Prenatal Exposure to PBDEs and Neurodevelopment

Julie B. Herbstman, Andreas Sjödin, Matthew Kurzon,
Sally A. Lederman, Richard S. Jones, Virginia Rauh,
Larry L. Needham, Deliang Tang, Megan Niedzwiecki,
Richard Y. Wang, and Frederica Perera

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Author names: Julie B. Herbstman[1], Andreas Sjödin[2], Matthew Kurzon[1], Sally A. Lederman[1], Richard S. Jones[2], Virginia Rauh[1], Larry L. Needham[2], Deliang Tang[1], Megan Niedzwiecki[1], Richard Y. Wang[2], and Frederica Perera[1]

Author affiliations:
[1] Columbia Center for Children's Environmental Health, Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY USA

[2] Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Name and address of corresponding author:
Julie Herbstman
Columbia Center for Children's Environmental Health
Mailman School of Public Health
100 Haven Avenue #25F
New York, NY 10032
jh2678@columbia.edu
phone: 212-304-7273
fax: (212) 544-1943

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. None of the authors have any competing financial interests.

Abbreviations:

ANOVA	Analysis of variance
BDE	Brominated diphenyl ether
BSID-II	Bayley Scales of Infant Development—Second Edition
CCCEH	Columbia Center for Children's Environmental Health
CDC	Centers for Disease Control and Prevention
DDE	Dichlorodiphenyldichloroethylene
GC-IDHRMS	Gas chromatography isotope dilution high resolution mass spectrometry
ETS	Environmental tobacco smoke
LOD	Limit of detection
MDI	Mental Development Index
MTBE	Methyl-*tert*-butyl ether
NHANES	National Health and Nutrition Examination Survey
NYU	New York University
PBB	Polybrominated biphenyl
PBDE	Polybrominated diphenyl ethers
PCB	Polychlorinated biphenyl
PDI	Psychomotor Development Index
T4	Thyroxine
TONI-2	Test of Non-Verbal Intelligence-Second Edition
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised edition
WTC	World Trade Center

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Abstract

BACKGROUND: Polybrominated diphenyl ethers (PBDEs) are widely-used flame retardant compounds that are persistent and bioaccumulative, and therefore have become ubiquitous environment contaminants. Animal studies suggest that prenatal PBDE exposure may result in adverse neurodevelopmental effects.

OBJECTIVE: In a longitudinal cohort initiated after 9/11/01 including 329 participants who delivered in one of three hospitals in lower Manhattan, we examined prenatal PBDE exposure and neurodevelopment at ages 1-4 and 6 years.

METHODS: 210 cord blood specimens were analyzed for selected PBDE congeners. Neurodevelopmental effects were assessed at ages 1, 2, 3, 4, and 6 years of age. There were 118, 117, 114, 104, and 96 children with available cord PBDE measurements assessed at 1, 2, 3, 4, and 6 years, respectively. Multivariate regression analyses were used to evaluate the associations between concentrations of individual PBDE congeners and neurodevelopmental indices.

RESULTS: Median cord blood concentrations of PBDE congeners 47, 99, and 100 were 11.2, 3.2, and 1.4 ng/g lipid, respectively. After adjustment for potential confounders, children with higher concentrations of BDE 47, 99, or 100 scored lower on tests of mental and physical development at 1-4 and 6 years. Associations were significant for 12-month Psychomotor Development Index (PDI) (BDE-47), 24-month Mental Development Index (MDI) (BDE-47, 99, and

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100), 36-month MDI (BDE-100), 48-month full-scale and verbal IQ (BDE-47, 99

and 100) and performance IQ (BDE-100), and 72 month performance IQ (BDE-

100).

CONCLUSIONS: This epidemiologic study demonstrates neurodevelopmental

effects in relation to cord blood PBDE concentrations. Confirmation is needed in

other longitudinal studies.

Introduction

Polybrominated diphenyl ethers (PBDEs) are widely-used flame retardant compounds that are applied to a wide array of textiles, building materials, and electronic equipment, including computers and televisions. Because they are additives rather than chemically bound to consumer products, they have the propensity to be released into the environment (Darnerud et al. 2001). PBDEs are persistent organic chemicals and some congeners can bioaccumulate; therefore they have become ubiquitous contaminants, detectable in the environment, in animals and in humans (Hites 2004; Sjodin et al. 2008).

A number of toxicological studies have demonstrated that exposure to PBDEs may have endocrine-disrupting effects. The majority of these studies have focused on thyroid hormone disruption and a smaller number on disruption of the estrogen/androgen hormone system (reviewed by Darnerud 2008). Endocrine disruption during critical developmental periods may result in irreversible effects on differentiating tissue, including the brain (Bigsby et al. 1999). Causal relationships between prenatal exposure to PBDEs and indices of developmental neurotoxicity have been observed in experimental animal models (reviewed by Costa and Giordano 2007). Thus, the disruption of endocrine pathways by prenatal exposure to hormonally active environmental chemicals may impact neurodevelopment in children.

While the association between prenatal exposure to PBDEs and adverse neurodevelopmental effects has been observed in animal models, it has not been adequately explored in human populations. In a longitudinal cohort study initiated by the Columbia Center for Children's Environmental Health (CCCEH), we

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examined the impact of prenatal exposures to selected toxicants, including

PBDEs, that may be present in the ambient environment but may also have been

emitted from the World Trade Center (WTC) buildings in New York City following

the September 11, 2001 terrorist attack. Here, we report the relationship

between prenatal PBDE and polybrominated biphenyl (PBB-153) measured in

umbilical cord blood in humans and indicators of neurodevelopment at ages 1-4,

and 6 years.

Methods

Study population

We established a prospective cohort study of women who were pregnant

on September 11, 2001, and subsequently delivered at one of three downtown

hospitals including Beth Israel, St. Vincent's (and St. Vincent's affiliated Elizabeth

Seton Childbearing Center), which are all approximately 2 miles from the WTC

site, and New York University (NYU) Downtown Hospital, which is within a half-

mile of the WTC site.   The study methods have been described previously

(Lederman et al. 2004). In brief, beginning December 12, 2001 (when

Institutional Review Board approval was obtained), women were approached in

the hospital when they presented for labor and delivery. The women were briefly

screened for eligibility, recruited, enrolled, and consented prior to delivery. This

study was conducted in accordance with all applicable requirements of the

U.S.A. (including IRB approval) and all human participants gave informed

consent prior to participation in this study. Eligible women included those who

were between 18 and 39 years of age, reported smoking <1 cigarette per day

during pregnancy, were pregnant on September 11, 2001 (based on their

estimated date of conception), and reported no diabetes, hypertension, HIV

infection or AIDS, or use of illegal drugs in the preceding year. Not all mothers

agreed to have their child followed after birth. For example, some of the Chinese

children were to be raised in China (see Supplemental Material, Table 1 for

follow-up information).

