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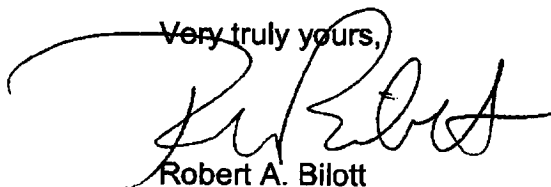
Re: Submission to IRIS and AR-226 Database For PFOA/PFOS: EPA-HQ-ORD-2003-0016

To IRIS Database for PFOA/PFOS:

In response to the Notice issued by USEPA on February 23, 2006, regarding USEPA's efforts to consider perfluorooctanoic acid ("PFOA") and perfluorooctane sulfonate ("PFOS") within the Integrated Risk Information System ("IRIS"), 71 Fed. Reg. 9333-9336 (Feb. 23, 2006), we are submitting the following additional information to USEPA for inclusion in that review, and for inclusion in the AR-226 database:

1. Stein, C.R., Savitz, D.A., and Dougan, M., "Serum Levels of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and Pregnancy Outcome," Am. J. Epidemiol. (online version) (doi: 10.1093/aje/kwp212 (August 19, 2009).

Very truly yours,



Robert A. Bilott

RAB:mdm
Enclosure

cc: Gloria Post (NJDEP)(w/ encl.) (via U.S. Mail)
Helen Goeden (MDH)(w/ encl.) (via U.S. Mail)
Lora Werner (ATSDR)(w/ encl.) (via U.S. Mail)



Original Contribution

Serum Levels of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and Pregnancy Outcome

Cheryl R. Stein, David A. Savitz, and Marcelle Dougan

Initially submitted March 27, 2009; accepted for publication June 19, 2009.

The authors examined the association of serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with self-reported pregnancy outcome in Mid-Ohio Valley residents (2000–2006) highly exposed to PFOA. Data on 1,845 pregnancies within the 5 years preceding exposure measurement were analyzed for PFOA, and data on 5,262 pregnancies were analyzed for PFOS. Generalized estimating equations were used to calculate adjusted odds ratios and 95% confidence intervals. Neither PFOA nor PFOS showed any association with miscarriage or preterm birth. Preeclampsia was weakly associated with PFOA (adjusted odds ratio = 1.3, 95% confidence interval: 0.9, 1.9) and PFOS (adjusted odds ratio = 1.3, 95% confidence interval: 1.1, 1.7) exposures above the median. PFOA was not associated with an increase in low birth weight, but PFOS showed an increased risk above the median (adjusted odds ratio = 1.5, 95% confidence interval: 1.1, 1.9) and a dose-response gradient. Birth defects were weakly associated with PFOA exposures above the 90th percentile (adjusted odds ratio = 1.7, 95% confidence interval: 0.8, 3.6). This study identified modest associations of PFOA with preeclampsia and birth defects and of PFOS with preeclampsia and low birth weight, but associations were small, limited in precision, and based solely on self-reported health outcomes.

congenital abnormalities; fluorocarbons; infant, low birth weight; pre-eclampsia; pregnancy; pregnancy outcome; premature birth

Abbreviations: CI, confidence interval; OR, odds ratio; PFC, perfluorinated compound; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

Perfluorooctanoic acid (PFOA) is a synthetic chemical that has been used in the manufacture of fluoropolymers since the 1950s (1) and may also result from the breakdown of a related group of chemicals called fluorinated telomers (2). Fluoropolymers are used in nonstick cookware and clothing made from waterproof, breathable fabric (2).

PFOA and another perfluorinated compound (PFC) with comparable industrial uses—perfluorooctane sulfonate (PFOS)—are persistent environmental pollutants that have been detected worldwide in both wildlife and humans, with higher exposure closer to urbanized and industrialized regions (3). In the general US population, PFOA and PFOS were detected in all serum samples from the 1999–2000 National Health and Nutrition Examination Survey (4) and in 99.7% and 99.9%, respectively, of serum samples from

the 2003–2004 National Health and Nutrition Examination Survey (5). In the 1999–2000 survey, geometric mean values were measured at 5.2 ng/mL for PFOA and 30.4 ng/mL for PFOS (4). These values dropped to 3.9 ng/mL and 20.7 ng/mL, respectively, in the 2003–2004 survey (5). PFOA and PFOS have been detected in maternal and umbilical cord blood (6–8) and breast milk (9–13). The serum elimination half-life is approximately 4 years for PFOA and 5 years for PFOS (14).

