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

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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 2 common PFCs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid. When the infants were 5 weeks of age, we measured their neurobehavior by using the Neonatal Intensive Care Unit 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, when we used latent profile analysis to categorize infants into neurobehavioral profiles based on performance on the NNNS (social/easygoing, high arousal/difficult, or hypotonic), a 10-fold increase in prenatal PFOA concentrations significantly increased the odds of being categorized as hypotonic compared with social/easygoing (aOR 3.79; 95% CI 1.1-12.8).

Conclusions Infants of mothers with greater 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. *(J Pediatr 2015;166:736-42)*.

The central nervous system is the body system most vulnerable to developmental injury[1]; however, there is limited evidence of the potential neurologic damage that may result from typical exposure levels to common environmental chemicals among pregnant women in the US, such as polybrominated diphenyl ethers (PBDEs) and polyfluoroalkyl chemicals (PFCs). In the 1970s, 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 US 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[13] detected perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), the most studied PFCs, in 98% of subjects. 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 US. Ongoing efforts also exist to limit manufacturing emissions of PFOA.[13] Exposure to PFCs have been associated with lower weight and body mass index, 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 7 years, and performance on neuropsychologic 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 neurologic outcomes are limited, and findings are not consistent across studies or ages at

NNNS	Neonatal Intensive Care Unit Network Neurobehavioral Scale
PBDE	Polybrominated diphenyl ether
PFC	Polyfluoroalkyl chemical
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
sum4BDE	Sum of PBDE -47, -99, -100, and -153

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which outcomes were measured. Furthermore, 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 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 4 hospitals and 2 laboratories approved the study protocol, and all participating women provided informed consent for themselves and their infants.

The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) is a comprehensive neurobehavioral assessment that evaluates neurologic 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 used in the past to assess the impact of in utero exposures to environmental toxicants, such as tobacco smoke and plastics.[25,27,28] NNNS examinations 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, nonoptimal reflexes, asymmetrical reflexes, hypotonicity, stress/abstinence, habituation, and hypertonicity. Although each of the scales is somewhat different in its construction, for each of the 13 scales, a greater score indicates more of that quality during the examination, regardless of whether the quality is favorable or unfavorable. Greater 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 examination but not overly excited or agitated. A high arousal score indicates an infant who is easily aroused to fuss and cry during an examination, or who cries during the examination, and who is highly active while being handled and while left alone; a low score indicates an infant who displays low levels of alertness and responsiveness during the examination.[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 3 discrete profiles based on the scores of their NNNS examination.[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 greatest mean standardized scores for handling, arousal, excitability, and stress/abstinence and the lowest mean standardized scores for attention, self-regulation, nonoptimal reflexes, asymmetric reflexes, and quality of movement. The hypotonic profile included infants with signs of hypotonia along with the greatest mean standardized scores for lethargy and nonoptimal 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 2 most commonly studied PFCs.

The serum concentrations of PBDEs and PFCs were measured at the Centers for Disease Control and Prevention Environmental Health Laboratories via published methods.[32,33] All samples were analyzed for 10 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. Because BDE-47 is detected most often, our analyses focused on serum BDE-47 individually, as well as the sum of the aforementioned 4 PBDE congeners (hereafter referred to as sum4BDE, or the sum of PBDE -47, -99, -100, and -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 greater than zero but below the limit of detection for PBDE congeners, values were replaced with the limit of detection divided by the square root of 2.[35]

Because of 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

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