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Perfluorooctanoic Acid Exposure and Pregnancy Outcome in a Highly Exposed Community

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Abstract

Background—We assessed the association between perfluorooctanoic acid (PFOA) and pregnancy outcome in an area with elevated exposure to PFOA from drinking water contaminated by chemical plant releases.

Methods—Serum PFOA was measured and reproductive and residential histories were obtained in 2005 – 2006. We estimated serum PFOA levels at the time of pregnancy for 11,737 pregnancies occurring between 1990 and 2006 based on historical information on PFOA releases, environmental distribution, pharmacokinetic modeling, and residential histories. We assessed the association between PFOA and the odds of miscarriage, stillbirth, preeclampsia, preterm birth, term low birthweight, and birth defects controlling for calendar time, age, parity, education, and smoking. PFOA exposure was evaluated as a continuous measure (with and without log-transformation) and in quintiles, combining the lowest two quintiles (<6.8 ng/mL) as the referent.

Results—Measures of association between PFOA and miscarriage, preterm birth, term low birthweight, and birth defects were close to the null. Odds of stillbirth were elevated in the 4th quintile only. For preeclampsia, the odds ratio was 1.13 (95% confidence interval = 1.00 – 1.28) for an interquartile shift in log-transformed PFOA, and the odds ratios were 1.1 – 1.2 across the upper three quintiles of exposure.

Conclusions—In this large, population-based study in a region with markedly elevated PFOA exposure, we found no associations between estimated serum PFOA levels and adverse pregnancy outcomes other than possibly preeclampsia. Conclusions are tempered by inherent limitations in exposure reconstruction and self-reported pregnancy outcome information.

Perfluorooctanoic acid (PFOA) is a chemical intermediate used in the manufacture of fluoropolymers, including nonstick cookware and waterproof fabrics. PFOA is ubiquitous and persistent, with measurable exposure throughout the developed world.[1] Starting around 2007, research on potential adverse reproductive effects of perfluorinated carbon pollutants began to appear, but does not yet allow even tentative conclusions regarding whether there is an association with one or more endpoints.[2,3] The most extensively studied outcome in

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humans is fetal growth, as reflected by birthweight and other indicators (small-for-gestational-age, head circumference), with some studies suggesting a small adverse effect of PFOA,[4,5] but others reporting no association.[6,7] The diversity of fetal-growth indices, low levels of PFOA in most studies, and varying analytic strategies leave the issue unresolved. Selected studies have considered other measures of reproductive health, including fertility,[8] pregnancy loss,[6] pregnancy complications,[6,9] preterm birth,[5–7] and birth defects,[6,9] none of which generated strong evidence within a study or replicated weak support across studies. Nonetheless, toxicological evidence clearly indicates the potential for PFOA and related compounds to exert adverse effects on fetal development.[2,10]

A chemical plant near Parkersburg, West Virginia began manufacturing fluoropolymers in the 1950s. In 2001, residents of the Ohio and West Virginia areas surrounding the plant filed a class action lawsuit upon discovering that drinking water supplies were contaminated with PFOA. One component of the lawsuit settlement called for a survey of the region's residents, conducted in 2005 – 2006 (the "C8 Health Project," with C8 referring to PFOA's 8-carbon chain), that included a detailed health survey and blood collection to assay PFOA.[11] A series of studies of potential health effects in that population is ongoing (www.c8sciencepanel.org). We previously reported on the association between PFOA and reproductive health in this population among pregnancies to a small subset of women who were residentially stable, allowing for extrapolation of the one-time serum measurement to the time period encompassing recent pregnancies.[6]

An extensive effort to reconstruct historical exposure based on documented PFOA releases, environmental fate and transport, and human exposure and excretion[12,13] has generated individual estimates of serum PFOA levels for C8 Health Project participants for each year beginning in 1951. With the completion of exposure reconstruction, we now have the opportunity to use the modeled estimates of PFOA exposure at the time of pregnancy to examine PFOA and pregnancy outcome in a population over six times larger and more broadly representative than our previous analysis.

