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Perfluorooctanoate (PFOA) and Neuropsychological Outcomes in Children

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Abstract

BACKGROUND—In animal studies, perfluorinated compounds affect fetal growth, development, viability, and postnatal growth. The limited epidemiologic findings on child neurobehavioral development are mixed.

METHODS—We recruited and evaluated 320 children who participated in the C8 Health Project, a 2005–2006 survey in a mid-Ohio-Valley community highly exposed to perfluorooctanoate (PFOA) through contaminated drinking water. We examined associations between estimated in utero PFOA exposure, measured childhood PFOA serum concentration, and subsequent performance on neuropsychological tests 3–4 years later at ages 6–12 years. We assessed IQ reading and math skills, language, memory and learning, visual-spatial processing, and attention. All multivariable linear-regression models were adjusted for age, sex, home environment, test examiner, and maternal IQ. Models with measured childhood PFOA were additionally adjusted for child body mass index.

RESULTS—Children in the highest as compared to lowest quartile of estimated in utero PFOA had increases in full scale IQ (β 4.6, 95% CI 0.7, 8.5) and decreases in characteristics of attention deficit/hyperactivity disorder as measured by the Clinical Confidence Index of Connors' Continuous Performance Test-II (β -8.5, 95% CI -16.1, -0.8). There were negligible associations between PFOA and reading or math skills or neuropsychological functioning.

CONCLUSION—These results do not suggest an adverse association between the levels of PFOA exposure experienced by children in this cohort and their performance on neuropsychological tests.

Perfluorooctanoate (PFOA) is among the most studied of 853 poly- and perfluorinated compounds (PFCs).¹ These synthetic chemicals have been used since the 1950s² as

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surfactants, surface treatment chemicals, and processing aids for many products, including oil, stain, grease, and water-repellent coatings on carpet, textiles, leather, and paper.³ Human exposure typically occurs through transfer from food packaging and preparation materials, bioaccumulation in the food chain, and household dust.⁴ Some PFCs are persistent organic pollutants⁵ and possible endocrine disrupting chemicals.⁶ PFCs are detected worldwide in wildlife and humans.⁷ In the 2007–2008 United States (U.S.) National Health and Nutrition Examination Survey (NHANES), the geometric mean concentration of PFOA was 4.1 ng/mL (95% confidence interval (CI) 4.0 – 4.3).⁸ Measurable levels of PFOA have been found in amniotic fluid,^{9,10} maternal and umbilical cord blood,^{11–13} and breast milk.^{14–18} PFOA's serum half-life is approximately 2 to 4 years.^{19,20} While the U.S. Environmental Protection Agency is working with 8 major companies on a voluntary phase-out of PFOA emissions and product content by 2015 in the U.S. and globally,²¹ the chemical's long half-life and worldwide dispersion mean that exposure will likely persist for some time.

Toxicology studies highlight the potential for PFCs to affect fetal growth, development, viability, and postnatal growth (reviewed in ^{1,22–24}). There are limited findings on child development from epidemiologic studies. In a sub-study of the Danish National Birth Cohort (n=1,400), early pregnancy plasma PFOA and perfluorooctanesulfonate (PFOS) levels were essentially unrelated to maternal report of motor or mental development through age 18 months.²⁵ There was no association between PFC exposure and maternally reported motor coordination or behavior at age 7.²⁶ Using NHANES 1999–2000 and 2003–2004 data (n=571), Hoffman et al reported increased odds of parent-reported attention deficit/hyperactivity disorder (ADHD) with higher serum PFC levels.²⁷ Using C8 Health Project data (n=10,546), the parent study of the present report, Stein and Savitz reported reduced odds of parent-reported ADHD at the highest PFOA exposure level and increased odds with increasing exposure to perfluorohexanesulfonate (PFHxS).²⁸ Gump et al (n=79) found that higher levels of several PFCs – although not PFOA – were associated with impulsivity, using a differential reinforcement of low rates of responding task among a cohort of children in New York.²⁹ No previous studies have included systematic evaluations of neuropsychological test performance, the most sensitive measures of effect.

In 2001, a group of residents from the West Virginia and Ohio communities surrounding a chemical plant near Parkersburg, West Virginia filed a class action lawsuit alleging health damage from drinking water supplies drawing on PFOA-contaminated groundwater.³⁰ The settlement of the class action lawsuit included a baseline survey, the C8 Health Project (C8 refers to PFOA's 8 carbon chain).³⁰ Geometric mean PFOA levels in this population were approximately 5 times the national average; exposure to most other PFCs reflected typical background levels. We examined the association between the estimated in utero PFOA exposure, measured childhood serum PFOA concentration, and child performance on neuropsychological tests at ages 6 to 12.