Data Collection

Medical records of the mother and newborn were abstracted for

information relating to pregnancy, delivery, and birth outcomes. Interviews were

conducted (generally the day after delivery) by bilingual interviewers in the

participants' preferred or native language (English, Spanish, or Chinese).

Demographic information, reproductive history, background environmental

exposures, occupational history, and the location of the woman's residences and

workplaces during each of the 4 weeks after September 11, 2001 were

determined during this interview.   Maternal intelligence was measured using the

Test of Non-Verbal Intelligence-Second Edition (TONI-2), a 15-minute, language-

free measure of general intelligence that is relatively stable and free of cultural

bias (Brown et al. 1990).

Developmental assessment

When the children were about 12, 24 and 36 months of age, the Bayley

Scales of Infant Development—Second Edition (BSID-II) were administered,

providing scores from the Mental Development Index (MDI) and the Psychomotor

Development Index (PDI). The BSID-II is a widely used developmental test

designed for children ages 12 - 42 months that is norm-referenced and can be

used to identify children with developmental delay. The assessment provides a Developmental Quotient (raw score/chronological age), generating a continuous MDI or PDI score, both with mean=100±15 (SD).

At 48 and 72 months, the Wechsler Preschool and Primary Scale of Intelligence-Revised Edition (WPPSI-R) was administered; it measures cognitive development and contains verbal and non-verbal performance tests. We used the WPPSI-R rather than the third edition because of its availability in Chinese.

Not all children were available for all developmental assessments, resulting in different numbers of children tested at each age. Assessments were conducted in the first language of the child (English or Chinese) by trained research technicians. In some cases, when the child's primary language was not English or Chinese (e.g. Yiddish), we relied on maternal translation. Statistical analyses for this study were conducted with and without the children for whom the child's primary language was not English or Chinese (n=30) and the results were similar (data not shown).

The majority of assessments were conducted at the CCCEH. However, a proportion of the assessments were conducted in the child's home, if the parents were unable or unwilling to come to the Center to complete the follow-up (see Supplemental Material, Table 1 for details).

Blood collection

Umbilical cord blood was collected at delivery and maternal blood was typically collected on the day after delivery. On average, 30.7 mL of blood was collected from the umbilical cord and 30-35 mL of blood was collected from the mothers. Samples were transported to the laboratory and processed within

several hours of collection. The buffy coat, packed red blood cells, and plasma were separated and stored at -70°C. Frozen plasma from 210 cord samples was transferred on dry ice to the Centers for Disease Control and Prevention (CDC) for laboratory analyses for the PBDEs and PBB-153. The concentrations of these chemicals in the cord blood were used as an indicator of fetal exposure during gestation (Mazdai et al. 2003; Qiu et al. 2009).

Laboratory methods

Details regarding the analysis of the plasma samples for PBDEs are given elsewhere (Hovander et al. 2000; Sjodin et al. 2004). Briefly, the samples were automatically fortified with ^{13}C-labeled internal standards. The samples were subjected to an initial liquid/liquid extraction with hexane:methyl-*tert*-butyl ether (MTBE) after denaturation with 1M HCl and isopropanol (Hovander et al. 2000). Thereafter, co-extracted lipids were removed on a silica:silica/sulfuric acid column using the Rapid Trace equipment for automation. Final determination of the target analytes was performed by gas chromatography isotope dilution high resolution mass spectrometry (GC-IDHRMS) employing a MAT95XP (ThermoFinnigan MAT, Bremen, Germany) instrument (Sjodin et al. 2004). Concentrations of target analytes were reported as pg/g whole weight (weight of plasma) and ng/g lipid weight (weight of plasma lipids). The plasma lipid concentrations were determined using commercially available test kits from Roche Diagnostics Corp. (Indianapolis, IN) for the quantitative determination of total triglycerides (Product No. 011002803-0600) and total cholesterol (Product No. 011573303-0600). Final determinations were made on a Hitachi 912 Chemistry Analyzer (Hitachi; Tokyo, Japan). Limits of quantification were

determined in relation to the method blanks and in relation to the instrument's quantification limit, which is proportional to the sample size. Cotinine concentrations were measured in cord and maternal blood by use of liquid chromatography in conjunction with atmospheric pressure ionization tandem mass spectrometry (Bernert et al. 1997).

The plasma samples were analyzed for the following PBDE congeners (by International Union of Pure and Applied Chemistry numbers): 2,2,2',4,4'-tetraBDE (BDE-47), 2,2',3,4,4'-pentaBDE (BDE-85), 2,2',4,4',5-pentaBDE (BDE-99), 2,2',4,4',6-pentaBDE (BDE-100), 2,2',4,4',5,5'-hexaBDE (BDE-153), 2,2',4,4',5,6'-hexaBDE (BDE-154), 2,2',3,4,4',5',6-heptaBDE (BDE-183), and 2,2',4,4',5,5'-hexaBB (BB-153).

Quality Control/Quality Assurance

Background levels were determined by measuring the level of target analytes in blank samples in the same run as the study samples (3 blanks per 24 study samples). All concentrations reported were corrected for the average amount present in the blank samples. The limit of detection (LOD) when no analytical background was detected in blank samples was defined as a signal-to-noise ratio > 3. When an analytical background was detected in the blanks, the LOD was defined as three times the SD of the blanks.

The plasma samples used in this cohort were not collected solely for the purpose of PBDE analysis. Due to this, we examined the ratio of BDE-99 over BDE-47 for any indication of contamination from indoor particulate matter with the assumption that a high ratio would be indicative of sample contamination during sample collection. The median ratio of BDE-99 over BDE-47 is 1.2 in

residential dust samples (Sjodin et al. 2008) while in human samples this ratio is

typically significantly lower. In the 2003-2004 National Health and Nutrition

Examination Survey (NHANES), the median ratio of BDE-99 to BDE-47 was 0.23

while the 95th percentile of this ratio was 0.43 (Sjodin et al. 2008). In our study,

we found that 16 out of 210 samples had a BDE-99 to BDE-47 ratio greater than

0.43, corresponding to 7.6% of the samples. This frequency of samples having a

ratio greater than 0.43 is similar to that of the NHANES survey and we can thus

conclude that no detectable contamination occurred during the collection of the

cord samples in this study. Statistical analyses for this study were conducted

both including and excluding the aberrant samples (n=16) and the results were

similar (data not shown).