Methods

The study population is derived from enrollees in the C8 Health Project, consisting of current and former residents of six water-supply districts in Ohio and West Virginia with elevated levels of PFOA in drinking water.[11] Participation rates were not directly ascertained, but are estimated at around 80% of residents of the eligible communities at the time of enrollment.[11] The C8 Health Project included a health survey, a detailed residential history, and a blood draw with assays for PFOA and other polyfluorinated chemicals, as well as a blood chemistry panel.[11] Women reported their reproductive history, noting the date and outcome of each pregnancy.

Local PFOA releases to both air and surface water began in the early 1950s, increased until the late 1990s, and then declined rapidly. Serum PFOA concentrations measured in 2005 – 2006 correlate only to a limited extent with historical PFOA serum concentrations due to changing water concentrations, varying intake over time, residential mobility, and a serum half-life of 2 to 4 years.[14,15] Consequently, historical PFOA exposures for all participants in the C8 Health Project were estimated through environmental, exposure, and pharmacokinetic modeling in conjunction with self-reported residential histories. Information on plant operations and chemical releases was combined with environmental characteristics of the region through a series of linked models to estimate air and water concentrations of PFOA from 1951 to 2008.[12] Using standard assumptions about individual air and water intake rates, and GIS linkage of participant address histories to public water distribution systems, yearly PFOA serum levels were estimated for each participant in the

C8 Health Project. For those who were served by private wells, serum PFOA levels were estimated based on residential geocodes and the environmental modeling. We assumed a half-life of 3.5 years in serum[15]. Details of the modeling approach are provided elsewhere.[12] The correlation between predicted and observed serum PFOA levels measured at the time of the C8 Health Project was 0.67 overall[13]; this correlation was somewhat higher for participants who provided the highest quality information on residence and water use (r = 0.81) and similar among women whose pregnancies were included in the present study (r = 0.64).

The exposure estimates are likely to be most reliable when serum concentrations substantially exceeded background levels. This is because the exposure modeling focused on contamination of air and drinking water rather than background exposure that comes largely from diet through sources such as food packaging, as well as fabric treatments and carpeting.[16] We restricted the epidemiologic analysis to pregnancies from 1990 through study enrollment in 2005 – 2006 to maximize our ability to distinguish among exposure levels dominated by industrial contaminants. Serum PFOA levels were estimated for each woman by calendar year. The calendar year assigned to the pregnancy was identified by going backwards from the end of pregnancy by 2 months for miscarriage and stillbirths, 7 months for preterm births, and 9 months for term live births, as a systematic way to capture the most relevant annual serum PFOA estimate.

The primary analysis uses the model-based estimates without any adjustment for measured serum PFOA concentrations. As alternative analytic approaches, we also considered serum PFOA estimates calibrated to the 2005 – 2006 measured PFOA serum concentrations (e Appendix, http://links.lww.con). Two calibration methods were used in a pharmacokinetic model. One was a Bayesian time-dependent calibration in which the retrospective annual exposure estimates served as the prior mean and the measured 2005 – 2006 serum concentration as the data used for updating. The Bayesian calibration primarily adjusts recent exposure estimates to obtain a match to the measured serum concentration. The second method was a standard calibration that assumes that a higher-than-expected 2005 – 2006 serum concentration reflects an entire lifetime of higher-than-expected exposures.

Because assignment of exposure depended on the self-reported residential history used for mapping a residence to a water district, we used the complete residential history, despite some gaps and inconsistencies that required assumptions in order to estimate exposure. Also, while we were able to assign water source (private or public well) historically, the modeling is thought to be most accurate when we were able to determine with certainty that a residence was served by a public source. The highest quality exposure assignment required either (1) a geocoded residential address that was in a location and time period in which we were able to assign exposure with greatest certainty, as described in detail elsewhere,[13] or (2) a valid zip code outside of the contaminated region. As a sensitivity analysis, we restricted analyses to the pregnancies with the highest quality reported residential history information for the 6 or 16 years preceding the pregnancy. The serum PFOA concentration can be viewed as a weighted sum of annual exposure contributions from previous years.[17,18] Given an estimated half-life of 3.5 years, the preceding 6 years account for approximately 70% of the weight and the preceding 16 years account for approximately 96% of the weight from historical exposures contributing to the serum concentration.