Toxicology studies highlight the potential for these PFCs to affect fetal growth and development. A series of studies suggest that in utero exposure to PFCs is associated with a range of nonspecific adverse infant outcomes in mouse, rat, and rabbit models (15), including reduced fetal weight and increased neonatal mortality. Several epidemiologic

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studies have evaluated the association between PFCs and reproductive health in the general population (16–19). These recently reviewed studies (20) suggest small, inconsistent decrements in birth weight and other infant anthropometric measures in relation to maternal PFOA and PFOS exposure. Two studies examining highly exposed populations found no association between PFC exposure and birth outcome (21, 22).

A chemical plant in the Mid-Ohio Valley near Parkersburg, West Virginia, has used PFOA in the manufacture of fluoropolymers since 1951. In 2001, a group of residents from the West Virginia and Ohio communities surrounding the plant filed a class action lawsuit alleging health damage from drinking water supplies drawing on PFOA-contaminated groundwater (23). Groundwater contamination from the Ohio River and air deposition is believed to be the primary exposure route for this population (24). The settlement of the class action lawsuit included a baseline survey, the C8 Health Project, conducted in 2005–2006 that gathered data from more than 69,000 people from 6 contaminated water districts surrounding the plant (23). (C8 is another name for PFOA, denoting its chain of 8 carbons.) The C8 Health Project included demographic and health questionnaires and measurement of 10 PFCs in serum. The current study used these data to examine the association between serum PFOA and PFOS measurements at C8 Health Project enrollment and pregnancy outcomes in the 5 years prior to enrollment.

MATERIALS AND METHODS

C8 Health Project population

The C8 Health Project enrolled subjects between August 2005 and July 2006. The Project's purpose was to collect health data from members of the class action lawsuit through written questionnaires and blood tests, including measurement of PFCs. This community was highly exposed to PFOA, but PFOS exposure reflects background levels. Individuals were eligible to participate in the C8 Health Project if they could provide documentation such as utility bills, property deeds, employment pay stubs, or school records proving they had consumed water for at least 1 year between 1950 and December 3, 2004, while living, working, or attending school in a water district supplied by Little Hocking Water Association of Ohio; City of Belpre, Ohio; Tupper Plains–Chester District of Ohio; Village of Pomeroy, Ohio; Lubeck Public Service District of West Virginia; Mason County Public Service District of West Virginia; or private water sources within areas of documented PFOA contamination. Participants were compensated \$400 for completing the questionnaire and providing blood.

The C8 Health Project collected data on 69,030 people. The total number of people eligible to join the class action lawsuit is unknown. Participation rates based on US Census counts of current residents of the eligible water districts are estimated at approximately 80% and, in some ZIP codes within eligible water districts, appear to be close to 100% (23). The overall participation rate is likely lower than 80% because former residents were also eligible to participate. In

this population, the strongest predictor of PFOA serum level was current residence in a contaminated water district, with distance to the plant directly affecting PFOA levels (25). PFOS exposure is not determined by residence in a PFOA-contaminated water district.

Study population

This analysis of serum PFOA and PFOS levels and recent pregnancy outcomes was restricted to pregnancies among female C8 Health Project participants with serum PFC measurements. For the PFOA analyses, we included singleton miscarriages, stillbirths, or livebirths in the 5 years prior to C8 Health Project enrollment to women who lived in the same contaminated water district from the approximate start of the pregnancy through the time of enrollment. The 5-year time frame and residency restrictions were used to ensure that the PFOA level measured at C8 Health Project enrollment would reflect the level at the time of pregnancy. For miscarriages, women must have lived in the same water district from 90 days before the pregnancy ended through enrollment. For stillbirths and livebirths, women must have lived in the same water district for 283 days before the pregnancy ended through enrollment. Each pregnancy was evaluated separately for eligibility. For the PFOS analyses, we included all singleton miscarriages, stillbirths, or livebirths in the 5 years prior to C8 Health Project enrollment. There was no need to restrict pregnancies to women living in the same water district from pregnancy through enrollment because PFOS exposure was not specific to the water district.

Measures

For laboratory analysis of PFCs, automated solid-phase extraction combined with reverse-phase high-performance liquid chromatography was used (12). Samples below the limit of detection (0.5 ng/mL) were assigned a value of 0.25 ng/mL. We examined PFCs as natural log-transformed continuous variables, and here we present the odds ratios reflecting a shift from the 25th to the 75th percentile, which corresponds to an increase from 10.3 ng/mL to 49.8 ng/mL for PFOA and from 9.0 ng/mL to 17.7 ng/mL for PFOS. We also categorized PFCs to enable identification of a high-exposure effect: <50th percentile (the referent), 50th–<75th percentile, 75th–90th percentile, and >90th percentile. The cutpoints for the interquartile shift in PFOA do not match the cutpoints for the categorical measure; the categorical cutpoints were based on all eligible pregnancies, and the interquartile shift reflects the pregnancies included in the analysis.