METHODS

Study Population

The C8 Health Project enrolled 69,030 people from 2005–2006.³⁰ People were eligible to participate if they could prove they had consumed water for at least one year since 1950 in 1

of 6 PFOA-contaminated water districts or private water sources within areas of documented contamination.

From 2009–2010 we conducted a follow-up to the C8 Health Project. We identified non-sibling children who had lived in the same PFOA-contaminated water district from the time of the mother's pregnancy until C8 Health Project enrollment, who had serum PFC measurements, and whose parents agreed to permit contact for additional studies. The goal was to recruit children aged 6 to 12 years.

Of the 777 identified children, 617 were successfully contacted, 524 of the contacted agreed to be screened, 440 of the screened met eligibility criteria, and 320 of the screened children and their biological mothers (73% of the known eligible) participated in the follow-up study. There was no material difference in measured serum PFOA concentration between those enrolled (mean = 92.5 ng/mL) and not enrolled (mean = 97.3 ng/mL) children ($p=0.69$). Reasons for not participating included inability to schedule an evaluation before the field study concluded ($n=99$) and parent or child refusal ($n=21$). Ineligibility included unavailability of the biological mother ($n=52$), child aging out ($n=14$), no longer living in the region ($n=11$), and child disability ($n=7$). Mothers provided informed consent and children provided verbal assent; child and mother each received \$50 for participation. The Mount Sinai Program for the Protection of Human Subjects and the Battelle Centers for Public Health Research & Evaluation Institutional Review Board approved all study procedures.

Exposure Assessment

PFOA was measured in serum collected at C8 Health Project enrollment in 2005–2006. Laboratory analysis (Exygen Research Inc., State College, PA, USA) used a protein precipitation extraction together with reverse-phase high-performance liquid chromatography/tandem mass spectrometry.^{30,31} The coefficient of variation based on multiple samples between batches was generally 0.10 over the range of 0.5–40 ng/mL. This serum PFOA concentration represents the “measured childhood PFOA” and corresponds to a time point 3–4 years prior to the neuropsychological assessment.

Additionally, we have an estimated in utero PFOA that corresponds to the mother's estimated serum PFOA concentration at the time she was pregnant with the study child. The considerable variation in PFOA exposure across calendar year and water district was taken into account in reconstructing an exposure estimate based on documented PFOA releases, environmental fate and transport modeling, human exposure and excretion pharmacokinetics, and geocoded residential history.^{32,33} Exposure modeling generated individual estimates of serum PFOA levels for C8 Health Project participants. The in utero PFOA estimate is the mother's estimated serum concentration during the year of her third trimester of pregnancy. The pharmacokinetic model does not include adjustments for pregnancy or lactation, and a woman's predicted serum for a given year was not adjusted for reproductive state. This limitation equally affects all pregnant women, and may contribute random error to the estimates. We excluded 35 children from the estimated in utero PFOA analyses: 25 children whose mothers did not participate in the original C8 Health Project study and so had no 3rd trimester estimate; and 10 children whose mothers reported working

at the chemical plant, making the estimate based solely on residential drinking-water exposure inaccurate. On average, the estimated in utero PFOA is higher than the child's measured PFOA because the mother had more time to accumulate PFOA than the child.

We examined the association between PFOA and the outcomes using restricted cubic splines.³⁴ There was no clear pattern to guide choice of a metric for calculating effect estimates. PFOA was treated as a natural log-transformed variable because the transformation provided a better model fit. We calculated effect estimates representing a 1-natural-log-unit increase in exposure, and also quartiles of exposure, with the lowest quartile as the referent. Quartile cutpoints were determined separately for the estimated in utero and measured childhood values.

Outcome Assessment

To collect information pertinent to clinically important behaviors, we selected a battery of tests that assess skills predictive of a child's ability to make adequate progress in school. These outcomes included general intelligence, reading, math computation, comprehension of instructions, memory for stories, visual-spatial skills, and attention/impulsivity. Eight examiners blinded to participants' exposure histories were trained and certified (by D.C.B.) to administer the assessments.

The Wechsler Abbreviated Scale of Intelligence consists of four subtests similar to subtests of the Wechsler Intelligence Scale for Children—Fourth Edition.³⁵ These two verbal (Vocabulary, Similarities) and two nonverbal (Block Design, Matrix Reasoning) subtests have the highest loadings on general intellectual function. The tests are normed and provide age-standardized scores for Full Scale Intelligence Quotient (IQ), Verbal IQ, and Performance IQ. IQ scores range from 50 to 160 with mean = 100 and standard deviation (SD) = 15.

We used three subtests from the Wechsler Individual Achievement Test—II to assess academic skills.³⁶ Two subtests measure word attack and decoding skills (Word Attack, Pseudoword Decoding); we averaged the standardized scores from these two subtests to create a composite measure of reading fluency. The third subtest measures arithmetic capabilities (Numerical Operations). Age-standardized scores range from 40 to 160 with mean = 100 and SD = 15; as with IQ, higher scores are better.