Self-reported information on pregnancy outcomes allowed us to identify miscarriages (<20 weeks' gestation) and stillbirths (≥20 weeks' gestation), with risk of miscarriage calculated with all pregnancies in the denominator, and risk of stillbirth calculated using pregnancies known to have survived to at least 20 weeks' gestation in the denominator. Analyses of other outcomes were restricted to singleton pregnancies resulting in live births. We

considered a series of (non-mutually exclusive) health endpoints of preeclampsia, preterm birth, low birth weight among term births (an indicator of fetal growth restriction), and birth defects. Assignment of preterm birth and low birth weight were based on the following questions: “Did the birth occur three or more weeks before the due date?” and “Did the child weigh more or less than 5.5 pounds when born?” Preeclampsia and birth defects were also identified by response to questions asking specifically about these conditions. The complete questionnaire is available at http://www.hsc.wvu.edu/som/cmed/c8/healthProject/pdfs/C8%20Health%20Project%20Questionnaire%20v7.29.05.pdf.

Estimated PFOA levels were examined both as continuous and categorical measures. We examined log-transformed measures, given the highly skewed distribution of predicted serum PFOA levels, as well as untransformed values. Results when considering natural log-transformed PFOA levels are presented as the estimated odds ratio for an interquartile shift (i.e., a change in exposure from the 25^{th} percentile to the 75^{th} percentile) in estimated PFOA serum levels. PFOA without log-transformation was presented as the odds ratio per 100 ng/mL increase in exposure. We also examined PFOA categorically, first dividing into quintiles of the distribution for analyses of each of the outcomes, then grouping the lowest two quintiles as the referent to ensure that the cutpoint for comparison was above typical US population levels. We compared the 3^{rd}, 4^{th}, and 5^{th} quintiles to the aggregated 1^{st} and 2^{nd} quintiles to generate odds ratios.

To address potential confounding, we used information on maternal age and parity at the time of pregnancy, and education and maternal smoking status at the time of enrollment in the C8 Health Project in 2005 – 2006 (i.e., not specific to the time of pregnancy). Analyses included adjustment for exposure year (natural cubic spline with 4 degrees of freedom), maternal age at the time of pregnancy (natural cubic spline with 3 degrees of freedom), parity (0, 1, ≥2), education (<12, 12, 13 – 15, ≥16 years), and smoking status at the time of the interview (current smoker, former smoker, never smoker).

Starting with 12,391 pregnancies that occurred between 1990 and 2006, we excluded pregnancies with multiple gestations (n=150), maternal age <14 or >45 years (n=22), chemical plant employees because the exposure model does not account for occupational exposure (n=462), and mothers with incomplete covariate information (n=20), leaving 11,737 pregnancies for analysis. To evaluate the association between PFOA and pregnancy outcome, we used generalized estimating equations (GEE) regression models with a logit link function and an exchangeable correlation structure to account for the correlation among multiple pregnancies to the same woman.[19] Crude and adjusted odds ratios relating continuous and categorical measures of PFOA were estimated, with adjustment for the covariates noted above. All analyses were performed using SAS 9.2 (Cary, NC) and R 2.12.1 (Vienna, Austria).

Results

The pregnancies included in the analysis were evenly distributed across the exposure time period (Table 1). Pregnancies were predominantly to mothers under age 30 who had completed high school or some college; approximately half were current or former smokers at the time of enrollment. Predicted serum concentrations of PFOA suggest that this was a highly exposed population during the study period, with medians 1.5 to 3 times the average background concentration of 4 ng/mL.[20] The distribution was highly skewed, with markedly larger means compared with medians (data not shown). Univariate analysis indicates that, on average, exposures rose during the period of interest, increased with advancing maternal age and education, and were higher among never smokers.

Frequency of self-reported adverse pregnancy outcomes was as expected for miscarriage, stillbirth, term low birthweight, and congenital defects, and above typical levels for preeclampsia and preterm birth (Table 2).[21] Covariates showed the expected patterns of association with birth outcomes (eTable1, http;//links.lww.com).