WTC exposure

In previous analyses in this cohort, we have used two indices to describe

exposure to the WTC: geographic proximity to the WTC during the first month

after 9/11 and timing of exposure relative to date of delivery. We found that

women who lived closest to the WTC during the first month after 9/11

(constituting the group we would estimate would have the largest exposure to the

WTC) did not have higher concentrations of PBDEs compared to those who lived

further from the towers in the first 4 weeks following the attack. However, we

found that women who delivered sooner after 9/11 (constituting the group who

were further along in their pregnancy on 9/11) tended to have higher cord blood

concentrations of PBDEs (in preparation). Because we quantify prenatal PBDE

exposure using a biological marker that integrates exposure from all sources, the

source of the PBDEs is not relevant to the effect of prenatal exposure to PBDEs

on neurodevelopment.   To our knowledge, PBDEs are not associated with any other neurotoxic exposure that could confound the observed associations.

Statistical methods

Concentrations of PBDEs were lipid- and natural log-adjusted. PBDEs commonly detected in cord blood (detected in >55% of samples) were handled as continuous variables in the statistical models. This was the case for BDE-47, 99, 100, and 153; we used the limit of detection (LOD) divided by the square-root of two for concentrations below the LOD. Based on the log-normal distribution of each of these BDE congeners, we also compared participants having cord concentrations in the highest 20% to those in the lowest 80% of the population distribution to evaluate the impact of having exposures at the high-end of the exposure distribution. This categorization was selected because it distinguished those with exposures in the tail of the log-normal distribution. The majority of cord samples (>50%) had levels below the limits of detection for BDE-85, 154, 183, and BB-153. We evaluated BDE-85 and BB-153 as dichotomous measures (detected versus non-detected) and did not analyze BDE-154 and 183 because only 6% and 4% of the samples, respectively, had detectable concentrations (Table 1).

We generated descriptive statistics and evaluated bivariate associations using analysis of variance (ANOVA) and chi-square tests to compare stratum-specific means and proportions, respectively. We examined the data using lowess curves and determined that linear models using natural logarithmic (ln) transformed PBDE concentrations fit the data well. Therefore, we conducted multivariate linear regression analyses to evaluate the relationships between

prenatal PBDE concentrations—using continuous measures for ln-transformed BDE-47, 99, 100, and 153 and dichotomous measures for BDE-85, 154, and 183—and continuous scores on developmental tests (MDI and PDI at 12, 24, and 36 months and full, verbal and performance scores at 48 and 72 months). We were not able to consider developmental test scores as dichotomous measures, using the test-specific recommended cut-offs for defining children as 'delayed' or 'borderline delayed' because of the small sample size and small number of children who met these criteria.

We selected covariates for inclusion in multivariate models based on their *a priori* association with neurodevelopment (Tong and Lu 2001) including age at testing, child's sex, ethnicity (Asian, Black, White, or other), environmental tobacco smoke (ETS) exposure in the home (yes/no; based on self-report, validated in this dataset by cotinine measured in cord blood, using methodology describe in (Jedrychowski et al. 2009)) and mother's IQ. We also considered the inclusion of additional covariates if they changed the beta coefficient for PBDEs >10% when they were added to the *a priori* set one at a time. This resulted in a final covariate set that added to our *a priori* set gestational age at birth (based on the best obstetric estimate), maternal age, maternal education, material hardship during pregnancy (defined as having gone without either food, shelter, gas/electric, clothing, or medication/medical care because of financial constraint), and breast feeding (considering both breast-feeding duration and exclusiveness, defined in (Lederman et al. 2008)). The results of these models are presented as "Model 1". We also created a "Model 2" that included all the previous covariates plus two study-specific variables: the language (including whether the

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mother aided in translation) and location (home or study site) of the interview and assessment. We explored the effects of whether the mother ate fish/seafood when she was pregnant (yes/no) and also the effects of cord blood total mercury and lead concentrations (continuous measures), but found that these covariates did not materially change the relationships between PBDE concentrations and developmental indicators.

To determine if only a few cases could have a substantial effect on the adjusted PBDE regression coefficients, we used AV-plots to examine the residuals from the regression lines for the adjusted PBDE regression coefficients to find possible influential cases.   These are cases that are outliers both for the outcomes (PDI, MDI, WPPSI) and the independent variables of interest (PBDE compounds). When the possible influential cases were removed, the largest changes in the regression coefficients were less than one point, with no changes in significance levels.

Results

Median cord concentrations of PBDE congeners 47, 99, and 100 in the full cohort were 11.2, 3.2, and 1.4 ng/g lipid; 81.4%, 59.5%, and 63.6%, respectively, were above the LOD (Table 1). Overall concentrations and the proportion of participants with PBDE concentrations above the LOD were not significantly different in the study subsample. The proportion of participants with detectable concentrations of BDE-85, 153, 154, and 183 ranged from approximately 4 to 50%. PBDE congeners 47, 99, and 100 were highly inter-correlated (r = 0.74 to 0.88).

Characteristics of the full cohort (N=329), the subset of 210 participants with cord PBDE (and PBB) measurements, and the subset of 152 with both cord measurement and a neurodevelopmental test are shown in Table 2. Those with cord blood measurements were similar to the full cohort except that there were proportionally more Chinese participants with cord blood measurements (34.3% as compared to 28.0% in the full cohort) and those with measurements were slightly smaller in birth length. The study sample and the full cohort were similar except that mothers included in the study sample were slightly older at the time of delivery (31.2 vs. 30.2 years, p<0.01) and were more educated (not statistically significant). Those in the study sample were more likely to have completed maternal IQ measurements, which is expected considering this measurement was collected at follow-up visits, not at the delivery hospital. There were no differences in the proportions working and/or living closest to the WTC (within 1 or 2 miles) at the time of the attack.

There were 118, 117, 114, 104, and 96 children with available cord PBDE measurements who also had a developmental assessment at 1, 2, 3, 4, and 6 years, respectively. For those assessed at all of these time points, the median cord plasma concentrations of BDE-47 and 99 were 12.1 ng/g lipid and 3.5 ng/g lipid. For BDE-100, median concentrations were approximately 1.5 ng/g lipid for children assessed in years 1-4; for those assessed at year 6, the median cord blood concentration was 1.4 ng/lipid.

