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Brominated Flame Retardants in Breast Milk and Behavioral and Cognitive Development at 36 Months

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Abstract

Background—Polybrominated diphenyl ethers (PBDEs) are persistent flame retardants found in the environment, in household dust, and in humans. Breast feeding is a prominent route of exposure in infancy. PBDEs adversely affect neurodevelopment in animals. Here, we estimate associations between PBDEs in breast milk and behavior and cognitive skills in children at 36 months of age.

Methods—We prospectively studied 304 mothers and their children. We measured PBDEs in breast milk collected at 3 months postpartum. At 36 months, we measured child behavior with the parent-rated Behavioral Assessment System for Children 2 (n = 192), and cognitive skills with the Mullen Scales of Early Learning (n = 184). We analysed data with robust regression.

Results—We detected BDE-28, −47, −99, −100, and −153 in >70% of milk samples. For each congener, the highest quartile of breast milk PBDE concentration, versus the lowest, was associated with more anxious behavior, after confounder adjustment. Select congeners were associated with increased withdrawal (BDE-28) and improved activity of daily living skills (BDE-153). Cognitive skills tended to be positively associated with PBDEs, especially language and fine motor skills. However, most estimates were imprecise.

Conclusions—Here, lactational PBDE exposure was modestly and imprecisely associated with anxiety and withdrawal, but was also associated with improved adaptive and cognitive skills. Positive factors associated with breast feeding may have mitigated some of the hypothesized adverse neurodevelopmental outcomes associated with PBDEs. Further research is needed to inform our understanding of PBDE neurotoxicity and how sources of exposure might confound neurodevelopmental studies.

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Keywords

PBDEs; halogenated diphenyl ethers; flame retardants; milk; human; environment; environmental pollutant; epidemiology; neurobehavioral manifestations

INTRODUCTION

Polybrominated diphenyl ethers (PBDEs) are high production-volume chemicals widely used as flame retardants in electronic devices, textiles, and the polyurethane foam used in furniture.[1–4] PBDEs are additive flame retardants, meaning that they are not chemically bound to products and therefore have the potential to leach out of materials over time.[5] As such, several PBDE congeners are ubiquitous in the environment.[6–8] PBDEs have been broadly detected in humans, including human breast milk.[9–11] Exposure sources may include indoor dust and possibly, to a lesser extent, contaminated food; however, the degree to which various exposure pathways contribute to human exposure remains unclear.[8, 12–14]

Because PBDEs are highly lipophilic, they concentrate in breast milk and can be ingested by nursing infants.[1] Animal studies suggest that early life PBDE exposure may adversely affect thyroid function and behavioral development, specifically hyperactivity and habituation, as well as cognitive development, including learning and memory (reviewed in Costa and Giordano[15]). However, little is known about the health risks to exposed infants. Studies of prenatal PBDE exposures have suggested some adverse neurodevelopmental effects, including lower mental and physical development scores at 12–48 and 72 months,[16] but findings are not entirely consistent across studies.[17, 18] Furthermore, few studies have investigated associations between postnatal exposures and neurodevelopment. Of the studies that have examined postnatal breast milk concentrations of PBDEs and neurologic outcomes, assessments are limited to very young children (< 18 months) and reported breast milk PBDE levels are low, with limited relevance to mothers and infants in the United States.[19, 20]

Previously, we reported that breast milk PBDE concentrations were associated with externalizing behavior problems in breast-fed children at age 30 months.[21] Here, we have investigated the association between PBDE exposures through breastfeeding and both behavioral and cognitive development at 36 months of age in a cohort of children followed in central North Carolina.