The NEPSY-II is a neuropsychologically-based instrument designed to test specific brain-behavior relationships and identify markers of atypical cognitive development.³⁷ We focused on three domains: Language (Comprehension of Instructions, Word Generation), Memory and Learning (Narrative Memory), and Visual-spatial Processing (Design Copying). We averaged the Semantic and Initial Letter scaled scores from the Word Generation subtest. Age-standardized scaled scores range from 1 to 19 with mean = 10 and SD = 3; again, higher scores are better.

The Connors' Continuous Performance Test-II is a computer-administered test that measures sustained attention and impulsivity.³⁸ The child is instructed to push the spacebar every time a letter appears on the screen except when the letter is "X." The Clinical Confidence Index

measures the extent to which the child's overall profile resembles the canonical profile of children with ADHD. The Clinical Confidence Index is a raw score ranging from 0 to 100; lower scores are better. We also analyzed age- standardized T-scores for Omission Errors (no response after non-X), Commission Errors (response after X), and Hit Reaction Time (mean response time in milliseconds). T-scores have mean = 50 and SD = 10; lower scores are better.

Covariate Assessment

We interviewed mothers to collect information to address confounding. The Home Observation for Measurement of the Environment—Short Form Mother Supplement measures the quality and extent of stimulation in the home based on maternal report.³⁹ Maternal IQ was measured using the Wechsler Abbreviated Scale of Intelligence. Mothers also completed an extensive interview to solicit data on factors that may have affected their child's neurobehavioral development, such as pregnancy and delivery complications, breastfeeding history, and presence of co-morbid health conditions in the child. We also measured the child's height and weight. The child's body mass index (BMI) z-score was calculated based on U.S. Centers for Disease Control and Prevention growth charts.

Statistical Analysis

We used linear regression to calculate the unadjusted association between the two measures of PFOA exposure and neuropsychological test performance. We identified an a priori set of covariates to be included in all models (child's age at neuropsychological assessment—continuous decimal years, child sex, cognitive and emotional Home Observation for Measurement of the Environment scores—continuous, test examiner—categorical, maternal Full Scale IQ—continuous). Separately for the two exposure measures, we determined the potential for confounding from additional covariates by examining the covariate - exposure and covariate - outcome associations for variables collected through the maternal interview, excluding potential intermediates linking PFOA to the outcomes.⁴⁰ To keep the list of additional covariates manageable, we included only those covariates with $p < 0.20$ for both associations in a full model with the a priori covariates. Of over 60 variables tested, only the child's BMI z-score at neuropsychological assessment fulfilled these criteria. Using a 10% change-in-estimate approach, BMI acted as confounder in models with measured childhood PFOA.⁴⁰ All final multivariable linear regression models included the shared set of a priori covariates to calculate the beta and 95% CI for each PFOA-outcome combination. The models with measured childhood PFOA were additionally adjusted for BMI. Analysis was performed using SAS Version 9.2 (Cary, NC).

Given the concern that PFOA may be hormonally active,⁶ we also examined the potential for sex of the child to modify the association between exposure and outcome, comparing the effect estimates of stratified and unstratified models and examining the likelihood ratio p-value for the PFOA-sex interaction term.⁴⁰ There was little evidence that sex modified the exposure-outcome associations; with one exception we present only the unstratified models.

We performed several secondary analyses. To assess the potential for low-dose exposure effects that may have been obscured in this highly exposed population, we restricted

analyses to the children with PFOA concentrations below the median. To incorporate the potential effect of exposure to other PFCs, we adjusted the measured childhood PFOA analyses for measured concentrations of PFOS, PFHxS, and perfluorononanoate (PFNA). To address our lack of information on lead exposure, we restricted the analyses to the children whose mothers reported that the child had received a blood lead test and that the result was below 10 µg/dL. Finally, to ensure that our findings for measured childhood PFOA were not an artifact of treatment for ADHD, we restricted the analyses to the children with no reported ADHD diagnosis.

RESULTS

The average age of children at neuropsychological assessment was 9.9 years (SD 1.7; range 6–12); 53 percent were girls (Table 1). Only 10 (3 percent) children were non-white. On average, the mothers were 38.4 years old (SD 5.9) at the time of follow-up, and 65 percent had at least some college education.

The median estimated in utero PFOA concentration was 43.7 ng/mL (interquartile range (IQR) 11.7–110.8; Table 1). The median measured childhood PFOA concentration was 35.0 ng/mL (IQR 15.3–93.2). The correlation between the estimated in utero and measured childhood exposures was 0.69. Correlations were weak between measured childhood PFOA concentration and measured PFOS ($r=0.15$), PFHxS ($r=0.04$), and PFNA ($r=-0.02$) concentrations.