We examined the relation between PFC level and self-reported pregnancy outcomes from the C8 Health Project questionnaire. Examined pregnancy outcomes included miscarriage (pregnancy loss from 6 weeks' to <20 weeks' gestation), preterm birth (livebirth at <37 weeks' gestation), and low birth weight (livebirth <5.5 pounds, approximately equivalent to 2,500 g). The number of reported stillbirths (fetal death from 20 weeks' to 42 weeks' gestation) was too small to analyze separately, but stillbirths were included in

the denominator in our analysis of miscarriages. We also evaluated preeclampsia and reported birth defects.

Because of the cross-sectional nature of the C8 Health Project, some of the covariates in the questionnaire were not specific to the time of pregnancy. Covariates defined explicitly for a given pregnancy were maternal age (15–19, 20–34, 35–55 years) and parity (0, ≥ 1 previous livebirths). Maternal education (<12 , 12, >12 years) and smoking status (never, current, former smoker) were defined at the time of enrollment. Additionally, we restricted the analysis to white women (97.3% of the population) with nonmissing covariate data and no prepregnancy diabetes, although missing outcome information was permitted because each outcome was analyzed separately. Institutional review board approval was granted from the Mount Sinai Program for the Protection of Human Subjects.

Statistical analysis

Analysis was performed by using SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina). Covariates associated with both outcome and exposure—age, parity, educational level at interview, smoking status at interview—were included in all adjusted models together with either PFOS or PFOA. We ran logistic regression models using generalized estimating equations and an exchangeable correlation structure to obtain crude and adjusted odds ratios and 95% confidence intervals accounting for the lack of independence across multiple pregnancies to the same woman.

RESULTS

Women in the C8 Health Project reported 5,663 singleton pregnancies ending in a miscarriage, stillbirth, or livebirth during the 5 years prior to enrollment. Of these pregnancies, 5,624 were to women with PFC measurements and 5,262 (93.6% of pregnancies with PFC measurements) were to white women with complete covariate data and no prepregnancy diabetes, and they were included in the analyses of PFOS (Table 1). Exclusion of pregnancies to women not living in the same water district from the approximate start of pregnancy through enrollment left 1,972 pregnancies. Much of this attrition occurred because we were unable to determine water district for at least part of the time from pregnancy through enrollment because of extensive missing information on self-reported water district. Restriction to pregnancies to white women with complete covariate data and no prepregnancy diabetes yielded 1,845 pregnancies (93.5% of those otherwise eligible) (Table 1) for the analyses of PFOA. The pregnancies excluded for lack of residential stability in a contaminated water district (i.e., pregnancies in the analysis of PFOS but not PFOA) were to younger (mean age, 26.5 years vs. 27.3 years), more nulliparous (48.3% vs. 45.4%) women, more of whom had fewer than 12 years of education (10.8% vs. 8.3%) and were current or former smokers (56.2% vs. 50.4%). The descriptive statistics presented in the text are for the smaller population relevant to PFOA; Table 1 provides descriptive statistics for both populations.

Mean serum PFOA was 48.8 ng/mL (standard deviation, 77.8), and the median value was 21.2 ng/mL (interquartile

range, 10.3–49.8) (Table 1). Mean and median serum PFOS concentrations were 15.0 (standard deviation, 8.2) and 13.6 ng/mL (interquartile range, 9.4–18.7), respectively. The correlation between PFOA and PFOS concentration was minimal (Spearman $\rho = 0.2$, $P < 0.001$). Most women were pregnant between ages 20 and 34 years (82.2%) and had at least 12 years of education (91.7%). Smoking was relatively common, with 30.8% smoking at enrollment in the C8 Health Project and 19.6% self-identifying as former smokers. Of all pregnancies, 249 (13.5%) were reported to have ended in miscarriage. Of livebirths, 329 (20.9%) were reported as preterm, 80 (5.0%) as low birth weight, and 156 (9.8%) as preeclampsia, and 74 women (4.7%) noted a birth defect.