METHODS

Study Sample

The Pregnancy, Infection and Nutrition (PIN) Babies Study included children born to central North Carolina women who had participated in the PIN3 and PIN Postpartum studies.[22] Births occurred from January 2004 to December 2006. The PIN studies recruited pregnant women of less than 20 weeks of gestation who were receiving prenatal care at University of North Carolina Hospitals. Sixty-four percent of eligible women participated in PIN during pregnancy and 73% of eligible PIN participants continued into PIN Postpartum, where eligibility was defined as having a singleton infant without major birth defects.[9] PIN

mothers completed several self-administered questionnaires, two phone interviews during pregnancy, and one in-hospital questionnaire after delivery. For PIN Babies, three inhome interviews were conducted at 3, 12, and 36 months postpartum regarding the participants' health and lifestyle during and after pregnancy. Rarely, interviews were conducted by phone if a home visit could not be performed. The protocols of all PIN studies have been approved by the Institutional Review Board of the University of North Carolina at Chapel Hill, and all participating mothers gave written informed consent. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

Among the 585 participants of the PIN Babies Study, 304 mothers were still lactating at 3 months postpartum and were willing to provide a breast milk sample. Participating mothers followed written instructions to pump both breasts at approximately 10 o'clock in the morning of the scheduled interview. They gently mixed milk and used a plastic pipette to transfer milk into three 1.5 ml tubes, which were stored in the freezer until interviewers arrived. Samples were then transported on ice to −80 ºC storage freezers.

Outcome Assessment

Behavioral development was assessed with the parent rating scale for preschool-age children (PRS-P) of the Behavior Assessment System for Children, 2nd Edition (BASC-2),[23] which is designed to measure both negative (Clinical) and positive (Adaptive) dimensions of behavior and personality. Parents, unaware of exposure status, completed and returned questionnaires by mail or at the 36-month home visit. The preschool parent scale for children ages 2–5 years includes 8 Clinical Scales and 4 Adaptive Scales (listed in Figure 1). Together, these scales combine into 4 Composite Scales: Externalizing Problems (hyperactivity and aggression), Internalizing Problems (anxiety, depression, somatization), Behavioral Symptoms Index (hyperactivity, aggression, depression, atypicality, withdrawal and attention problems), and Adaptive Skills (all Adaptive Scale items). Higher scores on Clinical Scales reflect more problematic (negative) behaviors, while higher scores on Adaptive Scales reflect more adaptive (positive) behaviors. Each raw scale and composite score was converted to an age-standardized T score with a mean of 50 and a standard deviation (SD) of 10. The validity of each parent questionnaire was evaluated with the BASC-2 internal measure, the F-Score, in which higher scores suggest more questionable results. One subject with an F-score of 2 was excluded from analyses; all included subjects had F-scores of 0 or 1.

Cognitive development was assessed with the Mullen Scales of Early Learning (MSEL), a comprehensive individual assessment for infants and young children. The MSEL is designed to assess five functionally distinct but related developmental scales (visual perception, expressive and receptive language, and fine and gross motor skills). The first four of these scales are combined to provide an early learning composite that reflects general intelligence.[24] Trained staff administered the MSEL in the child's home at 36 months of age, without knowledge of the child's exposure status.[25] The MSEL has been standardized on a large sample of children in the United States, and it has well-established validity and

reliability.[24] Each scale produces age-adjusted T-scores with a mean of 50 and an SD of 10; the early learning composite score is age-standardized at a mean of 100 and an SD of 15.

Exposure measurement

We analysed breast milk samples for 10 PBDE congeners (−17, −28, −47, −66, −85, −99, −100, −153, −154, −183) according to the existing methodology at the Organic Analytic Toxicology Branch of the National Center for Environmental Health at CDC,[26] as described previously.[9] We express all concentrations reported here on a lipid normalized basis (ng/g lipid). We do so to reduce the variability in lipid content between different milk samples and inhomogeneity originating from lipid separation during freezing of the samples. Our *a priori* criterion was to include only PBDEs detected in > 70% of samples in our analyses. As such, we included BDE −28, −47, −99, −100, −153, all of which were actually detected in ≥ 90% of samples. Concentrations of these congeners below the limit of detection (LOD) have been assigned a value of the LOD/√2. BDEs −28, −47, −99, −100, and −153 were also summed to produce a cumulative measure (ΣPBDE).