Estimated in utero and measured childhood PFOA exposures were associated with modest increases in IQ points at the highest as compared with the lowest PFOA quartile, although there was neither a monotonic nor consistent pattern (Table 2). After adjustment, Quartiles 1, 2, and 3 were similar, and Quartile 4 (β 2.8, 95% CI -0.9, 6.5) showed an increase as compared with Quartile 1 of measured childhood PFOA exposure. The adjusted betas for the estimated in utero exposure were all positive.

The pattern of results for academic skills showed effect estimates close to the null for the measured childhood exposure, but not for the estimated in utero exposure (Table 3). Quartiles 2 to 4 of estimated in utero exposure showed improved reading and arithmetic skills as compared with the lowest quartiles. The Numerical Operations standard score was the only outcome that exhibited an interaction with child sex ($p=0.01$) for measured childhood PFOA, with more modest evidence for interaction based on in utero PFOA ($p=0.14$). When exposure was dichotomized at the median value, boys with measured childhood exposure above the median had a 4.9 (95% CI 0.2, 9.6) increase in the Numerical Operations scaled score as compared with boys below the median. The effect among boys was comparable for estimated in utero PFOA (β 4.4, 95% CI -0.4, 9.2). Conversely, girls with measured childhood exposure above the median had a 4.1 score decrease (95% CI -8.6, 0.3) as compared with girls below the median; there was no effect of estimated in utero PFOA (β -0.6, 95% CI -5.0, 3.9).

There was minimal association between PFOA exposure and neuropsychological functioning (Table 4). The sole noteworthy result was for measured childhood PFOA and

the Design Copying total scaled score. The highest as compared with the lowest quartile of PFOA showed a 1.0 point increase (95% CI 0.0, 2.0), implying an increase in visual-spatial processing skills by approximately one-third a standard deviation at the highest PFOA exposure level.

We found favorable associations between PFOA exposure and attention, as measured by Connors' Continuous Performance Test (Table 5). The Clinical Confidence Index showed that increases in both estimated in utero and measured childhood PFOA exposure resulted in profiles less similar to the profile of children with ADHD. For example, children in the highest quartile of estimated in utero PFOA were close to a full standard deviation (β -8.5, 95% CI -16.1, -0.8) away from the mean – in the favorable direction – as compared with children in the lowest quartile of PFOA. The effect was similar for measured childhood PFOA.

Restricting to the population with PFOA exposure below the median did alter some results, but not in a consistent direction. The effect estimates for the associations between estimated in utero exposure and IQ scores were reduced to near null (eTable 1). On the Wechsler Individual Achievement Test, some of the reading fluency effect estimates dipped below the null (eTable 2). The Numerical Operations subtest, however, exhibited improved arithmetic skills with increased PFOA exposure, but without a coherent dose-response pattern. There was no change to the scores on the NEPSY subtests (data not shown). On Connors' Continuous Performance Test, this restriction reduced the favorable associations evident in the full population for estimated in utero exposure, and strengthened the favorable associations for measured childhood exposure (eTable 3).

Additionally adjusting the measured childhood PFOA analyses for PFOS, PFHxS, and PFNA had minor effects. On the Wechsler Individual Achievement Test, all effect estimates were negative – indicating reduced academic skills with increased exposure (eTable 4), but the magnitude of the effects remained small and ultimately differed little from the primary analyses. Including PFOS, PFHxS, and PFNA in the measured childhood model attenuated the effect estimates for the Clinical Confidence Index from Connors' Continuous Performance Test (eTable 5) although the overall interpretation remained that children more exposed to PFOA less closely matched the ADHD profile as compared with less exposed children. There was minimal change across the other assessments (data not shown).

Restricting to the population with no reported history of elevated blood lead tests accentuated the primary findings for Verbal IQ (data not shown). The decrease on the Clinical Confidence Index with increased PFOA exposure became even greater (data not shown). There was minimal change across the other assessments (data not shown).

There was no change to the pattern of results when we restricted to the 284 children with no reported ADHD diagnosis (data not shown). In particular, Connors' Continuous Performance Test results in this restricted population showed that children more highly exposed to PFOA less closely matched an ADHD profile.

DISCUSSION

Overall, the pattern of results does not suggest an adverse effect of PFOA exposure with performance on the administered tests. There was no consistent decrement in IQ, reading or math skills, neuropsychological functioning, or attention. In fact, in this study, children with the greatest exposure to PFOA were the most dissimilar to an ADHD profile according to the Clinical Confidence Index on Connors' Continuous Performance Test. This finding was apparent with the estimated in utero and measured childhood exposures, and consistent across all secondary analyses. Adjustment for other measured PFCs (PFOS, PFHxS, PFNA) attenuated but did not eliminate the positive association with PFOA. The remaining non-null findings – sporadic favorable (IQ, Numerical Operations, Design Copying) associations – were imprecise, inconsistent, and not markedly changed in any of the secondary analyses.