In cross-sectional analyses using multivariate linear regression, prenatal exposure to BDE-47 was negatively associated with neurodevelopmental indices (Table 3). These relationships were statistically significant for 12-month PDI

(borderline), 24-month MDI, and 48-month full and verbal IQ scores. For every ln-unit change in BDE-47, scores were, on average, 2.1 to 3.1 points lower on developmental indices. For BDE-99 (Table 4), statistically significant negative associations were detected for 24-month MDI (β = -2.82, 95% CI -4.86, -0.78). Prenatal exposure to BDE-100 was negatively associated with neurodevelopmental indices (Table 5), with statistically significant relationships observed for 24-month MDI, 48 month full, verbal, and performance IQ scores, and 72-month performance IQ scores. For every ln-unit change in BDE-100, scores were on average 3.4 to 4.0 points lower on developmental indices. For BDE-153 (Table 6), statistically significant negative associations were detected for 48- and 72-month full and performance IQ scores. For every ln-unit change in BDE-153, scores were, on average, 3.1 to 4.2 points lower. The strength of association between BDE-153 and IQ scores was much larger in the adjusted models compared to the univariate model. It appears that the strong positive effect of maternal education on IQ at ages 4 and 6 was responsible for much of this change.

We also evaluated the difference in mean developmental score comparing children who were in the highest 20% of the prenatal exposure distribution to those in the lower 80% of the distribution for BDE-47, 99, and 100 (Figure 1). We found that, on average, children with the higher prenatal concentrations of BDE-47, 99, and 100 scored lower than the rest of the population on nearly all neurodevelopmental indices at all time points (1-4 and 6 years). These differences ranged in magnitude; the largest differences were observed with all three congeners for the 24-month MDI (statistically significant differences of -7.7,

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-9.3, and -10.9 points for BDE-47, 99, and 100, respectively) and for 48-month verbal and full IQ scores (ranging from -5.5 to -8.0 points). For BDE-153, adjusting for the same covariate set, those in the highest 20% of the exposure distribution scored, on average, 6.3 points lower at 48 months (95% CI: -13.0, 0.4) and 8.1 points lower at 72 months (95% CI: -15.6, -0.6) on the performance IQ scale.

We used multivariate linear regression models to evaluate whether having detectable prenatal concentrations of BDE-85 and BB-153 was significantly related to developmental indices. Adjusting for child's exact age at test administration, ethnicity, mother's IQ, child's sex, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, and breast feeding, we found that those with detectable cord concentrations of BDE-85 scored, on average, 11 points lower on the 24 month MDI (95% CI: -17.0, -5.2), 6.4 points lower on 24 month PDI (95% CI: -11.8, -0.8), 7.7 points lower on 36 month PDI (95% CI: -15.0, -0.4), 6.5 points lower on 48 month verbal IQ (95% CI: -13.3, 0.2) and 6.9 points lower on 48 month full IQ (95% CI: -12.8, -0.9). There were no statistically significant associations between prenatal BB-153 levels with developmental indices measured at any other ages.

Discussion

We found evidence suggesting that children who had higher cord blood concentrations of BDE 47, 99, and 100 scored lower on tests of mental and physical development at ages 1-4 and 6 years. These associations were significant for 12-month PDI (BDE-47), 24-month MDI (BDE-47, 99, and 100), 48-

month full IQ (BDE-47, 100, and 153), verbal IQ (BDE-47 and 100) and performance IQ (BDE-100 and 153), and 72 month full and performance IQ (BDE-100 and 153). Children who were in the highest 20% of cord blood concentrations of PBDEs 47, 99, or 100 had significantly lower developmental scores compared to children who were in the lower 80% of the exposure distributions for these chemicals; these differences were particularly evident at 4 years of age.

Adverse neurodevelopmental effects associated with prenatal PBDE exposure can be detected both at early ages (1-3) and as the children age (4 and 6 years). Neurodevelopmental deficits documented by the WPPSI during the preschool period are an important predictor of subsequent academic performance (Kaplan 1993). Documenting the first appearance of potentially longer-term adverse effects at early ages is also important, as these indicators may identify children who could benefit from early intervention programs. The identification of later deficits may indicate the persistence of early effects and/or an increase in the magnitude of effect with age, as has been shown in some animal studies (e.g. (Viberg et al. 2003)).

Our results are consistent across congeners and over time. This may be predictable because the PBDE congeners are highly correlated and for individuals, repeated developmental scores are also correlated. While the number of participants lost to follow-up between year 1 and 6 was relatively low (81% of subjects available for analyses at year 1 were also assessed at year 6) and losses are independent of exposure, our overall sample is relatively small. Therefore, even small losses to follow-up may limit our power to detect significant

differences in multivariate models. The resulting small sample size precluded the analysis of exposure effects on developmental delay and we were unable to look at interactions. However, we note that developmental deficits of the magnitude we observed in this study are likely to have the largest functional impact on those who score the lower end of the population distribution.

The only other epidemiologic study reporting the neurodevelopmental effects of prenatal exposure to PBDEs was published recently (Roze et al. 2009). In this study of 62 Dutch children, the authors present correlations between exposure to PBDEs (measured during the 35th week of pregnancy) and over 20 indices of child development and behavior at age 5-6. They report that prenatal PBDE exposure was associated with some adverse effects on development (reduced fine manipulative abilities and increased attentional deficits) as well as some beneficial effects (better coordination, better visual perception, and better behavior). The authors evaluated but did not find statistically significant correlations between prenatal PBDE exposures and any of the WPPSI-R domains. Our results are not consistent with these findings. However, important differences in exposure (median exposure in our population was 4 times higher for BDE-47 and 99, 2.3 times higher for BDE-100 and one fifth their concentration for BDE-153), sample size, and statistical analyses performed may account for some of the observed inconsistencies.

Our results are consistent with published toxicological experiments (reviewed in (Costa and Giordano 2007)). For example, studies evaluating the neurodevelopmental effects of neonatal exposure to PBDEs in mice during critical developmental periods have reported altered habituation patterns (Viberg

et al. 2003), hyperactivity (Gee and Moser 2008), and learning and memory deficits (Dufault et al. 2005; Viberg et al. 2003). There is some evidence suggesting that BDE-99 is more potent than BDE-47 (Viberg et al. 2003) and also that effects worsen (or are more apparent) with age (Viberg et al. 2003). In general, we observed the largest effects with prenatal exposure to BDE-100 and the effects of prenatal exposures were still apparent, albeit not consistently significant, in our smaller sample examined at 6 years of age.

A number of potential mechanisms have been proposed to explain the cognitive and locomotive deficits observed in animals following PBDE exposure during critical developmental periods, including direct neurotoxic effects on neuronal and glial cells (Costa et al. 2008) resulting from changes in the quantity of cholinergic nicotinic receptors in the hippocampus (Viberg et al. 2003) and induction of apoptotic cerebellar granule cell death (Reistad et al. 2006). In addition, there is compelling experimental and epidemiologic evidence suggesting that PBDEs can interfere with thyroid hormone pathways (Legler 2008). Because thyroid hormones are critical for normal brain development, this provides an attractive explanation for observed neurodevelopmental effects following neonatal PBDE exposure (Bigsby et al. 1999; Porterfield 2000). Toxicological evidence corroborating this theory includes potentially causal associations between neonatal exposure to BDE-47, 99, or commercial PBDE mixtures (DE-71 and Bromokal 70-5 DE) and reduced thyroxine (T4) concentrations in experimental murine models (Fowles et al. 1994; Hallgren et al. 2001; Kuriyama et al. 2007).