Statistical Analysis

We analysed data by using SAS version 9.2 (SAS Institute Inc., Cary, NC). We examined crude associations between quartiles of natural log-transformed PBDE concentrations and outcomes (age-adjusted BASC-2 and MSEL T scores) to assess the linearity of the exposure and outcome relationships. The mean T scores across quartiles did not support a linear relationship for most comparisons; therefore, we modeled all milk PBDE concentrations as quartiles, defined by using all available samples (n = 304) (Table 3). In order to yield conservative estimates in the presence of influential outliers and the slight skewness in some outcome distributions, we used multivariable robust regression (M estimation) to estimate the mean difference in T scores for each BASC-2 and MSEL sub- and composite scale across quartiles of PBDE −28, PBDE-47, PBDE-99, PBDE-100, PBDE-153, and ΣPBDE using the 1st quartile (< 25th percentile) as the referent for all models (PROC ROBUSTREG).[27]

We included covariates as confounders if they had been associated with both lactational PBDE exposure and child neurodevelopment in relevant literature. These covariates included the child's sex, maternal age at start of pregnancy (≤ 25, 26–30, 31–35, >35 [BASC-2]; continuous years [MSEL]), parity (0 or ≥ 1), education (< or ≥ 16 years), maternal race (nonwhite or white), breastfeeding duration (< or ≥ 10 months), postpartum income (≤ or > $35,000/year), breast milk omega 3 fatty acid concentration (summed docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), quartiles), and fatty acid assay batch (1 or 2). We present results adjusted for these factors as our primary results. To assess the influence of the parenting and home environment on the association, we also ran models that adjusted for modified Home Observation for Measurement of the Environment (HOME) scores,[28] composed of HOME score items ascertained by interview only, and maternal stress, evaluated by the Perceived Stress Scale,[29] along with the covariates listed above. In addition to our primary results, we describe results that were affected by these additional adjustment factors, as warranted. Continuous variables were categorized as needed when distributional or linearity assumptions were not met.

RESULTS

The characteristics of the 304 mothers who provided milk samples at 3 months postpartum have been described previously.[9, 25] Of these, 184 (61%) of their children completed MSEL evaluations and maternal interviews in their home and 192 (63%) returned valid BASC-2 forms (Table 1), 16% of whom completed maternal interviews by telephone.

In general, this study sample included mothers who were mostly > 25 years of age, were college educated, were non-smokers (95%), and were white. A majority of infants were breastfed for at least 10 months. Compared to families who were lost to follow-up, mothers who completed the BASC-2 and whose children completed the MSEL were more likely to be white; BASC-2 mothers were also slightly older than those lost to follow-up. PIN subjects generally performed similarly to, or slightly better than, the normative population on the BASC-2 and MSEL assessments; most of the BASC-2 and MSEL subscale T scores were near the expected value of 50, while scores for most BASC-2 Adaptive subscales, MSEL Expressive Language, and MSEL Visual Reception were slightly elevated (Table 2). PBDE concentrations (Table 3) were correlated across congeners (r = 0.48 – 0.92), and they did not differ between retained participants and participants lost to follow-up (not shown).

Overall, associations between mothers' milk PBDE concentrations and children's BASC-2 scores were small and imprecisely estimated (Figure 1, supplemental Table 1). Within the Clinical Scales, higher PBDE breast milk concentrations were most consistently associated with higher (more problematic) anxiety scores (adjusted β, (β_{adj}) [95% confidence interval (CI)] for 4th Quartile vs. 1st Quartile: BDE-28: β_{adj} = 3.9 [95% CI 0.2, 7.6]; BDE-47: β_{adj} = 2.7 [95% CI −1.0, 6.4]; BDE-99: β_{adj} =4.2 [95% CI 0.6, 7.9]; BDE-100: β_{adj} = 4.1 [95% CI 0.4, 7.8]; BDE-153: β_{adj} = 2.9 [95% CI −1.0, 6.7]). Withdrawal scores also tended to increase with increasing milk concentration, particularly for BDE-28 (β_{adj} = 4.1 [95% CI 0.6, 7.7]). With respect to externalizing behaviors, associations between mothers' milk PBDE concentration and children's aggression and hyperactivity were generally null, with only suggested positive associations observed for aggression and the highest quartiles of BDE-99 and 153 (β_{adj} = 2.0 [95% CI −1.0, 5.0] and β_{adj} = 1.9 [95% CI −1.4, 5.1], respectively).

