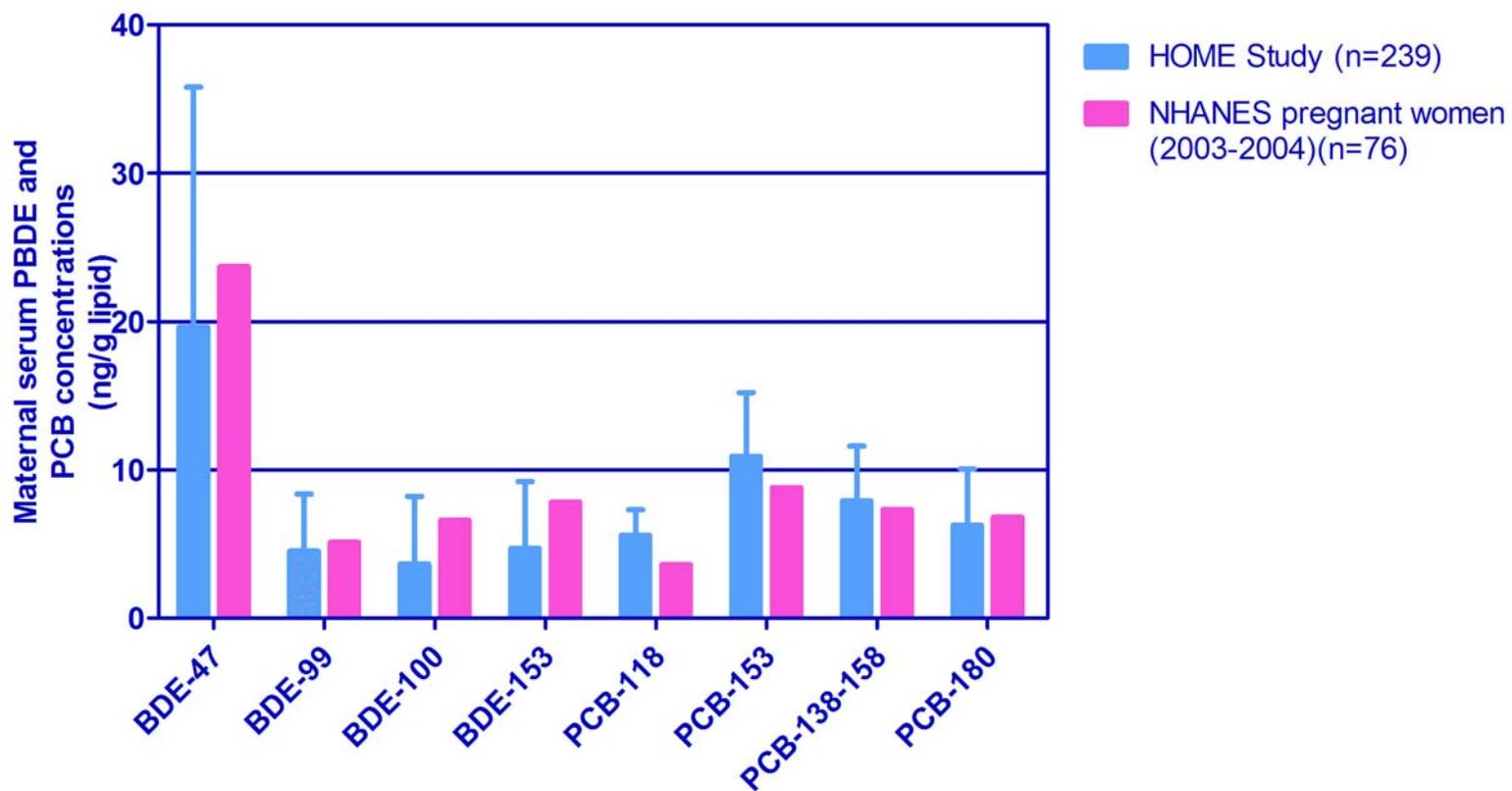


Figure 2.