Although only limited human epidemiologic data are available, increased levels of BDE-47, 99, and 100 in dust in the homes of adult human males recruited through a US infertility clinic were associated with altered hormone levels. PBDEs were inversely associated with free androgen index, and with luteinizing and follicle-stimulating hormones and were positively associated with inhibin B, sex hormone binding globulin, and free T4 (Meeker et al. 2009). In another study of adult males, increased serum concentrations of PBDEs were positively related to T4 and inversely related to total T3 and TSH (Turyk et al. 2008). The positive associations between PBDEs and T4 levels demonstrated in these human studies is not consistent with the results from experimental animal models, raising the possibility that the underlying mechanism of PBDEs' effect on thyroid disruption may differ among species. However, it is difficult to extrapolate findings from studies evaluating exposure effects in adults to prenatal exposures, as PBDE may exhibit differential effects on thyroid hormone levels at different stages of the lifespan.   A recent study of PBDEs measured in human cord blood of infants born to a cross-section of women delivering in Baltimore, Maryland showed a consistent non-significant negative association with both total and free T4 in infants (Herbstman et al. 2008). More research is necessary to fully characterize the effect of human prenatal exposure to PBDEs on thyroid hormone levels.

The exact mechanism of thyroid disruption by PBDEs in humans has not yet been elucidated, but two potential pathways through which PBDE exposure could lead to thyroid disruption have been proposed (reviewed in (Zhang et al. 2008)). The structural similarities of T4 and triiodothyronine (*T3*) to

polyhalogenated aromatic hydrocarbons suggest that hydroxylated PBDE

metabolites could displace thyroid hormones from thyroid transport proteins (i.e.

transthyretin), altering free thyroid hormone levels (Turyk et al. 2008).

Alternatively (or in addition), PBDEs might affect hormone levels by influencing

thyroid hormone synthesis and/or stimulating thyroid hormone metabolism

(Szabo et al. 2009; Turyk et al. 2008). Brain development in the fetus is

contingent upon the precise timing of thyroid hormone levels, particularly for T4,

and deviations above or below the normal levels can lead to developmental

deficits (Williams 2008). The fetus originally derives all thyroid hormone from the

mother, but over the course of the pregnancy, its thyroid gland develops, and

hormones produced within the fetus gradually replace the maternal source. The

surge in maternal T4 in the first trimester, coupled with TSH inhibition, is thought

to provide a supply of hormone during this critical developmental period, and

alteration of T4 levels by PBDEs at this time could alter neurodevelopment

(Williams 2008). While low serum T4 from maternal hypothyroidism during

gestation (e.g., iodine deficiency) is known to cause mental retardation in

children, elevated levels of T4 have been associated with increased rates of

miscarriage (Anselmo et al. 2004) and could potentially be linked to

neurodevelopmental problems.

Because of their similar chemical structures, PBDEs and polychlorinated

biphenyls (PCBs) have been compared in terms of their potential health effects.

Although PCBs were banned in most industrialized countries over 25 years ago,

they are still measurable in human and environmental samples because of their

long half-lives in the environment and in humans (Talsness 2008). Prenatal

exposure to PCBs has been shown in several cohort studies to significantly reduce cognitive function during childhood (reviewed in (Schantz et al. 2003)) and has also been associated in some studies with altered thyroid hormone levels (Chevrier et al. 2007; Herbstman et al. 2008). Because of the structural similarity of PCBs and PBDEs, it has been postulated that they exert biological effects through similar processes.

This study population is unique in that participants were initially recruited to measure the extent and the effects of prenatal exposure to contaminants (including PBDEs) that were potentially released by the destruction of the WTC towers. Studies examining environmental samples collected pre- and post-9/11 near the WTC site found indications of higher concentrations of PBDEs following the attacks (Litten et al. 2003) and nearer to the WTC disaster site (Butt et al. 2004). These trends may be due to debris containing office equipment known to be treated with PBDEs (de Wit 2002). In our study population, cord plasma levels of PBDEs were not significantly related to residential distance from the WTC site. There is some evidence suggesting that PBDE exposure may be related to the WTC attack based on the gestational age on 9/11/01, such that women who were in the second half of their pregnancy on 9/11 had children with higher cord concentrations of PBDEs (unpublished data). It is also possible that just after 9/11, some women had elevated levels of PBDEs but that these declined with the passage of time between the peak exposure and delivery, resulting in lower observed levels. In either scenario, it is not clear how much this apparent association between gestational age on 9/11 and exposure concentration contributes to the body burden and it is certain that sources other

than the WTC are also accountable.   In this report, our interest is in the association between the integrated prenatal PBDE exposure from multiple sources and neurodevelopment. It is also possible that there are other unknown factors that are associated with PBDEs that may confound the observed relationships between prenatal PBDE exposure and adverse neurodevelopment.

Levels of cord blood PBDEs in our population are consistent with those reported in other U.S. populations (Herbstman et al. 2007; Mazdai et al. 2003; Wu et al. 2007). Compared to cord blood measurements in an inner city population in Baltimore, our study population had slightly lower median concentrations (i.e., 11.2 ng/g lipid vs. 13.6 ng/g lipid for BDE-47) (Herbstman et al. 2007). In the Baltimore cohort as well as in this NYC cohort, higher cord PBDE concentrations were shown to be associated with the mother being African American, or non-Asian, although a higher proportion of the Baltimore population was African American (70% vs. 15%) and a lower proportion was Asian (8% vs. 30%). Increasing maternal age was associated with lower PBDE concentrations in the Baltimore cohort, but not in NYC; however the median maternal age was also lower in Baltimore (25 years vs. 30 years) (Herbstman et al. 2007).   The demographic differences between these two populations may explain the small differences in blood levels observed at the population level.

While dietary ingestion was once thought to be the largest route of PBDE exposure in humans, the similarity of PBDE levels in foods in Europe, Asia, and North America fails to adequately explain the high blood levels in the U.S. population (Frederiksen et al. 2009). Dust inhalation may be a more important exposure route to PBDEs, particularly the BDE-47, 99, and 100 congeners. In a

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review of median PBDE levels in dust and air samples, measured BDE-47 dust

levels in Europe and North America were 32 and 429 ng g/dw, respectively;

similar disparities were observed for BDE-99 and 100 levels (Frederiksen et al.