Within the Adaptive Scales, higher parent ratings on child competence in activities of daily living skills corresponded to increasing BDE-153 milk concentration, suggestive of a possible linear dose-response. Other Adaptive Scale associations tended to occur in the 2nd or 3rd milk concentration quartiles, but these associations varied with respect to magnitude and direction. No notable associations were observed among the BASC-2 Composite Scales.

As expected given the correlation across congeners, associations between BASC-2 measures and ΣPBDE concentrations followed similar patterns as those for the individual congeners, as described above (Supplemental Table 3; e.g.,4th Quartile vs. 1st Quartile, anxiety: β_{adj} = 2.3 [95% CI −1.3, 5.9]; withdrawal: β_{adj} = 2.4 [95% CI −1.0, 5.0]; activities of daily living: β_{adj} = 3.3 [95% CI −0.3, 6.9]). Furthermore, ordinary least squares regression did not yield substantially different associations or greatly improve precision over robust regression. Additional adjustment for modified HOME scores and maternal stress was associated with

small fluctuations in point estimates compared to the original model, but no there was change in the conclusions for most comparisons. Of note, suggested associations between high BDE-153 concentrations and somatization, and between high BDE-99 concentrations and aggression (as reflected in Figure 1), were attenuated when these additional adjustment factors were included in the model: BDE-153 and somatization: β_{adj} = −2.2 [95% CI 0= −5.7, 1.2]; BDE-99 and hyperactivity: β_{adj} = 1.2 [95% CI −1.9, 4.3] (highest vs. lowest quartiles of breast milk concentrations).

Estimated associations between PBDEs and MSEL scores were similarly small and imprecise, but were generally in a positive direction (Figure 2, supplemental Table 2). Across all BDE congeners, the highest milk concentration quartile, compared to the lowest, was associated with adjusted mean T score increases (β_{adj} [95% CI]) ranging from 1.6 [95% CI −2.3, 5.5] to 4.0 [95% CI 0.4, 7.7] for expressive language; 3.2 [95% CI −1.1, 7.5] to 4.1 [95% CI −0.2, 8.4] for receptive language; 1.7 [95% CI −4.0, 7.3] to 4.2 [95% CI −1.4, 9.8] for visual reception; and 3.7 [95% CI −2.5, 9.8] to 6.9 [95% CI 0.9, 12.9] for fine motor. Higher point estimates were suggested in MSEL composite scores as well. Additional adjustment for modified HOME score and maternal stress did not attenuate associations; many point estimates actually increased slightly with additional adjustment. As observed with the BASC-2, associations for ΣPBDE concentrations did not differ from those observed for individual congeners (Supplemental Table 4).

DISCUSSION

In this study, concentrations of PBDEs in breast milk samples at 3 months were not strongly associated with most behavioral and cognitive outcomes in children at 36 months of age, including hyperactivity and aggression. However, despite limited precision, we did observe suggestive patterns of association for other outcomes, both positive and negative. For example, the highest concentration quartile for most congeners was associated with increased anxiety as assessed by the BASC-2, as well as with improved language and fine motor skills in the MSEL cognitive assessment. Congeners were variably associated with increased withdrawal (BDE-28) and improved activities of daily living (BDE-153). The ΣPBDE measure yielded results that were similar to those obtained from the individual congeners. No single congener appeared to be more strongly associated with outcomes than the others, but because all congeners were highly correlated, it is difficult to disentangle individual associations.

Neurotoxicological studies of BDE-47, −99, and −153 in rodents have frequently reported hyperactivity[30–32] and altered habituation[33–35] in association with a range of pre- and postnatal PBDE exposures. A previous study of PBDEs and child behavior reported associations between prenatal maternal serum concentrations of BDE-47, −99, and −100 and impaired attention, along with improved internalizing and externalizing behaviors.[18] An association between cord blood concentrations (BDE-28, −99 and ΣBDEs) and delays in adaptive behavior has also been reported.[17] Previously, we reported that lactational PBDE concentrations were positively associated with increased externalizing behavior problems, specifically including activity, impulsivity, aggression, and defiance, as well as modestly increased anxiety at age 30 months.[21] Here, we did not find evidence that associations with

externalizing behaviors persisted at 36 months. We did, however, observe associations between PBDEs and anxiety. We also observed suggestive associations between PBDEs and increased withdrawal. These traits collectively—anxiety in particular—may be consistent with reports of impaired habituation in animal studies, described in part as reduced activity in the early stages of exposure to new surroundings.[15] The effect of PBDEs on habituation capabilities in animal studies appears to worsen with increasing age.[34]