Miscarriage showed no evidence of an association with PFOA based on continuous or categorical measures of PFOA exposure, with or without adjustment (Table 3 and eTable 2, http://links.lww.com). Overall, stillbirth showed no consistent evidence of an association, with an elevated odds ratio limited to the highest category of exposure (Table 3); this elevation was not apparent in other categories or for continuous exposure measures. Restriction to pregnancies preceded by 6 or 16 years of the highest-quality exposure data (eTable 3, http://links.lww.com) had little impact on the results for these outcomes.

Preeclampsia was weakly associated with PFOA exposure based on both continuous exposure indices and the analysis by quintiles (Table 4). These modest associations were strengthened somewhat with Bayesian calibration of the exposure estimates (eTable 2, http://links.lww.com) and when analyses were restricted to those women with the highest quality residential history (e Table 3, http://links.lww.com). In the uppermost quintile, the adjusted odds ratios were 1.4 with Bayesian calibration and in the restricted subset. We also stratified results by calendar year because reported frequency of preeclampsia was higher in the most recent period; we found modestly stronger associations for the 1995–1999 and 2000 – 2005 periods (eTable 4, http://links.lww.com).

Neither preterm birth nor term low birth weight (Table 4) was associated with estimated serum PFOA levels based on continuous or categorical exposure measures, before or after adjustment. Birth defects in the aggregate were likewise unrelated to PFOA (Table 4). Neither calibration of serum exposure estimates nor restriction based on residential history quality affected these patterns (eTables 2 and 3, http://links.lww.com). Congenital heart defects were weakly associated with PFOA (adjusted odds ratio for quintiles 3–5 combined versus quintiles 1–2 = 1.5 [95% CI = 0.9–2.4]), with little indication of association for any of the other subsets of birth defects, subject to imprecision resulting from limited numbers of cases (eTable 5, http://links.lww.com).

Because pregnancy [5] and breastfeeding [22] are thought to affect serum PFOA levels, we also conducted a sensitivity analysis restricting participants to nulliparous women (eTables 6 and 7, http://links.lww.com). The association of estimated serum PFOA and preeclampsia was modestly enhanced and the other essentially null findings were unchanged.

Discussion

The limited prior literature on PFOA and pregnancy outcomes included sporadic indications of subtle effects on fetal growth with very little information on other pregnancy outcomes.[3] While a number of these studies included exact measures of infant weight, head circumference, and anthropometry, which were not available in the present study, previous studies were based largely on exposure variation within the typical range of around 4 ng/mL; therefore they had the potential for spurious correlations due to subtle physiologic differences that may affect both metabolism of PFOA and fetal growth.[23] Our results build on previous findings from this cohort[6] restricted to the subset of births for which the measured serum PFOA values could approximate the values at the time of pregnancy. (Only 9% of the pregnancies included in the present analysis were included in the initial report on PFOA and pregnancy outcome.) The current analysis incorporates the important refinement of using modeled serum PFOA estimates based on documented chemical releases, environmental distribution, residential history, and human exposure and metabolism, with

the consequent ability to study a much larger population. For pregnancy loss, preeclampsia, and birth defects, our earlier analyses constitute the only pertinent evidence. The present findings tend to corroborate those preliminary results -- namely no association between PFOA and pregnancy loss (miscarriage or stillbirth), a possible weak association between PFOA and preeclampsia, and no association between PFOA and preterm birth or term low birth weight.

The notable strength of the present study is also an area of concern: the quality of exposure assessment. By focusing on a community with a well-defined, predominant source of exposure (namely, emissions from a nearby chemical plant), we could obtain detailed information on releases and environmental characteristics and link these data to individual residential histories -- thus enabling us to estimate historical PFOA serum concentration for each woman at the time of her pregnancy. However, these historical serum estimates are derived from complex prediction models with a large number of unverifiable assumptions (e.g., stable PFOA particle-size distributions, stable water-consumption rates, no contribution from local crops). Moreover, local drinking water was seldom tested for PFOA prior to 2000. Restriction of the analysis to pregnancies in the 1990 – 2006 time period, when the factory releases were the predominant source of exposure and overwhelmed background sources from diet and other sources,[16] is expected to improve the accuracy of exposure estimates. We also explored whether using serum PFOA estimates calibrated to the levels measured in 2005 – 2006 affected results, although it is not clear what type of calibration, if any, is best. The type of calibration method did not substantially change the results of the epidemiologic analyses for pregnancy outcomes.

