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Prenatal Exposure to Polybrominated Diphenyl Ethers and Polyfluoroalkyl Chemicals and Infant Neurobehavior

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Abstract

Objective—To assess the impact of prenatal exposure to polybrominated diphenyl ethers (PBDEs) and polyfluoroalkyl chemicals (PFCs) on early infant neurobehavior.

Study design—In a cohort of 349 mother/infant pairs, we measured maternal serum concentrations during pregnancy of PBDEs, including BDE-47 and other related congeners, as well as two common PFCs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). At age five weeks, we measured infant neurobehavior using the NICU Network Neurobehavioral Scale (NNNS).

Results—Neither PBDE nor PFC exposures during gestation were associated with the 11 individual NNNS outcomes included in our study. However, using latent profile analysis to categorize infants into neurobehavioral profiles based on performance on the NNNS (“social/easygoing,” “high arousal/difficult,” or “hypotonic”), a ten-fold increase in prenatal PFOA concentrations significantly increased the odds of being categorized as hypotonic compared with social/easygoing (adjusted OR 3.79; 95% CI: 1.1–12.8).

Conclusions—Infants of mothers with higher serum concentrations of PFOA during pregnancy were more likely to be categorized as hypotonic. No association between PBDE concentrations and hypotonia was found. Additional studies should further investigate possible associations of prenatal PFC exposure and muscle tone in infants and children.

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The central nervous system is the body system most vulnerable to developmental injury.(1) However, there is limited evidence of the potential neurological damage that may result from typical exposure levels to common environmental chemicals among pregnant women in the United States (US), such as polybrominated diphenyl ethers (PBDEs) and polyfluoroalkyl chemicals (PFCs). In the 1970's, PBDEs began being commercially produced for use as flame retardants in many consumer products, and they have since become pervasive and persistent organic pollutants.(2) A 2008 study reported measurable serum concentrations of PBDEs in 97% of a representative sample of U.S. residents between 2003 and 2004.(3) Despite discontinuation of the most common types of these chemicals in 2004 and 2013,(4, 5) levels of these persistent chemicals remain in the environment and in our homes. The high body burden in infants and toddlers has raised concerns for their potential developmental toxicity.(6) Recent studies indicate that prenatal exposure to PBDEs may have developmental effects, such as lower attention, adverse birth outcomes, lower scores tests of mental and physical development, and hyperactive behavior.(7-11)

PFCs, used to repel dirt, water and oils, have been used extensively since the 1950s in consumer products.(12-15) In a representative sample of the US population, Calafat et al detected perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), the most studied PFCs, in 98% of subjects.(13) Because of persistence in humans and the environment, widespread exposure in wildlife and people, and the potential adverse health impacts associated with such exposures,(16) in 2002, the main manufacturer of PFOS worldwide discontinued the production of PFOS precursors and related compounds in the United States. Ongoing efforts also exist to limit manufacturing emissions of PFOA.(13) Exposure to PFCs have been associated with lower weight and BMI, increased odds of developing attention deficit/hyperactivity disorder, impaired inhibition response, and, in infants, longer time to begin sitting without support.(17-20) However, some studies have found no association between prenatal PFC levels and Apgar score at birth or infant milestones (other than later sitting without support), behavioral and motor coordination problems at age seven, and performance on neuropsychological tests of cognition and language at 3-4 and 6-12 years of age.(14, 18, 21)

The results of studies assessing the effects of PBDEs and PFCs on neurological outcomes are limited, and findings are not consistent across studies or ages at which outcomes were measured. Further, the effects of PBDEs and PFCs on neurobehavioral outcomes in early infancy have not yet been studied. Our goal was to assess the impact of prenatal exposure to PBDEs and PFCs on the neurobehavioral organization of the young infant.