2009; Sjodin et al. 2008). Particular attention should be given to this exposure

route in young children, who are more likely to encounter dust due to their close

proximity to the floor. Dust is estimated to contribute from 80-93% of PBDE

exposure in toddlers, and their small body size compounds the effect of their

exposures (Costa and Giordano 2007). In this study, we were not able to control

for post-natal dust exposure.

In the general population, infants and toddlers have the highest body

burden of PBDEs, and along with dust exposure, exposure via breast milk is

thought to be a major contributor to this burden (Costa et al. 2008; Toms et al.

2009). Breast-fed infants are estimated to be exposed to 306 ng/kg body

weight/day of PDBE, compared to 1 ng/kg body weight/day in adults, with the

most prominent congeners being BDE-47, 99, and 153 (Costa et al. 2008). In

our study, breastfeeding rates were higher in children with higher cord PBDE

levels, indicating that PBDEs measured in cord blood may underestimate the

exposure of breastfed children. Breast feeding was, as expected, associated

with higher scores on neurodevelopmental indices, making it an important

potential confounder to include in multivariate statistical models.

Conclusions

This report is among the first epidemiologic studies to demonstrate inverse

associations between elevated cord blood concentrations of PBDEs and adverse

neurodevelopmental test scores. These findings indicate a need for additional work to advance our understanding of the effects of perinatal exposure to PBDEs on neurodevelopment and to evaluate the role of thyroid hormones in this process. Additional PBDE congeners not measured in our study should also be examined to determine whether other congeners, including those that are highly brominated, play a role in developmental outcomes. Future work should also explore the possibility of interactions of PBDEs with other chemicals such as PCBs and DDE. While additional studies exploring the associations between PBDE exposure and developmental effects are underway, the identification of opportunities to reduce exposure to these compounds should be a priority.

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Table 1. Concentrations (ng/g lipid) of PBDEs and BB-153 in cord blood

	Cord Blood Measurements (n=210)				Cord measurements with > one neurodevelopmental test (n=152)			
	N	%>LOD	Median	Maximum	N	%>LOD	Median	Maximum
BDE-47	210	81.4	11.2	613.1	152	83.6	11.2	613.1
BDE-85	189	18.5	0.7	16.6	141	17.7	0.7	16.6
BDE-99	210	59.5	3.2	202.8	152	57.9	3.2	202.8
BDE-100	209	63.6	1.4	71.9	152	69.1	1.4	71.9
BDE-153	201	49.8	0.7	28.9	143	55.9	0.7	28.9
BDE-154	200	6.0	0.6	11.1	146	6.2	0.6	11.1
BDE-183	204	3.9	0.6	2.8	147	4.1	0.6	2.8
BB-153	197	11.2	0.6	8.0	145	13.1	0.9	8.0

Table 2. Characteristics of all cohort members (n=329), participants with cord blood measurement for of PBDEs (n=210), and those included in our study sample (n=152)

	All participants (n=329)	Cord PBDEs* (n=210)	Cord measurements > one neurodevelopmental test[†] (n=152)
Maternal characteristics			
Maternal age (years, mean, SD)	30.2 (5.2)	30.4 (5.1)	31.2 (4.9)[‡]
Maternal education (n, %)			
< High school	61 (18.5)	45 (21.4)	21 (13.8)
High school	56 (17.0)	36 (17.1)	25 (16.4)
Some college	73 (22.2)	46 (21.9)	34 (22.4)
Four year college degree	72 (21.9)	41 (19.5)	34 (22.4)
Post college education	67 (20.4)	42 (20.0)	38 (25.0)
Race (n, %)			
Chinese	92 (28.0)	72 (34.3)**	41 (27.0)
Asian (non-Chinese)	21 (6.4)	13 (6.2)	9 (5.9)
Black	50 (15.2)	27 (12.8)	23 (15.1)
White	133 (40.4)	77 (36.7)	62 (40.8)
Other	33 (10.0)	21 (10.0)	17 (11.2)
Married/ living with partner (n, %)	265 (80.6)	172 (81.9)	126 (82.9)
TONI score (mean±SD)	95.8 (11.4)	95.8 (11.3)	95.8 (13.0)
Missing TONI (n, %)	118 (35.9)	82 (39.0)	26 (17.1)[‡]
Maternal exposure to ETS reported smoker in home (%)	59 (17.9)	36 (17.1)	26 (17.1)
Ate fish during the pregnancy (n, %)	233 (70.8)	150 (71.4)	110 (72.4)
Material hardship (n, %)	31 (9.4)	20 (9.5)	16 (10.5)
Infant characteristics			
Birth weight (g, mean, SD)	3419.5 (469.1)	3399.2 (472.5)	3412.0 (487.4)
Birth length (cm, mean, SD)	50.8 (2.8)	50.5 (2.7)**	50.6 (2.7)
Birth head circumference (cm mean±SD)	34.2 (1.5)	34.2 (1.4)	34.3 (1.5)
Gestational age (days, mean, SD)	276.8 (9.9)	276.4 (10.4)	276.6 (9.5)
Male (n, %)	161 (48.9)	105 (50.0)	77 (50.7)
Proportion of first yr breast fed (% of 1 year, mean, SD)	0.24 (0.28)	0.22 (0.27)	0.26 (0.28)
Residential characteristics			
Worked and/or lived within 1 mile of the WTC during any of the 4 weeks after 9/11/01 (n, %)	62 (18.8)	43 (20.5)	32 (21.0)
Worked and/or lived within 2 mile of the WTC during any of the 4 weeks after 9/11/01 (n, %)	141 (42.8)	94 (44.8)	73 (48.0)

* Statistical comparison between those in the full cohort and those with cord blood measurements
** p<0.05
† Statistical comparison between those in the full cohort and those in our study sample
‡ p<0.05