Neither PFOA nor PFOS was related to miscarriage (Table 2). Preeclampsia was weakly associated with PFOA (Table 3) (adjusted odds ratio (OR) = 1.3, 95% confidence interval (CI): 0.9, 1.9) and PFOS (adjusted OR = 1.3, 95% CI: 1.1, 1.7) for exposures above the median, but without a dose-response gradient. The adjusted odds ratio for preeclampsia for PFOS exposure above the 90th percentile (adjusted OR = 1.6, 95% CI: 1.2, 2.3) was elevated. Preterm birth (Table 4) was unrelated to PFOA. The only suggested association between PFOS and preterm birth was for exposures above the 90th percentile (adjusted OR = 1.4, 95% CI: 1.1, 1.7).

Low birth weight followed no discernable pattern in relation to PFOA (Table 5), with some tendency for risk to decrease as exposure increased, but was compatible with no effect in the analysis of a continuous measure of PFOA. When the categorical exposure measure was used, women in the 75th to 90th percentile of exposure were markedly less likely to deliver a low birth weight baby (adjusted OR = 0.3, 95% CI: 0.1, 0.9) compared with women below the 50th percentile of PFOA exposure, but no dose-response gradient was found. PFOS showed evidence of a positive association with all 3 exposure metrics. The adjusted odds ratio for exposure above the median was 1.5 (95% CI: 1.1, 1.9). There was also a dose-response gradient when the categorical measure was used, with adjusted odds ratios ranging from 1.3 (95% CI: 0.9, 1.8) for the 50th to 75th percentile of exposure to 1.8 (95% CI: 1.2, 2.8) for exposures above the 90th percentile, compared with exposures below the 50th percentile.

Birth defects (Table 6) were weakly associated with PFOA, but not PFOS. For PFOA, the elevation in risk was found only above the 90th percentile (adjusted OR = 1.7, 95% CI: 0.8, 3.6). This estimate was based on 12 cases in the uppermost exposure category. In the PFOS analysis, the association with birth defects remained imprecise and was weaker than for PFOA (adjusted OR = 1.3, 95% CI: 0.8, 2.1).

Overall, results were similar, but less precise when PFOS was analyzed by using the population restricted to women living in a single contaminated water district from the time of pregnancy through enrollment (data not shown). The primary differences were for low birth weight, with an increased risk above the median but no dose-response gradient, and for birth defects, with the association with PFOS exposure stronger in the smaller population.

We then restricted our analyses to the 1,197 pregnancies within the 3 years prior to measurement, presumably

Table 2. Crude and Adjusted^a Associations Between Serum Perfluorinated Compounds and Singleton Miscarriage^b Within 5 Years of C8 Health Project Enrollment, Mid-Ohio Valley, 2000–2006

Serum PFC	PFOA Exposure (n = 1,845)				PFOS Exposure (n = 5,252)			
	No. of Cases	Crude OR	Adjusted		No. of Cases	Crude OR	Adjusted	
			OR	95% CI			OR	95% CI
Per increase from the 25th to the 75th percentile ^c	249	0.9	0.9	0.7, 1.2	657	1.1	1.0	0.9, 1.1
<50th percentile	122	1.0	1.0		470	1.0	1.0	
≥50th percentile	127	1.0	1.0	0.7, 1.4	187	1.2	1.0	0.9, 1.3
<50th percentile	122	1.0	1.0		295	1.0	1.0	
50th–<75th percentile	74	1.3	1.2	0.8, 1.7	175	1.1	1.1	0.9, 1.3
75th–90th percentile	35	0.8	0.8	0.5, 1.3	114	1.2	1.1	0.8, 1.4
>90th percentile	18	0.7	0.9	0.5, 1.6	73	1.2	0.9	0.7, 1.3

Abbreviations: CI, confidence interval; OR, odds ratio; PFC, perfluorinated compound; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

^a Adjusted for maternal age, parity, educational level at interview, smoking status at interview, and PFOS in the analysis of PFOA and PFOA in the analysis of PFOS.

^b Modeled by using generalized estimating equations with an exchangeable correlation structure to account for multiple pregnancies per woman.

^c Change from the 25th to the 75th percentile corresponds to a shift from 10.3 ng/mL to 49.8 ng/mL for PFOA and from 9.0 ng/mL to 17.7 ng/mL for PFOS.

value, but with imprecise confidence intervals. Nonetheless, these authors found that prenatal PFOA levels were inversely associated with mean adjusted birth weight (−10.6 g, 95% CI: −20.8, −0.5) per ng/mL increase (17). A smaller effect was observed for PFOS.