Methods

The study cohort comprised mother/infant pairs participating in the Health Outcomes and Measures of the Environment (HOME) Study, an ongoing, prospective pregnancy/birth cohort in the Cincinnati, Ohio, metropolitan area.(22-24) Recruitment of pregnant women took place between March 2003 and January 2006. Specific recruitment procedures have been described in detail elsewhere.(22, 23) Institutional review boards of four hospitals and two laboratories approved the study protocol, and all participating women provided informed consent for themselves and their infants.

The NICU Network Neurobehavioral Scale (NNNS) is a comprehensive neurobehavioral assessment that evaluates neurological functioning, provides a behavioral profile, and measures signs of stress in young infants.(25) It is the most comprehensive validated assessment of infant neurobehavioral organization that currently exists.(26) The NNNS has been utilized in the past to assess the impact of in utero exposures to environmental toxicants, such as tobacco smoke and plastics.(25, 27, 28) NNNS exams were administered during a home visit by certified examiners trained to reliability against a gold standard and masked to all prenatal exposure information. Analysis of raw NNNS data yields scores describing 13 dimensions of neurobehavior: attention, self-regulation, quality of movement, arousal, excitability, special handling required to acquire orientation items, lethargy, non-optimal reflexes, asymmetrical reflexes, hypotonicity, stress/abstinence, habituation, and hypertonicity. Though each of the scales is somewhat different in its construction, for each of the 13 scales, a higher score indicates more of that quality during the exam, regardless of whether the quality is favorable or unfavorable. Higher scores are favorable for the scales habituation, attention, regulation, and quality of movement, and lower scores are favorable for the scales excitability, handling, lethargy, nonoptimal reflexes, asymmetry, hypertonicity, hypotonicity, and stress/abstinence.(29) For the arousal scale, a moderate score is optimal, as it describes an infant who is alert and responsive during the exam but not overly excited or agitated. A high arousal score indicates an infant who is easily aroused to fuss and cry during an exam, or who cries during the exam, and who is highly active while being handled and while left alone, and a low score indicates an infant who displays low levels of alertness and responsiveness during the exam.(30) The number of infants receiving scores on the habituation and hypertonicity scales of the NNNS was too small for meaningful interpretation, so we excluded these measurements from analyses, as we have in our previous work with the NNNS.(25, 27) Sucharew et al used latent profile analysis to classify infants in this cohort into three discrete profiles based on the scores of their NNNS exam.(31) The summary profiles that were identified were labeled as “social/easy going” (44% of infants), “high arousal/difficult” (32% of infants), and “hypotonic” (24% of infants). Social/easy-going infants showed the ‘best’ neurobehavioral performance during the NNNS examination. The high arousal/difficult infants had the highest mean standardized scores for handling, arousal, excitability and stress/abstinence and the lowest mean standardized scores for attention, self-regulation, non-optimal reflexes, asymmetric reflexes, and quality of movement. The hypotonic profile included infants with signs of hypotonia along with the highest mean standardized scores for lethargy and non-optimal reflexes.(31) Maternal serum obtained at one time point, about 16 weeks gestation, was analyzed for PBDEs. One maternal serum sample was also collected and analyzed for PFCs, although we were unable to collect all of these samples at about 16 weeks gestation. Therefore, we supplemented a small percentage of our PFC samples with those collected at about 26 weeks gestation (10%) and at delivery (5%). Although we measured several PFCs, we focus our analysis only on PFOA and PFOS, the two most commonly studied PFCs.