Table 3. Association (and 95% CI) between prenatal exposure to BDE-47 and indices of neurodevelopment at 12, 24, 36, 48, and 72 months of age

	age	n	Univariate	Model 1	Model 2	
			change in score per ln-unit	change in score per ln-unit	change in score per ln-unit	change in score per increase from the 25th to 75th percentile (IQR*)
MDI	12 mo	118	-0.88 (-2.20, 0.44)	-0.60 (-2.04, 0.83)	-0.64 (-2.11, 0.82)	-1.06 (-3.49, 1.36)
	24 mo	117	-2.88** (-5.20, -0.55)	-2.65** (-4.82, -0.48)	-3.12** (-5.25, -0.99)	-5.16** (-8.68, -1.64)
	36 mo	114	-0.34 (-2.60, 1.93)	-0.34 (-2.65, 1.98)	-1.05 (-3.35, 1.26)	-1.74 (-5.54, 2.08)
PDI	12 mo	118	-1.01 (-2.99, 0.97)	-2.10** (-4.16, -0.04)	-2.09 (-4.20, 0.03)	-3.46 (-6.95, 0.05)
	24 mo	115	-0.21 (-2.13, 1.70)	-0.11 (-2.11, 1.89)	-0.29 (-2.37, 1.79)	-0.48 (-3.92, 2.96)
	36 mo	109	-1.52 (-4.13, 1.08)	-1.64 (-4.52, 1.23)	-1.81 (-4.69, 1.07)	-2.99 (-7.76, 1.77)
Full	48 mo	104	-1.98 (-4.49, 0.53)	-2.13 (-4.31, 0.06)	-2.42** (-4.71, -0.12)	-4.00** (-7.79, -0.20)
	72 mo	96	1.02 (-2.03, 4.08)	-0.12 (-2.92, 2.69)	-1.17 (-4.03, 1.69)	-1.94 (-6.67, 2.80)
Verbal	48 mo	104	-1.41 (-4.00, 1.19)	-2.16 (-4.60, 0.27)	-2.75** (-5.28, -0.22)	-4.55** (-8.73, -0.36)
	72 mo	96	2.31 (-0.94, 5.57)	1.10 (-1.78, 3.97)	0.09 (-2.82, 3.01)	0.15 (-4.66, 4.98)
Perform	48 mo	104	-2.27 (-5.04, 0.50)	-1.76 (-4.27, 0.74)	-1.67 (-4.32, 0.98)	-2.76 (-7.15, 1.62)
	72 mo	96	-0.54 (-3.54, 2.46)	-1.27 (-4.22, 1.68)	-2.14 (-5.20, 0.93)	-3.54 (-8.60, 1.54)

* IQR (interquartile range) for BDE-47 is 19.57 ng/g lipid
** confidence intervals do not include 0.00

Model 1: Adjusted for age at testing, ethnicity, mother's IQ, child's sex, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, and breast feeding
Model 2: Adjusted for all covariates in Model 1 plus language and location of interview

Table 4. Association (and 95% CI) between prenatal exposure to BDE-99 and indices of neurodevelopment at 12, 24, 36, 48, and 72 months of age

	age	n	Univariate change in score per ln-unit	Model 1 change in score per ln-unit	Model 2	
					change in score per ln-unit	change in score per increase from the 25th to 75th percentile (IQR*)
MDI	12 mo	118	-0.56 (-1.82, 0.71)	-0.47 (-1.85, 0.92)	-0.52 (-1.92, 0.88)	-0.83 (-3.08, 1.41)
	24 mo	117	-3.12** (-5.38, -0.85)	-2.67** (-4.78, -0.56)	-2.82** (-4.86, -0.78)	-4.52** (-7.79, -1.25)
	36 mo	114	-0.63 (-2.83, 1.57)	-0.80 (-3.03, 1.43)	-1.09 (-3.29, 1.11)	-1.75 (-5.27, 1.78)
PDI	12 mo	118	0.36 (-1.53, 2.25)	-0.80 (-2.81, 1.22)	-0.74 (-2.79, 1.31)	-1.19 (-4.47, 2.10)
	24 mo	115	-0.33 (-2.19, 1.54)	0.01 (-1.93, 1.95)	-0.06 (-2.03, 1.90)	-0.10 (-3.25, 3.04)
	36 mo	109	-0.66 (-3.18, 1.86)	-0.71 (-3.47, 2.05)	-0.89 (-3.62, 1.84)	-1.43 (-5.80, 2.95)
Full	48 mo	104	-1.39 (-3.76, 0.99)	-1.41 (-3.46, 0.64)	-1.42 (-3.53, 0.61)	-2.28 (-5.66, 0.98)
	72 mo	96	0.30 (-2.65, 3.25)	-0.18 (-2.88, 2.53)	-0.22 (-2.97, 2.52)	-0.35 (-4.76, 4.04)
Verbal	48 mo	104	-1.11 (-3.55, 1.34)	-1.72 (-3.99, 0.55)	-1.88 (-4.16, 0.40)	-3.01 (-6.67, 0.64)
	72 mo	96	0.99 (-2.18, 4.16)	0.56 (-2.22, 3.35)	0.76 (-2.02, 3.54)	1.22 (-3.24, 5.67)
Perform	48 mo	104	-1.49 (-4.11, 1.14)	-0.94 (-3.28, 1.41)	-0.86 (-3.23, 1.52)	-1.38 (-5.18, 2.44)
	72 mo	96	-0.54 (-3.44, 2.35)	-0.89 (-3.74, 1.96)	-1.20 (-4.16, 1.75)	-1.92 (-6.67, 2.80)

* IQR (interquartile range) for BDE-99 is 5.60 ng/g lipid
** confidence intervals do not include 0.00

Model 1: Adjusted for age at testing, ethnicity, mother's IQ, child's sex, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, and breast feeding
Model 2: Adjusted for all covariates in Model 1 plus language and location of interview

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Table 5. Association (and 95% CI) between prenatal exposure to BDE-100 and indices of neurodevelopment at 12, 24, 36, 48, and 72 months of age

	age	n	Univariate change in score per ln-unit	Model 1 change in score per ln-unit	Model 2	
					change in score per ln-unit	change in score per increase from the 25th to 75th percentile (IQR*)
MDI	12 mo	118	-0.99 (-2.39, 0.41)	-0.62 (-2.16, 0.92)	-0.72 (-2.29, 0.85)	-1.00 (-3.17, 1.18)
	24 mo	117	-3.27** (-5.71, -0.83)	-2.95** (-5.33, -0.56)	-3.67** (-6.00, -1.34)	-5.09** (-8.32, -1.86)
	36 mo	114	-0.56 (-2.97, 1.85)	-1.04 (-3.55, 1.47)	-1.89 (-4.36, 0.58)	-2.62 (-6.04, 0.80)
PDI	12 mo	118	-0.72 (-2.83, 1.38)	-1.98 (-4.20, 0.24)	-1.93 (-4.21, 0.35)	-2.68 (-5.84, 0.49)
	24 mo	115	-0.10 (-2.13, 1.93)	0.26 (-1.97, 2.49)	0.10 (-2.22, 2.41)	0.14 (-3.08, 3.34)
	36 mo	109	-1.14 (-3.90, 1.62)	-0.97 (-4.10, 2.15)	-1.25 (-4.38, 1.87)	-1.73 (-6.07, 2.59)
Full	48 mo	104	-3.29** (-5.95, -0.63)	-3.30** (-5.61, -0.98)	-3.68** (-6.05, -1.28)	-5.10** (-8.39, -1.77)
	72 mo	96	-1.36 (-4.79, 2.07)	-2.18 (-5.36, 0.99)	-3.10 (-6.27, 0.06)	-4.30 (-8.69, 0.08)
Verbal	48 mo	104	-2.29 (-5.06, 0.48)	-2.87** (-5.49, -0.25)	-3.46** (-6.14, -0.79)	-4.80** (-8.51, -1.10)
	72 mo	96	0.64 (-3.06, 4.34)	-0.70 (-4.01, 2.60)	-1.46 (-4.74, 1.81)	-2.02 (-6.57, 2.51)
Perform	48 mo	104	-3.90** (-6.82, -0.98)	-3.32** (-5.98, -0.66)	-3.37** (-6.14, -0.60)	-4.67** (-8.51, -0.83)
	72 mo	96	-3.20 (-6.51, 0.11)	-3.12 (-6.45, 0.21)	-4.02** (-7.41, -0.63)	-5.57** (-10.27, -0.87)