Previously we reported reduced odds of parent-reported ADHD at the highest PFOA exposure level using cross-sectional data from the C8 Health Project.²⁸ 193 of the children in the current study were included in the previous analysis. We had suggested that those findings might be due to unmeasured confounding. In the current study where exposure measures pre-dated outcome determination, we collected extensive covariate data on pregnancy health, child health, and household demographics. While many of these variables were associated with the outcome, few were associated with exposure. The shared exposure source from public drinking water systems does make this study less susceptible to confounding by socioeconomic surrogates that could be related to exposure in other settings, such as diet and use of stain resistant carpeting or water repellant clothing. Even with high-quality exposure biomarkers and covariate data some measurement error remains.

One recent epidemiological study has suggested that PFOA may have neuroprotective effects.⁴¹ In a cross-sectional analysis of NHANES data, Power et al observed protective associations between PFC exposure and cognition in older adults, in particular among non-medicated diabetics.⁴¹ PFOA activates human in vitro peroxisome proliferator-activated receptor (PPAR) alpha (and to a lesser extent gamma), which function as agonists, or partial agonists of these nuclear receptors.⁴² PPAR-gamma agonists appear to have neuroprotective and central-nervous-system anti-inflammatory properties that have been exploited for treatment of neurodegenerative diseases.^{43,44} Interestingly, the thiazolidinedione anti-diabetic drugs are also PPAR-gamma agonists. Neuroprotective properties of PPAR-gamma agonists, such as PFOA, may hypothetically manifest in children as higher IQ and improved attention skills.

There is little existing epidemiologic research with which to compare these results. In addition to our earlier study of ADHD, there is a second cross-sectional study of PFC exposure and ADHD.²⁷ Hoffman et al reported increased prevalence of parent-reported ADHD with increased exposure to PFOA, despite a considerably lower median PFOA concentration. Gump et al measured greater impulsivity among children with higher exposure to several PFCs, although not PFOA.²⁹ Fei et al looked at maternally reported infant developmental milestones and child behavior, and observed no associations with PFOA.^{25,26} Our results are consistent with those studies observing no effect of PFOA on

selected child developmental outcomes. While our methods are the most rigorous and objective, our outcomes may have less direct clinical relevance.

Lack of measured blood lead levels is a limitation of this study. Childhood lead exposure causes lower IQ and higher rates of behavioral problems even at very low levels.⁴⁵ If we had observed negative effects of PFOA, then unmeasured confounding by lead concentration may have been a plausible explanation. Unmeasured confounding by lead, though, is unlikely to explain the pattern of results we report unless lead and PFOA are inversely correlated.

Multiple comparisons of both exposure and outcome measures are another aspect of our results to consider. With little a priori guidance on the kinds of deficits that may result from prenatal and childhood PFOA exposure, we chose to use several neurodevelopmental assessments. While this choice allowed us to report on various domains of neurodevelopment, it also necessitated a large number of statistical tests; random variation may have resulted in spurious positive and inverse associations. We reported all results from the primary analyses regardless of direction of association or p-values.

Limitations notwithstanding, this study is by far the most comprehensive investigation to date of PFOA exposure and child neurobehavioral development. We included two measures of PFOA exposure that pre-dated the outcomes assessment. The estimated in utero concentration reflects a developmentally relevant window of susceptibility, but may suffer from exposure misclassification inherent in the exposure modeling process.^{32,33} The childhood exposure is a measured value, but may represent a less susceptible developmental window for the outcomes assessed. Results from the two exposure measures were largely consistent, which is not surprising given their strong correlation ($r=0.69$). To best characterize the outcomes, we assessed the children with standardized, validated, normed, neuropsychological tests. We instituted rigorous standards for data collection (trained examiners, standardized testing setting) and amassed extensive covariate details from the biological mother including IQ. The quality of the exposure, outcome, and covariate data were all high. We examined the data in multiple ways to account for factors such as the unusually high PFOA exposure (restricted to below the population median), potential non-linear effects of PFOA (splines), potential hormonally mediated effects (stratified by child's sex), and other related exposures (PFOS, PFHxS, PFNA). Ultimately we detected no consistent negative effect of PFOA exposure on IQ, reading or math skills, neuropsychological functioning, or attention.