The serum concentrations of PBDEs and PFCs were measured at the Centers for Disease Control and Prevention (CDC) Environmental Health Laboratories using published methods.(32, 33) All samples were analyzed for ten PBDE-congeners. Of these, BDE-47, BDE-99, BDE-100, and BDE-153 were selected for inclusion, given that other studies found these

congeners to be the most frequently detected PBDEs in pregnant mothers. As BDE-47 is detected most often, our analyses focused on serum BDE-47 individually, as well as the sum of the aforementioned four PBDE congeners (hereafter referred to as sum4BDE: -47, -99, -100, -153).(3, 8, 34) Serum PBDE concentrations were calculated on a lipid basis (ng/g lipid) to account for the PBDEs lipophilicity. For a small number of participants (2%) who had serum concentrations above zero but below the limit of detection (LOD) for PBDE congeners, values were replaced with the LOD divided by the square root of two.(35)

Due to the skewed distribution of PBDEs and PFCs concentrations we applied a $\log_{10}$ transformation to normalize the data. We conducted the analysis of bivariate associations between serum PBDEs and serum PFCs and NNNS outcomes. Various multivariate analytic methods were selected, depending upon the distributional properties of the outcome variable responses. The NNNS hypotonicity scale was dichotomized and analyzed with logistic regression due to a distribution in which the majority of infants received a score of zero, and very few infants had a score greater than one. The asymmetric reflexes scale was analyzed using Poisson regression because the outcome variable was distributed as a count. All other NNNS scales were analyzed using linear regression. Using the NNNS profiles (“Social/Easy Going,” “High arousal/Difficult,” or “Hypotonic”) developed by Sucharew et al from individual NNNS scales in this same cohort of children, we were also able to compare concentrations of PBDEs and PFCs by NNNS profile.(31) We used logistic regression to examine whether infants with higher maternal PBDEs and PFCs concentrations were more likely to be categorized into the “High arousal/Difficult” profile or the “Hypotonic” profile, as opposed to the “Social/Easy Going” profile.

For the individual NNNS scales and NNNS profiles that demonstrated bivariate associations ($p<0.15$) with maternal serum concentrations of PBDEs and PFCs, multivariable models were constructed. Potential covariates included infant sex and age at NNNS exam (these variables were retained in all models as they are known contributors to NNNS performance), maternal age, race, household income, marital status, maternal depression, maternal body mass index at 13-19 weeks gestation, reported alcohol use during pregnancy, reported marijuana use during pregnancy, maternal serum cotinine, infant weight change per month from birth to five weeks, and maternal blood lead level during pregnancy (maternal blood lead was measured at 16 weeks gestation, 26 weeks gestation, and at delivery, and the maximum value was included for analyses). In addition, we included a variable that identified potentially high-risk infants based on gestational age less than 37 weeks, birth weight less than 2500 g, and/or stay in the neonatal intensive care unit (NICU) following birth. With the exception of infant sex and age at NNNS exam, covariates were removed from the multivariate model if they were insignificant and their removal did not modify the regression coefficient of PBDEs or PFCs by >10%. Each covariate was removed individually, beginning with the covariate that demonstrated the weakest association with the outcome. All statistical analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Of the 389 women with singleton live births who comprised the cohort, measures of prenatal PBDE and PFC exposure were collected and NNNS exams were performed on 349 infants at approximately five weeks of age. Characteristics of the sample are displayed in Table I. Women averaged 29.6 years at delivery of the infant, and the majority of women were non-Hispanic, white and married. Infants averaged 34 days at the time of the five-week NNNS assessment.

Maternal PBDE serum concentrations at 16 weeks gestation were measured for 326 women (326 for PBDE47, 292 for congeners -99, -100 and -153). Maternal PFC serum concentrations were measured for 327 women (279 at 16 weeks, 33 at 26 weeks, and 15 at delivery). Measurements are displayed in Table II. Serum concentrations of PBDE-47 and PFOS were similar to estimated national levels of pregnant females during 2003-04. During this time, PBDE levels were reported to be rising in North America, and PFC levels were reported to be decreasing.(13, 36) However, serum concentrations of PFOA were more than twice as high as estimated national levels of pregnant females during 2003-04.(37) With regard to the NNNS Summary Profiles, mean PBDE and PFC concentrations did not differ significantly between the three profiles. Mean scores of the NNNS subscales for these 349 infants were similar to those reported by Tronick and Lester in a normative sample of infants assessed at four weeks.(38, 39)