Two highly exposed populations have been studied to date (21, 22). An occupational cohort from a facility manufacturing PFOS-based chemicals and specialty films included 421 livebirths (21). No association was found between maternal PFOS exposure, as determined by geometric

mean exposure for various job categories, and self-reported birth weight. The second study, in the same geographic area as the present study, used ZIP code–based ecologic measures of PFOA exposure, US Census–derived indicators of socioeconomic status, and gestational age and birth weight data from vital records for 1,555 singleton births (22). Among women in PFOA-exposed ZIP code areas, mean adjusted birth weight was reduced by 8.8 g (95% CI: −86.1, 68.5), while the adjusted odds ratio for birth weight of less than 2,500 g was 0.43 (95% CI: 0.17, 1.12), which

Table 3. Crude and Adjusted^a Associations Between Serum Perfluorinated Compounds and Preeclampsia^b Within 5 Years of C8 Health Project Enrollment, Mid-Ohio Valley, 2000–2006

Serum PFC	PFOA Exposure (n = 1,589)				PFOS Exposure (n = 4,566)			
	No. of Cases	Crude OR	Adjusted		No. of Cases	Crude OR	Adjusted	
			OR	95% CI			OR	95% CI
Per increase from the 25th to the 75th percentile ^c	156	1.2	1.1	0.9, 1.4	407	1.2	1.1	0.9, 1.3
<50th percentile	64	1.0	1.0		280	1.0	1.0	
≥50th percentile	92	1.5	1.3	0.9, 1.9	127	1.5	1.3	1.1, 1.7
<50th percentile	64	1.0	1.0		163	1.0	1.0	
50th–<75th percentile	52	1.8	1.5	1.0, 2.3	117	1.4	1.3	1.0, 1.7
75th–90th percentile	27	1.3	1.2	0.7, 2.1	65	1.3	1.1	0.8, 1.6
>90th percentile	13	0.9	0.9	0.5, 1.8	62	2.0	1.6	1.2, 2.3

Abbreviations: CI, confidence interval; OR, odds ratio; PFC, perfluorinated compound; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

^a Adjusted for maternal age, parity, educational level at interview, smoking status at interview, and PFOS in the analysis of PFOA and PFOA in the analysis of PFOS.

^b Modeled by using generalized estimating equations with an exchangeable correlation structure to account for multiple pregnancies per woman.

^c Change from the 25th to the 75th percentile corresponds to a shift from 10.3 ng/mL to 49.8 ng/mL for PFOA and from 9.0 ng/mL to 17.7 ng/mL for PFOS.

Table 4. Crude and Adjusted^a Associations Between Serum Perfluorinated Compounds and Singleton Birth at Less Than 37 Weeks' Completed Gestation^b Within 5 Years of C8 Health Project Enrollment, Mid-Ohio Valley, 2000–2006

Serum PFC	PFOA Exposure (n = 1,571)				PFOS Exposure (n = 4,512)			
	No. of Cases	Crude OR	Adjusted OR	95% CI	No. of Cases	Crude OR	Adjusted OR	95% CI
Per increase from the 25th to the 75th percentile ^c	329	0.9	0.8	0.8, 1.1	1,015	1.1	1.1	1.0, 1.3
<50th percentile	166	1.0	1.0		745	1.0	1.0	
>50th percentile	163	0.9	1.0	0.7, 1.3	270	1.1	1.1	1.0, 1.3
<50th percentile	166	1.0	1.0		481	1.0	1.0	
50th–<75th percentile	89	1.1	1.1	0.8, 1.5	264	1.1	1.1	0.9, 1.3
75th–90th percentile	42	0.7	0.7	0.5, 1.1	153	1.0	1.1	0.9, 1.3
>90th percentile	32	0.9	0.9	0.6, 1.5	117	1.3	1.4	1.1, 1.7

Abbreviations: CI, confidence interval; OR, odds ratio; PFC, perfluorinated compound; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

^a Adjusted for maternal age, parity, educational level at interview, smoking status at interview, and PFOS in the analysis of PFOA and PFOA in the analysis of PFOS.

^b Modeled by using generalized estimating equations with an exchangeable correlation structure to account for multiple pregnancies per woman.

^c Change from the 25th to the 75th percentile corresponds to a shift from 10.3 ng/mL to 49.8 ng/mL for PFOA and from 9.0 ng/mL to 17.7 ng/mL for PFOS.

conversely suggests a lower risk in the exposed community. Cumulatively, these studies provide little basis for suggesting a positive relation between PFOA and PFOS exposure and low birth weight.