As documented elsewhere,[24] residential water district and year were the primary determinants of measured serum PFOA levels, thus facilitating the use of an exposure reconstruction model. Because exposure was estimated independently of pregnancy occurrence or outcome, exposure misclassification would most likely be nondifferential, making it a potential basis for spurious null results. Pregnancy itself appears to alter the serum levels of PFOA,[5] but there is insufficient information about this physiologic change to include in the pharmacokinetic models. The estimated serum PFOA levels should be interpreted as applicable at the onset of pregnancy, but not necessarily during the pregnancy; this has the advantage of avoiding the potential for reverse causality (pregnancy affecting serum PFOA levels), which is possible in the calibrated exposure models.

While we were not able to directly assess the magnitude of exposure misclassification, we could examine the ability to predict serum measurements in 2005 – 2006. The exposure model reliably, albeit imperfectly, predicted the measured serum levels, with an overall correlation of 0.67.[13] This correlation is similar to the levels for women in these analyses (r = 0.64) and those who had a pregnancy in the 5 years preceding the assays of serum PFOA (r = 61). Relative to studies that measured PFOA during pregnancy,[4,5] our estimates undoubtedly introduced some misclassification; however, given the extraordinarily high levels and wide range of exposure in this population driven by water source and calendar time, we are likely to have more, not less ability to detect effects of PFOA on pregnancy outcome than even the most precisely assessed populations with much lower levels of exposure.

The second major concern that bears on the validity of our findings is the quality of self-reported pregnancy outcome information. For several of the outcomes (notably miscarriage, preeclampsia, and birth defects), there is no opportunity to validate self-report with medical records or other higher quality data. For gestational age and birth weight, we will be considering a subset of these births that could be linked to birth certificate data in a subsequent examination. Indications of reporting quality are indirect, with some reassuring

and some worrisome results. The absolute frequency of miscarriage (12%), stillbirth (0.9%), term low birth weight (1.6%), and birth defects (4.4%) were in the range that might be expected from the literature.[21] However, the frequency of reported preeclampsia (7%) and preterm birth (18%) are somewhat high, perhaps suggesting for preeclampsia some misreporting based on any type of pregnancy-induced hypertension, not just the subset that was accompanied by proteinuria as is required for diagnosis of preeclampsia.[25] These prevalences are elevated but not to the point of being implausible. More reassuring is the pattern of association between known risk factors and these outcomes. As expected, maternal age was strongly associated with miscarriage; smoking was strongly associated with term low birth weight, weakly with miscarriage and preterm birth, and inversely with preeclampsia; and first births had markedly higher odds of preeclampsia (e Table 1, http://links.lww.com). Birth defects are highly susceptible to reporting errors given the complexity of diagnosis and classification, and so results for this outcome should be interpreted with particular caution. While it is not possible to quantify the error from inaccurate self-report (both over- and under-reporting), interpretation of results must be tempered due to this inherent limitation.

Given the origins of the exposure, confounding would arise only if residential location and time period -- the primary determinants of exposure -- were related to risk factors for these pregnancy outcomes (such as social or behavioral factors). Levels of PFOA were not known until rather recently and were unlikely to have negatively affected property values or be related to indicators of socioeconomic status. In fact, there is a gradient of increasing median income with increasing levels of PFOA. For example, the two highest-exposure water districts in the region (Little Hocking and Lubeck) had median incomes of $42,204 and $44,162, respectively, in 2000, whereas the two lowest-exposure water districts (Mason County and Pomeroy) in 2000 had median incomes of $27,991 and $23,537, respectively. For outcomes with increased risk with lower socioeconomic status (in these data, primarily stillbirth and term low birth weight), residual confounding would likely be toward the null. However, use of bottled water may well be related to socioeconomic status, introducing differential error into the exposure estimates (which did not account for bottled water rather than tap water consumption), making the consequences difficult to predict. Also, we did not have pregnancy-specific smoking information, which is particularly a concern for term low birth weight.