Table III displays the bivariate and multivariable associations of each of the four chemical exposures examined (ie, sum4PBDE, PBDE47, PFOS, PFOA) with each of the 11 NNNS outcomes. Bivariately, a ten-fold increase in maternal serum concentration of BDE -47 was associated with a significantly decreased (more favorable) score in the asymmetry scale ($p = 0.0499$). No other bivariate associations were observed at the significance level of 0.05. Several other NNNS scales (arousal, lethargy, hypotonicity, and stress/abstinence) with p-values <0.15 were further examined in multivariable analyses. After adjustment of important covariates, neither PBDE nor PFC exposure measures were significantly associated with any of the NNNS scales. However, two near-significant trends ($p<0.10$) were observed. The first was the association of PFOA and the hypotonicity scale, in which increased serum concentrations of PFOA were associated with an increased odds of being categorized as hypotonic ($p = 0.0613$; adjusted odds ratio (aOR) 2.72; 95% CI: 0.95 – 8.785). The second near-significant trend was the association of PFOS and the NNNS stress/abstinence scale, in which serum concentrations of PFOS were positively associated with increased signs of stress/abstinence in the infant ($p = 0.0532$).

Table IV displays the association of each of the four chemical exposures examined with the NNNS profiles. We did not find a significant association between maternal sum4BDE, BDE-47, PFOA, and PFOS serum concentrations and the likelihood of infants being categorized into the high arousal/difficult compared with the social/easy going profile on the NNNS at five weeks. We also did not find an association between maternal sum4BDE, BDE-47, and PFOS and likelihood of infants being categorized into the hypotonic compared with the social easy going NNNS profile. However, a ten-fold increase in maternal PFOA serum concentration significantly increased the odds of being categorized into the hypotonic

profile compared with the social/easy going profile (aOR: 3.79; 95% CI: 1.1 – 12.8). Because the percentage of subjects represented by each profile is greater than 10%, in which case the use of the odds ratio may exaggerate the relative risk, we also calculated the adjusted relative risk (2.20; 95% CI: 1.06 – 4.59).

Discussion

We did not find significant associations between prenatal exposure to PBDEs or PFOS and infant neurobehavior as measured by the NNNS. However, we did find a significant association between prenatal exposure to PFOA and hypotonicity in infants at approximately five weeks of age. Infants born to mothers with higher serum PFOA concentration during pregnancy were at significantly higher risk of being categorized into a hypotonic profile versus a social/easy going profile (aOR: 3.79; 95% CI: 1.1 – 12.8) than other infants. Based on the individual NNNS scale, we found supportive evidence in that we observed a near-significant positive association of PFOA with an increased NNNS hypotonic score (aOR 2.72; 95% CI: 0.95 – 8.785). The hypotonic profile within this cohort, originally described by Sucharew et al(31) includes the 24% of infants who demonstrated reduced muscle tone during the NNNS assessment, which includes an evaluation of active and passive muscle tone, reflexes, and motor function. These hypotonic infants were also more lethargic during the exam and displayed more non-optimal reflexes. Fei et al evaluated infant developmental milestones at six and 18 months and did not find that increased prenatal exposure to PFOA or PFOS impacted these milestones.(18) However, Fei's outcome was measured by maternal report on a highly structured questionnaire, whereas our outcome was measured by individuals trained to conduct a comprehensive, standardized neurological exam. It should be noted, however, that Fei reported that children born to mothers with higher PFOS concentrations were slightly more likely to be sitting without support at a later age. Though we found an association with PFOA (rather than PFOS) with hypotonicity, together these studies do provide the evidence to suggest that PFC exposure may be associated with reduced muscle tone and increased hypotonicity during early and mid-infancy.