To our knowledge, no associations have been observed between gestational age examined either continuously (16, 22) or dichotomized as birth at less than 37 completed weeks' gestation (17, 22). Studies of other indications of fetal growth, such as head and abdominal circumference, birth length, and

ponderal index, have yielded equivocal results (16, 18, 19) that are not directly comparable to the measures used in the present study. Ours is the first known epidemiologic study to assess the association between PFC exposure and miscarriage, preeclampsia, and birth defects, with no opportunity to compare findings with those of previous studies.

A central concern regarding interpretation of our results is the quality of the information on self-reported pregnancy outcome. Numerous studies show high concordance

Table 5. Crude and Adjusted^a Associations Between Serum Perfluorinated Compounds and Singleton Birth Weight of Less Than 5.5 Pounds^{b,c} Within 5 Years of C8 Health Project Enrollment, Mid-Ohio Valley, 2000–2006

Serum PFC	PFOA Exposure (n = 1,589)				PFOS Exposure (n = 4,561)			
	No. of Cases	Crude OR	Adjusted OR	95% CI	No. of Cases	Crude OR	Adjusted OR	95% CI
Per increase from the 25th to the 75th percentile ^d	80	0.7	0.7	0.5, 1.0	243	1.2	1.3	1.1, 1.6
<50th percentile	47	1.0	1.0		168	1.0	1.0	
≥50th percentile	33	0.7	0.7	0.5, 1.2	75	1.4	1.5	1.1, 1.9
<50th percentile	47	1.0	1.0		102	1.0	1.0	
50th–<75th percentile	21	0.9	1.0	0.6, 1.7	66	1.2	1.3	0.9, 1.8
75th–90th percentile	5	0.3	0.3	0.1, 0.9	43	1.4	1.6	1.1, 2.3
>90th percentile	7	0.7	0.8	0.3, 1.9	32	1.6	1.8	1.2, 2.8

Abbreviations: CI, confidence interval; OR, odds ratio; PFC, perfluorinated compound; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

^a Adjusted for maternal age, parity, educational level at interview, smoking status at interview, and PFOS in the analysis of PFOA and PFOA in the analysis of PFOS.

^b Modeled by using generalized estimating equations with an exchangeable correlation structure to account for multiple pregnancies per woman.

^c One pound = 0.454 kg.

^d Change from the 25th to the 75th percentile corresponds to a shift from 10.3 ng/mL to 49.8 ng/mL for PFOA and from 9.0 ng/mL to 17.7 ng/mL for PFOS.

Table 1. Univariate Characteristics of Singleton Pregnancies Within 5 Years of C8 Health Project Enrollment, Mid-Ohio Valley, 2000–2006

	PFOA Population (<i>n</i> = 1,845)		PFOS Population (<i>n</i> = 5,262)	
	No.	%	No.	%
<i>All pregnancies</i>				
Unique women	1,505		3,996	
Pregnancies per woman				
1	1,215	80.7	2,942	73.6
2	247	16.4	870	21.8
3	38	2.5	159	4.0
4	3	0.2	22	0.5
5	2	0.1	3	0.1
Pregnancy outcome				
Miscarriage	249	13.5	657	12.5
Stillbirth	6	0.3	36	0.7
Livebirth	1,590	86.2	4,569	86.8
Serum PFOA (ng/mL) at interview				
Mean (SD)	48.8 (77.8)		32.1 (59.7)	
Median (IQR)	21.2 (10.3–49.8)		13.6 (7.4–29.2)	
Serum PFOA (ng/mL) at interview				
0.25–<21.3 ng/mL (<50th percentile)	925	50.1	n/a	
21.3–<50.0 ng/mL (50th–<75th percentile)	460	24.9	n/a	
50.0–<120.6 ng/mL (75th–90th percentile)	281	15.2	n/a	
120.6–894.4 ng/mL (>90th percentile)	179	9.7	n/a	
Serum PFOS (ng/mL) at interview				
Mean (SD)	15.0 (8.2)		14.1 (7.7)	
Median (IQR)	13.6 (9.4–18.7)		12.8 (9.0–17.7)	
Serum PFOS (ng/mL) at interview				
0.25–<12.7 ng/mL (<50th percentile)	n/a		2,582	49.1
12.7–<17.7 ng/mL (50th–<75th percentile)	n/a		1,345	25.6
17.7–<23.2 ng/mL (75th–90th percentile)	n/a		802	15.2
23.2–83.4 ng/mL (>90th percentile)	n/a		533	10.1
Water district				
Belpre, Ohio	163	8.8	n/a	
Little Hocking, Ohio	350	19.0	n/a	
Pomeroy, Ohio	73	4.0	n/a	
Tupper Plains–Chester, Ohio	471	25.5	n/a	
Lubeck, West Virginia	301	16.3	n/a	
Mason County, West Virginia	487	26.4	n/a	

Table continues

generating values with more concordance between the measurement and the exposure at the time of the pregnancy. Results for PFOA and PFOS were similar, but less precise (data not shown).