Some animal studies have also suggested that PBDEs may cause cognitive impairment, specifically related to learning, memory, and visual discrimination,[34, 36, 37] while others have shown no effect on learning and attention.[36, 38] Small epidemiologic studies have recently reported on cognitive effects of early life exposures to PBDEs, also with inconsistent results. Cord blood PBDEs have been positively associated with cognitive function in 8–12 month infants (BDE-99, Σ BDEs) (n = 36),[17] but they have not been associated with cognitive function at age 4 years (BDE-47) (n = 88).[39] Cord blood concentrations have also been strongly negatively associated with developmental indices and IQ at ages 12–72 months (BDE-47, 99, 100) (n = 96–118).[16] BDE-153 concentrations in prenatal maternal serum have been associated with decreased verbal memory at age 5–6 years (n = 62), but other congeners and cognitive measures, including IQ, were not so associated.[18]

Because most previous studies have measured PBDE concentrations in maternal serum or cord blood, we cannot directly compare our breast milk PBDE concentrations with concentrations reported in the studies described above. However, we have previously demonstrated that the breast milk PBDE concentrations in our study are comparable to or slightly higher than concentrations reported in other exposure-based studies of breast milk in the United States.[9] To our knowledge, these other small U.S. cohorts have not examined neurodevelopmental outcomes in relation to breast milk PBDE exposure, but two recent studies based in Taiwan (n = 70) and Spain (n = 290) have assessed postnatal breast milk PBDE concentrations and cognitive outcomes.[19, 20] In both of these studies, breast milk PBDE concentrations were at least an order of magnitude lower than in our study (e.g., median BDE-47 (ng/g lipid): 27.7 (PIN); 0.475 (Taiwan);[19] 0.56 (Spain)[20]). Most of the PBDE congeners we examined were not associated with cognition in these studies, with the exception that BDE-100 was positively correlated with language scores in 8–12 month infants (p = 0.048; median BDE-100: 0.172 ng/g lipid).[19] However, both reported negative cognitive outcomes in association with BDE-209, a congener we were unable to measure.

Along with the congeners and matrix (serum/cord blood vs. breast milk) used for exposure assessment, inconsistencies between the present study and previous studies of PBDEs [16, 18–20, 39] may be attributable to several methodological factors, including differences in the timing of measurement (prenatal vs. postnatal) and in the age at assessment, along with the variability in how diverse assessment instruments characterize specific domains of behavior and cognition. Differences may also be attributed to cohort characteristics or residual confounding. In our study, all women were breastfeeding at 3 months postpartum as a condition of inclusion, and most were highly educated. It is possible that adverse effects of PBDE exposure on cognitive development may have been mitigated by the positive effects of prolonged breastfeeding or by residual socioeconomic factors. Our

results may also have been influenced by a positive unmeasured confounder if PBDE exposure was associated with an environmental factor that also produced increased stimulation in early childhood. Alternatively, the strongly adverse outcomes associated with PBDE exposures described by Herbstman et al.[16] may have been modified or confounded by other negative exposures, stresses, or unique susceptibilities associated with temporal and geographic proximity to the September 11, 2001 attack, an event upon which study enrollment was based. We adjusted for the HOME score and maternal stress as markers of how maternal characteristics may influence the child's development, which did not appreciably change results. However, in interpreting results from this literature, we must consider that a mother's own behavioral traits may affect her child's development, as well as how she completes self-administered questionnaires.