In a study of the same cohort, Chen et al found that prenatal exposure to PBDEs was associated with cognitive deficits at five years of age, as well as externalizing behavior problems, yet prenatal PBDE exposure was not associated with the infant neurobehavior in our analyses.(7) However, Chen did not find that PBDE exposure was associated with cognitive and motor development measured at one to three years, which may partially explain why no significant association was found at five weeks of age. Some studies have demonstrated that expression of a deficit caused by early neuron loss may lead to increased functional impairment at older age, and that the expression of the deficit may not occur for some time after the injury.(40, 41) This may partially explain the delayed effect that is observed with this cohort. As developmental stage may be an important factor in the relationship between PBDEs and neurological outcomes, we plan to conduct additional analyses of neurobehavioral outcomes at later time points in development within this cohort of children.

This study has several limitations that should be taken into consideration. One limitation is that PFC measurements were not taken at consistent time points during the pregnancy for all

women. Some studies have shown that the effect of prenatal exposures on neurological outcomes can vary depending on the developmental stage of the organism.(1, 41, 42) However, greater than 85% of our 327 subjects who provided samples for PFC measurements did so at the first collection time point at 16 weeks gestation. We were also limited by our moderate sample size, and the fact that women in our sample were older, more highly educated, and more affluent than the general population, and of prima gravidas in particular. Younger, more impoverished women may be more likely to live in areas with greater environmental toxicants, and their total body burden of toxicants may therefore be greater. This could potentially lead to a greater frequency and/or severity of developmental problems and a higher correlation with the targeted toxicants. However, maternal age and household income were included as potential covariates in each of our multivariate models. Finally, we found a single significant effect and a marginal effect out of the numerous tests that were conducted, and it is possible that our findings reflect a type I error. However, given similar findings by Fei et al,(18) we feel that it is important that our findings be represented in the literature. A major strength of our study is that the neurobehavioral outcome assessed is based on a validated, standardized exam that was performed by a trained examiner, rather than relying on parental report.

As PBDEs and PFCs are ubiquitous in our environment, with various exposure routes, (43-45) it is critical that we understand their impact on human health. Some studies have attempted to identify potential risk factors for prenatal and neonatal exposure to PBDEs and PFCs, but additional studies are needed to confirm these findings as well as to identify the most relevant sources of exposure.(46, 47) Further studies should be conducted in order to better understand primary exposure routes of these substances. The specific source contributions of PFCs are not well characterized,(20) and the relative concentration of PBDE sources to overall body burden has not yet been well established.(48) In addition, studies should further investigate the impact of prenatal exposure of PBDEs and PFCs on neurological outcomes, and to determine the significance of aging in this relationship. Also, there are many different PBDE congeners that are likely to differ in their developmental toxicity.(45) Therefore, in the future it will be important to more clearly elucidate the different effects that each of the congeners may have.(45) Finally, additional studies should be conducted in order to further investigate the effect of prenatal PFC exposure on hypotonic behavior in infants and children.

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Abbreviations and Acronyms

PBDE	polybrominated diphenyl ether
PFC	polyfluoroalkyl chemical
NNNS	NICU Network Neurobehavioral Scale

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Table 1

Characteristics of the sample

	Full sample (N = 349)	
Maternal characteristics		
Maternal Age at Delivery[a]	29.6	5.7
Race		
White, non-Hispanic	222	(64%)
Black, non-Hispanic	105	(30%)
Other	22	(6%)
Marital Status		
Married	235	(67%)
Not married, living with someone	46	(13%)
Not married, living alone	68	(19%)
Household income[b]	55 K	(28 K, 85 K)
Employed during prengnacy	287	(82%)
Education		
≤HS or GED	46	(22%)
Some college or college graduate	195	(56%)
Graduate or professional school	77	(22%)
Maternal BMI		
Underweight	2	(1%)
Normal	146	(42%)
Overweight	119	(34%)
Obese	82	(24%)
Moderate to severe depression (during pregnancy or postpartum)	83	(24%)
Alcohol use during pregnancy		
Never drank alcohol during pregnancy	192	(55%)
Drank <1 alcoholic drink per month	106	(30%)
Drank >1 alcoholic drink per month	51	(15%)
Marijuana use during pregnancy	24	(7%)
Maximum blood lead (μg/dL, geomean)[c]	0.83	(0.27 - 2.49)
Maximum serum cotinine (μg/L, geomean)[c]	0.10	(0.003 - 2.77)
Infant characteristics	-	-
Male	164	(47%)
Birth weight (grams)[a]	3387.26	(610.12)
Birth length (cms)[a]	50.92	(2.92)
Head circumference (cms)[a]	34.21	(1.85)
Gestational age (weeks)[a]	39.03	(1.70)