DISCUSSION

We found little or no support for a possible association between PFOA or PFOS exposure and miscarriage or preterm birth, nor between PFOA and low birth weight. Both

PFOA and PFOS were weakly related to preeclampsia and PFOA was weakly associated with birth defects, but without dose-response gradients. The association between PFOS and low birth weight was stronger and indicated increasing risk with increasing exposure, warranting examination in other suitable populations.

The limited reproductive and developmental toxicology literature suggests possible adverse effects of PFOA and PFOS on fetal growth and viability and on postnatal growth (26, 27). The evidence regarding teratogenicity is unclear,

Table 1. Continued

	PFOA Population (n = 1,846)		PFOS Population (n = 5,262)	
	No.	%	No.	%
Age at pregnancy, years				
15-19	123	6.7	426	8.1
20-34	1,517	82.2	4,367	83.0
35-55	205	11.1	469	8.9
Parity				
0 previous livebirths	838	45.4	2,528	48.0
≥ 1 previous livebirths	1,007	54.6	2,734	52.0
Education at interview				
<12 years	154	8.3	493	9.4
12 years	614	33.3	1,706	32.4
>12 years	1,077	58.4	3,063	58.2
Smoking status at interview				
Never	915	49.6	2,415	45.9
Former	362	19.6	1,136	21.6
Current	568	30.8	1,711	32.5
<i>Pregnancies ending in livebirths</i>				
Unique women	1,395		3,748	
Births per woman				
1	1,207	86.5	2,986	79.7
2	181	13.0	706	18.8
3	7	0.5	53	1.4
4	0		3	0.1
Preeclampsia				
Yes	156	9.8	407	8.9
No	1,433	90.2	4,159	91.1
Preterm birth				
Preterm birth <37 weeks	329	20.9	1,015	22.5
Term birth	1,242	79.1	3,497	77.5
Low birth weight				
Birth weight <5.5 pounds ^a	80	5.0	243	5.3
Birth weight >5.5 pounds	1,509	95.0	4,318	94.7
Birth defect				
Yes	74	4.7	188	4.1
No	1,516	95.3	4,381	95.9

Abbreviations: IQR, interquartile range; n/a, not applicable; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; SD, standard deviation.

^a One pound = 0.454 kg.

with adverse effects observed for PFOS possibly attributable to maternal toxicity at higher doses (27).

Few epidemiologic studies have examined the association between PFC exposure and birth outcome in humans. Of these studies, most have looked at a continuous measure of birth weight and found mixed results. In a pregnancy cohort in Japan ($n = 428$), adjusted analyses showed an association between higher PFOS in maternal serum and reduced infant birth weight (19). For each log-10 change in PFOS, infants weighed 148.8 g less (95% CI: -297.0,

-0.5). PFOA had less of an effect on birth weight (-75.1 g, 95% CI: -191.8, 41.6) (19). A reduction in mean adjusted birth weight (-104 g, 95% CI: -213, 5) per log-unit increase in cord serum PFOA was also noted in a hospital-based study ($n = 293$) in Baltimore, Maryland (16). In this study, PFOS, compared with PFOA, had a smaller effect on birth weight (-69 g, 95% CI: -149, 10). A subset of the Danish National Birth Cohort ($n = 1,400$) examined birth weight of less than 2,500 g and reported no association with either PFC (17). The adjusted odds ratios were above the null

Table 6. Crude and Adjusted^a Associations Between Serum Perfluorinated Compounds and Singleton Birth Defects^b Within 5 Years of C8 Health Project Enrollment, Mid-Ohio Valley, 2000–2006

Serum PFC	PFOA Exposure (n = 1,500)				PFOS Exposure (n = 4,589)			
	No. of Cases	Crude OR	Adjusted		No. of Cases	Crude OR	Adjusted	
			OR	95% CI			OR	95% CI
Per increase from the 25th to the 75th percentile ^c	74	1.2	1.1	0.8, 1.6	188	1.0	1.1	0.9, 1.3
<50th percentile	35	1.0	1.0		135	1.0	1.0	
≥50th percentile	39	1.1	1.0	0.6, 1.7	53	1.0	1.0	0.8, 1.4
<50th percentile	35	1.0	1.0		92	1.0	1.0	
50th–<75th percentile	18	1.1	1.0	0.5, 1.8	43	0.9	0.9	0.6, 1.3
75th–90th percentile	9	0.8	0.7	0.3, 1.6	29	1.0	1.1	0.7, 1.6
>90th percentile	12	1.8	1.7	0.8, 3.6	24	1.3	1.3	0.8, 2.1

Abbreviations: CI, confidence interval; OR, odds ratio; PFC, perfluorinated compound; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

^a Adjusted for maternal age, parity, educational level at interview, smoking status at interview, and PFOS in the analysis of PFOA and PFOA in the analysis of PFOS.