Our study is one of the few to assess postnatal PBDE exposures from concentrations in breast milk, one of the most prominent sources of early life PBDE body burden. This single measure, however, prevents us from investigating the potential influence of PBDEs on *in utero* brain development, particularly because PBDE partitioning between maternal serum, the placenta, and breast milk is not uniform by congener.[40] Those studies that most strongly suggest adverse developmental effects are those that characterize prenatal exposures. Despite small sample size in these studies, their findings may suggest that the prenatal period is uniquely susceptible. Our study is strengthened by the fact that it is one of the largest epidemiologic studies to assess developmental impacts of PBDE exposures. However, it was still subject to imprecise effect estimation, and was not adequately powered to assess sex-specific effects that have been suggested in some animal studies.[41]

CONCLUSION

In general, the results of our study do not suggest strong adverse associations between breast milk PBDE concentrations and behavioral and cognitive outcomes in children at 36 months of age. While we did observe modest associations between PBDEs and increased anxiety and withdrawal, we also observed associations between PBDEs and improvement in certain adaptive behaviors and most cognitive outcomes. These results were imprecisely estimated and few reached statistical significance, and therefore should be interpreted cautiously.

Since PBDEs are persistent compounds with demonstrated neurotoxicity, our results do not preclude the need for further monitoring of neurodevelopmental effects as children age. Future studies should also investigate both prenatal and postnatal exposures as they relate to neurodevelopment, as well as further elucidate sources of PBDE exposure. However, with respect to the congeners measured in this sample, lactational PBDE exposures do not appear to challenge the extensive benefits of breastfeeding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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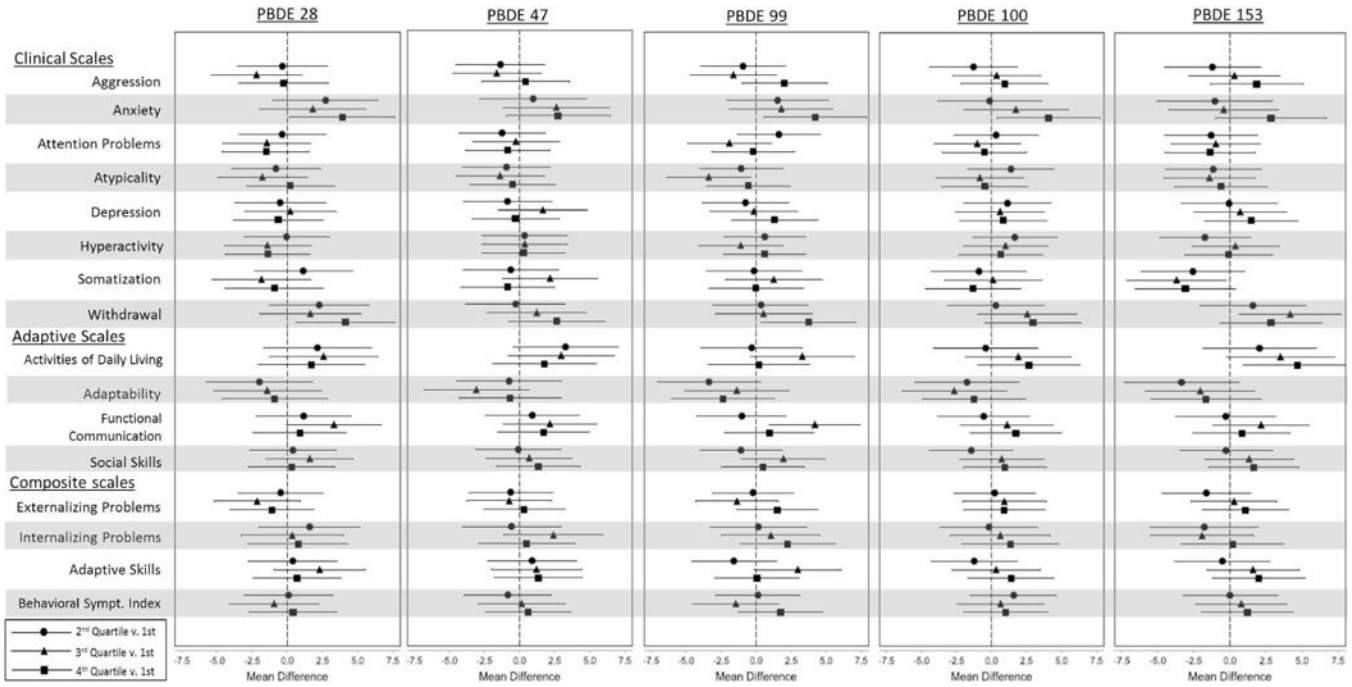

Figure 1.