Given the study's limitations it would be premature to conclude that there is no adverse association between PFOA and neuropsychological development. With ubiquitous exposure to PFOA, even a small effect of this chemical would have broad ramifications at the population level. It is also important to note that in this study we focused on PFOA because the population was exposed to high levels of PFOA through contaminated drinking water. The results we report for PFOA are not applicable to other PFCs, and in this study adjustment for 3 other common PFCs did attenuate the positive association found between PFOA and the Clinical Confidence Index.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Univariate Characteristics of Children 6 to 12 Years of Age, C8 Health Project Neurobehavioral Follow-up Study, Mid-Ohio Valley, 2009 – 2010 (n=320)

Characteristic	No.	Mean (SD)
Child age at neuropsychological assessment(years);	320	9.9 (1.7)
Child age at childhood PFOA measurement(years);	320	5.7 (1.8)
Child sex (%)		
boys	149	47
girls	171	53
Child race (%)		
Non-white	10	3
White	308	97
Child Body Mass Index (kg/m ²)		
Z-score	319	0.7 (1.3)
Underweight (<5 th percentile)	7	2
Healthy weight (5 – <85 th percentile)	178	56
Overweight (85 – <95 th percentile)	49	15
Obese (>95 th percentile)	85	27
Reported ADHD diagnosis (%)		
Yes	36	11
No	284	89
Reported blood lead test above 10 µg/dL (%)		
Yes	6	4
No	144	96
Maternal age, years	320	38 (5.9)
Maternal education (%)		
Less than high school	11	3
High school graduate	100	31
Some college	132	41
College graduate	77	24
Maternal live births		
1	41	12.8
2	154	48.1
3	87	27.2
4+	38	11.9
Mother's original study record available (%)		
No	25	8
Yes	295	92
Mother worked at manufacturing facility (%)		
No	285	97
Yes	10	3
Maternal Full-scale IQ	320	99.3 (12.4)

Characteristic	No.	Mean (SD)
Home Observation for Measurement of the		
Cognitive scale	320	6.8 (1.8)
Emotional scale	320	9.8 (1.5)
Estimated in utero PFOA, ng/mL (%)	285	115.9
Quartile 1: 4.5 – <11.7	72	
Quartile 2: 11.7 – <43.7	71	
Quartile 3: 43.7 – <110.8	71	
Quartile 4: 110.8 – 649.2	71	
Measured childhood PFOA, ng/mL (%)	320	91.9 (139.8)
Quartile 1: 0.7 – <15.3	80	
Quartile 2: 15.3 – <35.0	80	
Quartile 3: 35.0 – <93.2	80	
Quartile 4: 93.2 – 838.6	80	
Measured childhood PFOS, ng/mL	320	21.1 (13.3)
Measured childhood PFHxS, ng/mL	320	9.8 (14.1)
Measured childhood PFNA, ng/mL	318	1.9 (1.1)
Wechsler Abbreviated Scale of Intelligence		
Full Scale IQ	320	101.0 (13.1)
Verbal IQ	320	102.5 (13.5)
Performance IQ	320	98.9 (13.3)
Wechsler Individual Achievement Test		
Word Reading/Pseudoword Decoding	304	101.9 (11.4)
Numerical Operations standard score	320	97.5 (15.1)
NEPSY		
Comprehension of Instructions scaled score	319	10.6 (2.9)
Design Copying Total scaled score	302	8.3 (3.4)
Narrative Memory Free and Cued Recall scaled	318	9.4 (2.8)
Semantic/Initial Letter scaled score mean	298	9.5 (2.5)
Connors' Continuous Performance Test		
Clinical Confidence Index	304	51.1 (23.7)
Omissions T-score	304	53.7 (12.4)
Commissions T-score	304	55.9 (8.5)
Hit Reaction Time T-score	304	48.0 (10.5)

PFOA = Perfluorooctanoate; PFOS = perfluorooctanesulfonate; PFHxS = perfluorohexanesulfonate; PFNA = perfluorononanoate; ADHD = Attention Deficit/Hyperactivity Disorder

Table 2

Crude and Adjusted Associations Between Perfluorooctanoate (PFOA) Exposure and IQ Among Children 6 to 12 Years of Age, C8 Health Project Follow-up Study, Mid-Ohio Valley, 2009 – 2010^a