Several other concerns bear on the validity of our findings. The reported frequency of preeclampsia was greater in the more recent period, possibly because of better recall in the more recent period. To the extent that the exposure modeling uses calendar time for prediction and there is the potential for confounding by calendar time (despite the careful attempts at adjustment), the reported association for PFOA and preeclampsia may be a product of residual confounding. We also recognize that other perfluorinated compounds are present in the environment and correlate to some extent with serum PFOA in this population, particularly perfluorooctane sulfonate (PFOS).[24] In the previous analysis of recent pregnancies in this population,[6] PFOS showed somewhat stronger evidence of association with adverse pregnancy outcome, particularly low birth weight, than did PFOA - despite PFOS being at typical US levels. Historical values should be less highly correlated than serum measured at a point in time, given that only PFOA was released from the nearby chemical plant and a contaminant in the local water supplies.

On the other hand, our study has several strengths in comparison with prior studies, including markedly elevated PFOA exposures, the ability to discriminate across a wide range of exposure levels, high community participation rates, and a large number of events. Stillbirth and term low birth weight were the most susceptible to imprecision, whereas

miscarriage, preterm birth, and birth defects in the aggregate were sufficiently common to generate statistically precise results.

In conclusion, combined with the previous studies of PFOA and pregnancy outcome, the current evidence does not support an association with most of the clinically important events examined, although our study cannot address the subtle shifts in infant size examined by others. The possibility of an association between PFOA and preeclampsia warrants consideration, with possible parallels to the concerns with an effect of PFOA on immunologic changes or cardiovascular risk factors.[26] Evaluation of these hypotheses in populations with more accurate outcome assessment would be warranted, although given the nature of the metabolic alterations associated with preeclampsia, the susceptibility to distortion of PFOA biomarkers as a consequence rather than cause of the disease would have to be carefully addressed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Predictors of Estimated Maternal PFOA Serum Concentration among Singleton Pregnancies, Mid-Ohio Valley, 1990–2006

Maternal Characteristic	No. (%)	Estimated PFOA (ng/mL) Median (25th, 75th percentiles)
Exposure Year		
1990 – 1994	3899 (33)	6.0 (4.5, 27.6)
1995 – 1999	3802 (32)	10.7 (5.1, 50.4)
2000 – 2005	4036 (34)	15.9 (5.9, 56.2)
Maternal Age (years)		
14 – 20	2045 (17)	7.3 (4.8, 28.7)
20 – 24	3895 (33)	9.2 (4.9, 36.7)
25 – 29	3262 (28)	13.0 (5.2, 58.4)
30 – 34	1834 (16)	13.6 (5.2, 59.1)
35 – 45	701 (6)	15.3 (5.2, 59.7)
Parity		
0	5769 (49)	10.0 (5.0, 41.3)
1	3954 (34)	11.2 (5.1, 50.7)
≥ 2	2014 (17)	10.8 (5.0, 43.5)
Education at interview (years)		
<12	995 (9)	8.0 (4.9, 20.3)
12	3885 (33)	8.8 (4.9, 36.7)
13 – 15	5041 (43)	11.7 (5.1, 51.1)
≥16	1816 (16)	14.1 (5.2, 66.2)
Smoking status at interview		
Current	3920 (33)	8.4 (4.9, 31.4)
Former	2365 (20)	11.0 (5.1, 44.3)
Never	5452 (47)	12.1 (5.1, 55.9)

Table 2

Singleton Pregnancy Outcomes, Mid-Ohio Valley, 1990–2006

Pregnancy Outcome	No.	(%)
All Pregnancies		
Miscarriage	1,443	(12.3)
Stillbirth	105	(0.9)
Live birth	10,189	(86.8)
Live Births		
Preeclampsia		
Yes	730	(7.2)
No	9456	(92.8)
Preterm birth		
Yes	1843	(18.3)
No	8237	(81.7)
Term low birth weight		
Yes	133	(1.6)
No	8093	(98.4)
Birth defect (any)		
Yes	449	(4.4)
No	9740	(95.6)
Specific birth defects		
Congenital heart defect	79	(0.8)
Club or other foot defect	17	(0.2)
Oral clefts	16	(0.2)
Genital or urinary defect	31	(0.3)
Eye defect	31	(0.3)