* IQR (interquartile range) for BDE-100 is 2.12 ng/g lipid
** confidence intervals do not include 0.00

Model 1: Adjusted for age at testing, ethnicity, mother's IQ, child's sex, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, and breast feeding
Model 2: Adjusted for all covariates in Model 1 plus language and location of interview

Table 6. Association (and 95% CI) between prenatal exposure to BDE-153 and indices of neurodevelopment at 12, 24, 36, 48, and 72 months of age

	age	n	Univariate change in score per ln-unit	Model 1 change in score per ln-unit	Model 2	
					change in score per ln-unit	change in score per increase from the 25th to 75th percentile (IQR*)
MDI	12 mo	111	-0.24 (-1.74, 1.26)	0.05 (-1.59, 1.69)	0.02 (-1.65, 1.68)	0.02 (-1.51, 1.54)
	24 mo	113	-0.42 (-2.90, 2.06)	-1.26 (-3.68, 1.17)	-1.71 (-4.07, 0.65)	-1.57 (-3.73, 0.60)
	36 mo	107	1.78 (-0.54, 4.09)	0.29 (-2.17, 2.75)	-0.05 (-2.46, 2.37)	-0.05 (-2.25, 2.17)
PDI	12 mo	111	-1.44 (-3.65, 0.77)	-2.02 (-4.37, 0.33)	-1.95 (-4.34, 0.43)	-1.79 (-3.98, 0.39)
	24 mo	111	0.90 (-1.12, 2.92)	1.20 (-1.03, 3.44)	1.21 (-1.06, 3.49)	1.11 (-0.97, 3.20)
	36 mo	102	-0.04 (-2.62, 2.54)	0.04 (-2.96, 3.05)	0.03 (-3.00, 3.05)	0.03 (-2.75, 2.79)
Full	48 mo	97	-0.30 (-3.14, 2.55)	-2.69** (-5.17, -0.21)	-3.09** (-5.64, -0.54)	-2.83** (-5.17, -0.49)
	72 mo	92	0.02 (-3.28, 3.32)	-3.40** (-6.57, -0.22)	-3.25** (-6.35, -0.15)	-2.98** (-5.82, -0.14)
Verbal	48 mo	97	0.24 (-2.63, 3.12)	-1.93 (-4.71, 0.85)	-2.46 (-5.32, 0.41)	-2.25 (-4.87, 0.38)
	72 mo	92	1.74 (-1.82, 5.29)	-1.91 (-5.28, 1.47)	-1.79 (-5.05, 1.47)	-1.64 (-4.63, 1.35)
Perform	48 mo	97	-1.22 (-4.37, 1.92)	-3.46** (-6.36, -0.57)	-3.62** (-6.62, -0.63)	-3.32** (-6.07, -0.58)
	72 mo	92	-2.03 (-5.23, 1.17)	-4.35** (-7.63, -1.06)	-4.19** (-7.48, -0.89)	-3.84** (-6.85, -0.82)

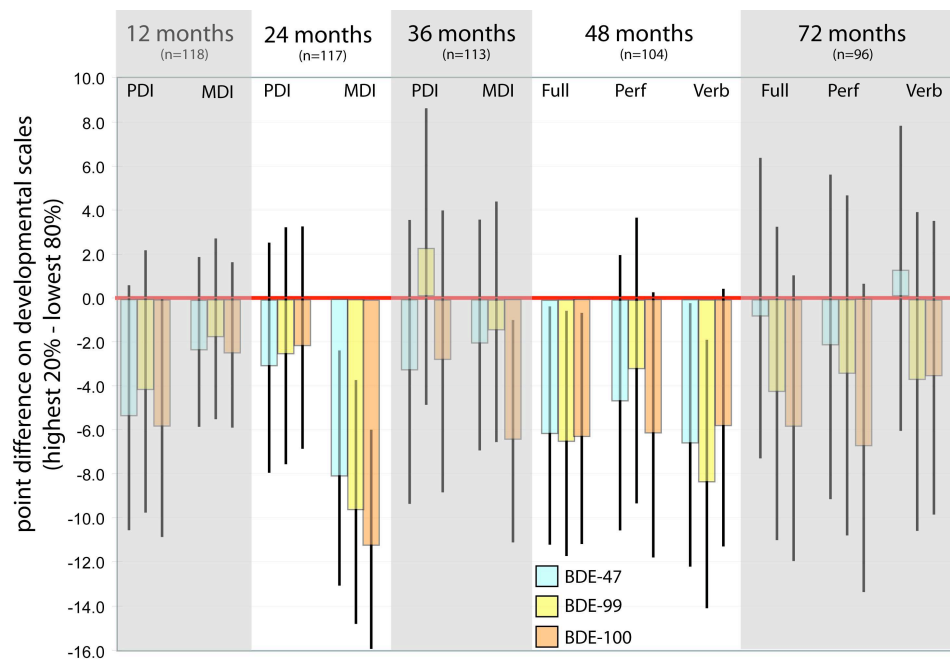* IQR (interquartile range) for BDE-153 is 0.85 ng/g lipid
* confidence intervals do not include 0.00

Model 1: Adjusted for age at testing, ethnicity, mother's IQ, child's sex, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, and breast feeding
Model 2: Adjusted for all covariates in Model 1 plus language and location of interview

Figure 1. Difference in mean developmental score[*] comparing individuals in the highest quintile (20%) of exposure to those in the lower 80% of BDE-47, 99, and 100

[*] mean differences adjusted for: age at testing, ethnicity, mother's IQ, child's sex, gestational age at birth, maternal age, ETS (yes/no), maternal education, material hardship, breast feeding, language and location of interview

259x174mm (300 x 300 DPI)