^b Modeled by using generalized estimating equations with an exchangeable correlation structure to account for multiple pregnancies per woman.

^c Change from the 25th to the 75th percentile corresponds to a shift from 10.3 ng/mL to 49.8 ng/mL for PFOA and from 9.0 ng/mL to 17.7 ng/mL for PFOS.

between maternal report of birth weight and birth weight recorded in a medical record (28–31). Recall of gestational age is also fairly accurate (29, 32). The validity of self-reported preeclampsia is less clear. Maternal recall of preeclampsia had low to moderate sensitivity and high specificity compared with medical records (33) and a positive predictive value of only 59.2% (34). Whether maternal recall would be comparable in our population, with relatively low educational attainment but recent births, is unknown.

A high proportion of births in this population were reported to have ended in miscarriage (13.5%), with frequencies of 10% more common based on self-report. Of livebirths, 20.9% were reported to be preterm, higher than would be expected in a white population (8%–15%). Preeclampsia was likewise reported more commonly (9.8%) than through medical record review (3%–7%). Reported birth defects in 4.7% of livebirths are near the range of that expected (3%). Given the limited quality of self-reported information on such outcomes, it seems likely that these high frequencies are an artifact of reporting quality rather than a reflection of a high background risk in the study area. Even with the frequency of self-reported pregnancy outcomes qualitatively higher than expected, there was no clear indication that these outcomes were associated with PFC exposure.

Despite the limitations of relying on maternal report to evaluate pregnancy complications and birth outcomes, we noted several associations consistent with expectation. Advanced maternal age was clearly associated with an increased risk of miscarriage. Smokers had a small increase in preterm births and a larger increase in low birth weight. Risk of preeclampsia was reduced for both smokers and parous women, as expected. Our focus on, at most, 5 years between pregnancy and recall should facilitate better recall. The potential for differential recall in relation to exposure

status is unlikely, except insofar as residents of the more highly exposed water districts were aware of their exposure and reported adverse outcomes either more completely or excessively. The generally null results make differential recall unlikely, although nondifferential misclassification could have attenuated our results. Potential bias from non-participation is also a concern; however, none of the known participation biases (smaller proportion of men, elderly, young children, nonlocal residents) would have impacted our study findings for PFOA because these potential participants would not have been eligible for our study. Although residents of more highly exposed areas, or people experiencing more health problems, may be more likely to participate, it is unlikely that there would have been a joint effect of exposure and outcome on participation, as needed to produce biased measures of association (35).

The laboratory-determined exposure measurement does not suffer from the same quality issues as self-reported pregnancy outcomes. Our restriction to pregnancies occurring in the 5 years prior to exposure measurement, and for PFOA residential stability within affected water districts, should ensure that the measured value reflects the level at the time of pregnancy. Maternal serum PFOA and PFOS values appear to drop during pregnancy, but they remain highly correlated (6, 17). To the extent that pregnancy modifies exposure levels, the measurements will be inaccurate. However, the relative ranking of women based on the measurements would still have value.

Although other populations can be studied to corroborate or refute our findings, the large study size and high PFOA exposure call for more complete evaluation of current and past residents of the Mid-Ohio Valley. We are developing exposure reconstruction models that will enable us to include greater numbers of pregnancies to women enrolled in the C8 Health Project, enhance precision, and refine

exposure estimates even for the recent pregnancies included in this paper. We are also planning to link self-reported information on livebirth outcomes to birth records from Ohio and West Virginia, with vital records superior to maternal recall for birth weight and preterm birth. With the link to vital records, we will also gain additional relevant information on preeclampsia and birth defects, despite the known limitations in vital records pertaining to these outcomes (36, 37). The ubiquitous exposure, suggestive evidence from toxicology, and sporadic indications in epidemiologic studies of possible adverse reproductive effects warrant continued and more refined evaluation of the association between PFC exposure and pregnancy outcome.

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