PFOA Exposure	Full Scale IQ		Verbal IQ		Performance IQ	
	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)
PFOA measured in utero (n=285)						
1 LN unit increase Quartiles (ng/mL)	1.24	0.83 (-0.13 to 1.79)	0.85	0.41 (-0.60 to 1.42)	1.03	0.58 (-0.39, 1.55)
4.5 – <11.7	0	0	0	0	0	0
11.7 – <43.7	4.20	2.81 (-1.17 to 6.78)	2.88	0.89 (-3.32 to 5.09)	4.93	3.62 (-0.40 to 7.65)
43.7 – <110.8	4.73	1.74 (-2.17 to 5.65)	3.48	0.67 (-3.46 to 4.80)	5.22	2.48 (-1.48 to 6.44)
110.8 – 649.2	5.72	4.61 (0.68 to 8.54)	3.48	2.03 (-2.12 to 6.19)	5.03	3.83 (-0.15 to 7.81)
PFOA measured in childhood (n=320)						
1 LN unit increase Quartiles (ng/mL)	1.67	0.99 (-0.06 to 2.04)	1.04	0.29 (-0.83 to 1.40)	1.53	0.94 (-0.14 to 2.01)
0.7 – <15.3	0	0	0	0	0	0
15.3 – <35.0	0.53	-0.29 (-3.89 to 3.30)	0.70	-0.62 (-4.43 to 3.19)	0.31	-0.29 (-3.98 to 3.40)
35.0 – <93.2	1.54	-1.11 (-4.78 to 2.56)	-0.23	-3.07 (-6.96 to 0.82)	2.74	0.52 (-3.24 to 4.29)
93.2 – 838.6	4.98	2.80 (-0.90 to 6.50)	2.61	0.20 (-3.72 to 4.12)	4.69	2.81 (-0.98 to 6.61)

^a Sample size is identical for crude and adjusted models

^b All analyses adjusted for child age at neuropsychological assessment, child sex, test examiner, Home Observation for Measurement of the Environment score, maternal Full Scale IQ; measured childhood analyses additionally adjusted for child BMI at neuropsychological assessment

Crude and Adjusted Associations Between Perfluorooctanoate (PFOA) Exposure and Academic Skills Among Children 6 to 12 Years of Age, C8 Health Project Follow-up Study, Mid-Ohio Valley, 2009 – 2010^a

Table 3

PFOA Exposure	Word Reading/Pseudoword Decoding standard score mean		Numerical Operations standard score	
	Crude β	Adjusted β^a (95% CI)	Crude β	Adjusted β^a (95% CI)
PFOA measured in utero				
1 LN unit increase Quartiles (ng/mL)	1.15	0.50 (–0.40 to 1.41)	1.01	0.65 (–0.48 to 1.78)
4.5 – <11.7	0	0	0	0
11.7 – <43.7	4.16	1.72 (–2.05 to 5.48)	4.96	4.45 (–0.25 to 9.14)
43.7 – <110.8	3.57	0.61 (–3.07 to 4.30)	6.65	4.75 (0.13 to 9.36)
110.8 – 649.2	4.69	2.27 (–1.43 to 5.96)	4.15	3.12 (–1.51 to 7.76)
PFOA measured in childhood				
1 LN unit increase Quartiles (ng/mL)	0.70	–0.02 (–1.01 to 0.98)	0.74	0.15 (–1.17 to 1.46)
0.7 – <15.3	0	0	0	0
15.3 – <35.0	–0.44	–1.32 (–4.70 to 2.06)	0.71	0.36 (–4.17 to 4.88)
35.0 – <93.2	0.57	–1.91 (–5.34 to 1.52)	3.11	1.11 (–3.51 to 5.73)
93.2 – 838.6	1.36	–1.09 (–4.54 to 2.36)	1.34	–0.41 (–5.06 to 4.25)

^a Sample size is identical for crude and adjusted models

^b All analyses adjusted for child age at neuropsychological assessment, child sex, test examiner, Home Observation for Measurement of the Environment score, maternal Full Scale IQ; measured childhood analyses additionally adjusted for child BMI at neuropsychological assessment

Table 4

Crude and Adjusted Associations Between Perfluorooctanoate (PFOA) Exposure and Neuropsychological Functioning Among Children 6 to 12 Years of Age, C8 Health Project Follow-up Study, Mid-Ohio Valley, 2009 – 2010^a