Mean difference estimates by quartile of PBDE congener (1st quartile, referent) for the BASC-2, adjusted for sex, parity, maternal education, maternal race, breastfeeding duration, income, maternal age, fatty acids (quartiles), and fatty acid analysis batch.

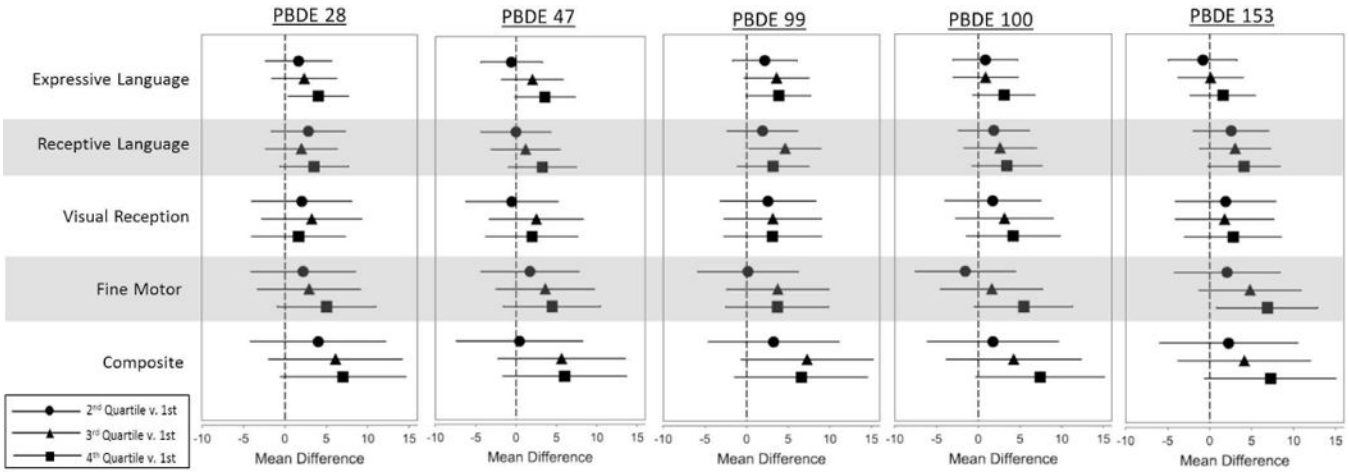

Figure 2.

Mean difference estimates by quartile of PBDE congener (1st quartile, referent) for the MSEL, adjusted for sex, parity, maternal education, maternal race, breastfeeding duration, income, maternal age, fatty acids (quartiles), and fatty acid analysis batch.

Table 1

Characteristics of infants and mothers who provided milk samples at 3 months postpartum during their participation in the PIN Babies Study in central North Carolina, 2004–2006.

	PIN Babies (n = 304)		BASC-2[a] (n = 192)		MSEL (n = 184)	
Characteristic	**n**	**Percent**	**n**	**Percent**	**n**	**Percent**
Gender						
Male	163	54	104	54	97	53
Female	141	46	88	46	87	47
Maternal Age, years						
≤ 25	46	15	24	12	26	14
26–30	104	34	60	31	58	31
31–35	114	38	78	41	73	40
>35	40	13	30	16	27	15
Education, years						
≤ 15	54	18	30	16	33	18
≥ 16	250	82	162	84	151	82
Household Income[b]						
≤ $35,000/year	51	17	28	15	28	15
>$35,000/year	252	83	164	85	156	85
Maternal Race						
White	262	86	176	92*	165	90*
Non-White	42	14	16	8*	19	10*
Parity						
0	160	53	99	52	92	50
1+	144	47	93	48	92	50
Breastfeeding Duration, months[b]						
<10	100	34	71	37	69	37
≥ 10	190	66	121	63	115	63
	mean	**SD**	**mean**	**SD**	**mean**	**SD**

	PIN Babies (n = 304)		BASC-2[a] (n = 192)		MSEL (n = 184)	
Characteristic	**n**	**Percent**	**n**	**Percent**	**n**	**Percent**
Child Age, months	--	--	36.7	2.2	35.9	1.2
Maternal Age, years	30.7	4.9	31.3*	4.7	31.1	4.8
HOME Score (modified)[b]	--	--	29[c]	14–33[c]	29[c]	14–33[c]
Maternal Stress Score[b]	--	--	12[c]	0–27[c]	13[c]	0–27[c]

BASC-2: Behavior Assessment System for Children, 2nd Edition; MSEL: Mullen Scales of Early Learning

*p< 0.05, compared to subjects lost to follow up

[a]Includes PIN Babies subjects with a milk sample, complete BASC-2 and an F-Score of 0 or 1.