Table 3

Crude and Adjusted[a] Association of Estimated Maternal PFOA Serum Concentration with Pregnancy Loss among Singleton Pregnancies, Mid-Ohio Valley, 1990–2006

	Miscarriage			Stillbirth		
Estimated PFOA	**No.**	**Crude OR**	**Adjusted[a] OR (95% CI)**	**No.**	**Crude OR**	**Adjusted[a] OR (95% CI)**
IQR(lnPFOA)[b] increase	1443	0.95	0.92 (0.84 – 1.02)	105	1.02	1.06 (0.81–1.39)
100 ng/mL increase	1443	0.98	0.98 (0.93 – 1.03)	105	0.89	0.91 (0.76–1.10)
Percentiles						
<40th (3.9 – <6.8 g/mL)[c]	596	1.0	1.0	36	1.0	1.0
40 – <60th (6.8 – <16.6 ng/mL)	286	0.9	0.8 (0.7 – 1.0)	22	1.2	1.2 (0.7–2.0)
60 – <80th (16.6 – <63.1 ng/mL)	282	0.9	0.8 (0.7 – 0.9)	30	1.7	1.7 (1.0–2.8)
≥80th (63.1 – 934.3 ng/mL)	279	0.9	0.9 (0.7 – 1.0)	17	0.9	1.0 (0.5–1.8)

[a] Adjusted for exposure year, maternal age, parity, education level at interview, smoking status at interview

[b] Effect estimates represent the change in outcome for a shift from the 25th percentile to the 75th percentile in estimated PFOA serum levels (IQR (lnPFOA) = 2.19)

[c] Reference category

Table 4

Crude and Adjusted[a] Association of Estimated Maternal PFOA Serum Concentration with Preeclampsia and Birth Outcomes among Singleton Live Births, Mid-Ohio Valley, 1990–2006

	Preeclampsia			Preterm Birth			Term Low Birthweight			Birth Defect		
Estimated PFOA	**No.**	**Crude OR**	**Adjusted[a] OR (95% CI)**	**No.**	**Crude OR**	**Adjusted[a] OR (95% CI)**	**No.**	**Crude OR**	**Adjusted[a] OR (95% CI)**	**No.**	**Crude OR**	**Adjusted[1] OR (95% CI)**
IQR(lnPFOA)[b] increase	730	1.18	1.13 (1.00–1.28)	1843	1.02	0.96 (0.89–1.05)	133	0.78	0.89 (0.66–1.20)	449	0.96	1.00 (0.86–1.16)
100 ng/mL increase	730	1.07	1.08 (1.01–1.15)	1843	0.98	0.97 (0.93–1.02)	133	0.90	0.96 (0.79–1.16)	449	0.96	0.97 (0.90–1.06)
Percentiles												
<40th (3.9 – <6.8 ng/mL)[c]	237	1.0	1.0	691	1.0	1.0	54	1.0	1.0	178	1.0	1.0
40 – <60th (6.8 – <16.6 ng/mL)	172	1.4	1.2 (1.0–1.5)	404	1.2	1.0 (0.9–1.2)	31	1.2	1.2 (0.8–1.9)	89	1.0	1.0 (0.7–1.3)
60 – <80th (16.6 – <63.1 ng/mL)	154	1.3	1.1 (0.9–1.4)	384	1.1	1.0 (0.8–1.1)	29	1.1	1.2 (0.7–1.9)	95	1.0	1.1 (0.8–1.4)
≥80th (63.1 – 934.3 ng/mL)	167	1.4	1.2 (1.0–1.6)	364	1.1	1.0 (0.8–1.1)	19	0.6	0.8 (0.4–1.4)	87	1.0	1.0 (0.8–1.3)

[a] Adjusted for exposure year, maternal age, parity, education level at interview, smoking status at interview

[b] Effect estimates represent the change in outcome for a shift from the 25th percentile to the 75th percentile in estimated PFOA serum levels (IQR (lnPFOA) = 2.19)

[c] Reference copy