PFOA exposure	Comprehension of Instructions Scaled Score		Design Copying Total Scaled Score		Narrative Memory Free and Cued Recall Scaled Score		Word Generation Semantic/Initial Letter Scaled Score Mean	
	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)
PFOA measured in utero		(n=284)		(n=267)		(n=284)		(n=265)
1 LN unit increase Quartiles (ng/mL)	0.22	0.14 (–0.08 to 0.36)	0.30	0.21 (–0.06 to 0.48)	–0.11	–0.14 (–0.36 to 0.08)	0.14	0.10 (–0.09 to 0.30)
4.5 – <11.7	0	0	0	0	0	0	0	0
11.7 – <43.7	0.63	0.46 (–0.46 to 1.38)	–0.02	0.10 (–1.01 to 1.22)	0.03	–0.09 (–1.02 to 0.83)	0.03	0.02 (–0.79 to 0.83)
43.7 – <110.8	1.17	0.76 (–0.14 to 1.67)	0.85	0.56 (–0.55 to 1.66)	0.07	–0.02 (–0.92 to 0.89)	0.26	0.02 (–0.77 to 0.81)
110.8 – 649.2	0.96	0.76 (–0.15 to 1.67)	1.05	0.75 (–0.36 to 1.86)	–0.35	–0.41 (–1.32 to 0.50)	0.43	0.41 (–0.39 to 1.21)
PFOA measured in childhood		(n=319)		(n=302)		(n=318)		(n=298)
1 LN unit increase Quartiles (ng/mL)	0.16	0.03 (–0.22 to 0.28)	0.46	0.26 (–0.04 to 0.55)	0.01	–0.07 (–0.31 to 0.17)	0.10	0.03 (–0.19 to 0.25)
0.7 – <15.3	0	0	0	0	0	0	0	0
15.3 – <35.0	0.50	0.28 (–0.57 to 1.13)	0.61	0.58 (–0.41 to 1.57)	0.13	–0.07 (–0.91 to 0.76)	–0.09	–0.29 (–1.04 to 0.46)
35.0 – <93.2	0.55	0.11 (–0.76 to 0.97)	0.65	0.00 (–1.02 to 1.01)	0.09	–0.12 (–0.97 to 0.73)	0.11	–0.07 (–0.83 to 0.68)
93.2 – 838.6	0.66	0.26 (–0.62 to 1.13)	1.67	1.02 (0.00 to 2.04)	–0.12	–0.37 (–1.23 to 0.49)	0.07	–0.23 (–1.00 to 0.53)

^a Sample size is identical for crude and adjusted models

^b All analyses adjusted for child age at neuropsychological assessment, child sex, test examiner, Home Observation for Measurement of the Environment score, maternal Full Scale IQ; measured childhood analyses additionally adjusted for child BMI at neuropsychological assessment

Crude and Adjusted^b Associations Between Perfluorooctanoate (PFOA) Exposure and Attention among Children 6 to 12 years of Age, C8 Health Project Follow-up Study, Mid-Ohio Valley, 2009 – 2010^a

Table 5

PFOA exposure	Clinical Confidence Index		Omissions T-score		Commissions T-score		Hit Reaction Time T-score	
	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)	Crude β	Adjusted β^b (95% CI)
PFOA measured in utero								
1 LN unit increase Quartiles (ng/mL)	-2.44	-2.37 (-4.24 to -0.50)	-0.14	-0.02 (-1.06 to 1.03)	-0.35	-0.17 (-0.89 to 0.55)	-0.39	-0.37 (-1.22 to 0.49)
4.5 – <11.7	0	0	0	0	0	0	0	0
11.7 – <43.7	2.78	-2.14 (-9.86 to 5.57)	2.12	0.10 (-4.21 to 4.42)	0.99	1.52 (-1.46 to 4.51)	0.58	-1.69 (-5.24 to 1.86)
43.7 – <110.8	-7.26	-7.68 (-15.32 to -0.04)	-0.04	-0.40 (-4.68 to 3.88)	-0.09	0.16 (-2.79 to 3.12)	-1.59	-1.88 (-5.40 to 1.63)
110.8 – 649.2	-7.66	-8.49 (-16.14 to -0.84)	0.09	0.10 (-4.19 to 4.38)	-0.76	0.03 (-2.93 to 2.99)	-0.91	-1.38 (-4.90 to 2.14)
PFOA measured in childhood								
1 LN unit increase Quartiles (ng/mL)	-2.82	-2.15 (-4.19 to -0.10)	-0.69	0.12 (-0.66 to 0.91)	-0.22	0.12 (-0.66 to 0.91)	-0.90	-0.70 (-1.63 to 0.24)
0.7 – <15.3	0	0	0	0	0	0	0	0
15.3 – <35.0	-4.88	-5.62 (-12.52 to 1.27)	-2.32	-2.20 (-5.95 to 1.55)	0.38	0.95 (-1.71 to 3.61)	-1.62	-1.67 (-4.84 to 1.49)
35.0 – <93.2	-4.61	-3.23 (-10.37 to 3.91)	-1.00	0.07 (-3.82 to 3.95)	-1.12	-0.32 (-3.08 to 2.44)	-2.35	-1.76 (-5.04 to 1.52)
93.2 – 838.6	-9.24	-6.90 (-14.04 to 0.25)	-2.36	-0.57 (-4.46 to 3.31)	-0.51	0.60 (-2.16 to 3.36)	-2.53	-1.73 (-5.01 to 1.55)

^a Sample size is identical for crude and adjusted models

^b All analyses adjusted for child age at neuropsychological assessment, child sex, test examiner, Home Observation for Measurement of the Environment score, maternal Full Scale IQ; measured childhood analyses additionally adjusted for child BMI at neuropsychological assessment