[b]Missings: Household Income, n = 1; Breastfeeding duration, n = 14; HOME score, n = 3 (BASC-2); Stress score, n = 4 (BASC-2), n = 1 (MSEL)

[c]median (range)

Table 2

Distribution of BASC-2 and MSEL scores among PIN Babies participants

Instrument Subscale	Mean (SD)	Range
BASC-2 (n = 192)		
Clinical Scales		
Aggression	47 (8)	34–69
Anxiety[a]	51 (9)	36–82
Attention Problems	48 (7)	29–73
Atypicality	49 (8)	39–75
Depression	48 (7)	32–71
Hyperactivity	49 (7)	34–75
Somatization	48 (8)	33–79
Withdrawal	48 (9)	30–82
Adaptive Scales		
Activities of Daily Living	49 (9)	29–72
Adaptability	54 (8)	36–70
Functional Communication	53 (8)	32–74
Social Skills	55 (7)	36–73
Composite Scales		
Externalizing Problems	48 (7)	36–74
Internalizing Problems[a]	49 (8)	32–69
Adaptive Skills	53 (7)	33–70
Behavioral Symptoms Index	48 (7)	31–65
MSEL (n = 184)		
Expressive Language[a]	57 (11)	20–76
Receptive Language[a]	53 (11)	20–76
Fine Motor	49 (14)	20–80
Visual Reception[a]	57 (14)	20–80
Composite[a]	109 (20)	49–148

BASC-2: Behavior Assessment System for Children, 2nd Edition; MSEL: Mullen Scales of Early Learning

[a]missings: BASC-2 Anxiety, n = 1; BASC-2 Internalizing Problems, n = 1; MSEL Expressive Language, n = 7; MSEL Receptive Language, n = 4; MSEL Visual Reception, n = 5; MSEL Composite, n = 8.

Table 3

Distribution of lipid-adjusted PBDE concentrations (ng/g lipid) in breast milk samples for all PIN participants providing milk samples at 3 months postpartum and for those whose children also completed developmental assessments at 3 years of age.

	PIN (n = 304)	BASC-2 (n = 192)			MSEL (n = 184)		
PBDE	Median (IQR)[a]	Mean (Median)	Range[b]	%[c]	Mean (Median)	Range[b]	%[c]
28	2.0 (1.3, 3.7)	3.4 (2.0)	ND–49.6	97	3.4 (2.0)	ND–49.6	96
47	27.7 (15.7, 54.2)	51.3 (28.0)	4–1430	100	52.9 (27.6)	ND–1430	99
99	5.2 (2.7, 11.2)	10.6 (5.1)	ND–299	90	11.1 (5.5)	ND–299	90
100	5.2 (2.4, 10.4)	10.8 (5.3)	ND–188	98	11.0 (5.3)	ND–188	98
153	5.6 (2.7, 13.5)	14.9 (5.6)	ND–229	99	14.9 (5.5)	ND–229	99

PBDE: Polybrominated diphenyl ether; BASC-2: Behavior Assessment System for Children, 2nd Edition; MSEL: Mullen Scales of Early Learning

[a] IQR: interquartile range (25th, 75th percentiles); 25th, 50th (median), and 75th percentiles correspond to quartile cut-points used in analysis

[b] ND (non-detect) values are treated as the limit of detection (LOD) divided by the square root of 2 in the calculation of the mean. LOD values (ng/g lipid) for each congener are as follows: BDE 28: 0.3; BDE 47: 1.3; BDE 99: 1.1; BDE 100: 0.3; BDE 153: 0.3.

[c] Percent of samples above LOD.