	Full sample (N = 349)	
Age at 5-week exam (days)[a]	34.50	(5.03)
Birth order		
First child	152	(44%)
Second child	112	(32%)
>Second child	85	(24%)
At risk for neurodevelopmental deficits	43	(12%)
Preterm (<37 weeks)	31	(9%)
Low birth weight (<2500 g)	18	(5%)
NICU stay	17	(5%)

[a] Mean(SD)

[b] Median (25th, 75th percentile)

[c] Geometric Mean (95% confidence interval)

Table 2

Polybrominated Diphenyl Ether (PBDE) and Polyfluoroalkyl Chemical Levels in HOME Study Maternal Serum and Urinary Samples in Comparison with National Levels of Pregnant Women during 2003-04

Exposure	National Levels Pregnant Females 2003-04[a]		HOME Study	
	Geometric Mean[b]	Geometric Standard Error	Geometric Mean[b]	Geometric Standard Error
PBDE47	23.90	0.24	19.96	0.05
Sum4PBDE[c]	Not reported		37.12	0.06
PFOA[d]	2.39	0.24	5.49	0.03
PFOS[e]	12.29	1.02	13.25	0.03
NNNS Summary Profile: Hypotonic (n = 84)				
PBDE47			18.72	0.10
Sum4PBDE[c]			35.55	0.11
PFOA[d]			6.06	0.06
PFOS[e]			13.6	0.05
NNNS Summary Profile: High arousal/difficult (n = 108)				
PBDE47			21.05	0.10
Sum4PBDE[c]			39.39	0.11
PFOA[d]			5.54	0.06
PFOS[e]			13.55	0.07
NNNS Summary Profile: Social/Easy going (n = 157)				
PBDE47			19.95	0.07
Sum4PBDE[c]			36.61	0.08
PFOA[d]			5.18	0.04
PFOS[e]			12.86	0.04

[a] Environmental Chemicals in Pregnant Women in the United States: NHANES 2003-2004 Woodruff, et al., 2011

[b] Reported as ng/g lipid for PBDEs and μg/L for PFCs

[c] Sum of PBDE -47, -99, -100, -153

[d] Perfluorooctanoic acid

[e] Perfluorooctane sulfonic acid

Table 3

Association of Prenatal Exposure to Polybrominated Diphenyl Ethers (PBDEs) and Polyfluoroalkyl Chemicals (PFCs) on NICU Network Neurobehavioral Exam

Variables		Bivariate			Multivariable[a]		
NNNS Outcome	**Exposure**	**Beta**	**Standard Error**	**p-value**	**Beta**	**Standard Error**	**p-value**
Attention	Sum4PBDE[b]	−0.07	0.06	0.2440			
	PBDE47	−0.08	0.06	0.1706			
	PFOA	0.01	0.06	0.8129			
	PFOS	0.01	0.06	0.8493			
Self-Regulation	Sum4PBDE	−0.01	0.06	0.8157			
	PBDE47	−0.03	0.06	0.5888			
	PFOA	−0.02	0.06	0.6956			
	PFOS	−0.03	0.06	0.6277			
Quality of Movement	Sum4PBDE	−0.02	0.06	0.7909			
	PBDE47	−0.04	0.06	0.4482			
	PFOA	−0.01	0.06	0.9194			
	PFOS	−0.01	0.06	0.9126			
Arousal	Sum4PBDE	−0.02	0.06	0.7092			
	PBDE47	0.00	0.06	0.9798			
	PFOA	0.08	0.06	0.1262	0.09	0.06	0.1000
	PFOS	0.05	0.06	0.3886			
Excitability	Sum4PBDE	−0.02	0.06	0.6738			
	PBDE47	0.01	0.06	0.9192			
	PFOA	0.06	0.06	0.2784			
	PFOS	0.08	0.06	0.1707			
Special Handling Required	Sum4PBDE	0.03	0.06	0.6639			
	PBDE47	0.05	0.06	0.3274			
	PFOA	0.03	0.06	0.5886			
	PFOS	0.05	0.06	0.3609			
Lethargy	Sum4PBDE	0.07	0.06	0.2541			
	PBDE47	0.07	0.06	0.2144			
	PFOA	−0.09	0.06	0.0864	−0.09	0.06	0.1126
	PFOS	−0.10	0.06	0.0631	−0.09	0.06	0.1244
Non-Optimal Reflexes	Sum4PBDE	0.06	0.06	0.3252			
	PBDE47	0.05	0.06	0.3743			
	PFOA	0.02	0.06	0.6589			
	PFOS	0.07	0.06	0.1908			

Variables		Bivariate			Multivariable[a]		
NNNS Outcome	**Exposure**	**Beta**	**Standard Error**	**p-value**	**Beta**	**Standard Error**	**p-value**
Asymetrical Reflexes	Sum4PBDE	−0.09	0.05	0.0649	−0.07	0.05	0.1256
	PBDE47	−0.09	0.05	0.0499	−0.09	0.05	0.0726
	PFOA	0.03	0.05	0.5108			
	PFOS	0.07	0.05	0.1239	0.07	0.05	0.1355
Hypotonicity	Sum4PBDE	−0.03	0.08	0.6468			
	PBDE47	−0.05	0.07	0.4787			
	PFOA	0.13	0.07	0.0720	0.14	0.07	0.0613
	PFOS	0.04	0.07	0.6170			
Stress/Abstinence	Sum4PBDE	0.04	0.06	0.4718			
	PBDE47	0.05	0.06	0.3621			
	PFOA	0.01	0.06	0.8163			
	PFOS	0.08	0.06	0.1374	0.11	0.06	0.0532

[a] Assessed if univariate p-value <0.15.

[b] Sum4PBDE: sum of PBDE congeners -47, -99, -100, -153

Table 4

Association of Prenatal Exposure to Polybrominated Diphenyl Ethers (PBDEs) and Polyfluoroalkyl Chemicals (PFCs) on NICU Network Neurobehavioral Exam Profile Category

Variables		Bivariate		Multivariable[a]	
NNNS Profile[b]	Exposure	Odds Ratio	p-value	Odds Ratio	p-value
Difficult	Sum4PBDE	1.216	0.5724		
	PBDE47	1.147	0.6639		
	PFOA	1.657	0.3533		
	PFOS	1.488	0.4678		
Hypotonic	Sum4PBDE	0.921	0.8236		
	PBDE47	0.837	0.6138		
	PFOA	3.529	0.0399	3.785	0.0322
	PFOS	1.780	0.3996		

[a] Assessed if univariate p-value <0.15. Potential covariates included infant's sex and age at NNNS exam (retained in all models), maternal age, race, household income, marital status, maternal depression, maternal body mass index at 13-19 weeks gestation, maternal blood lead level during pregnancy, reported alcohol use during pregnancy, reported marijuana use during pregnancy, maternal serum cotinine, infant weight change per month from birth to five weeks, and a variable that identified potentially high-risk infants based on gestational age less than 37 weeks, birth weight less than 2500 g, and/or stay in the neonatal intensive care unit (NICU) following birth

[b] Reference is Social/Easy Going profile