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AR 226-3911

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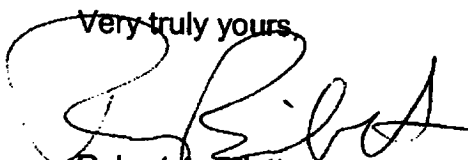
Re: Submission to IRIS and AR-226 Database For PFOA/PFOS: EPA-HQ-ORD-2003-0016

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. Steenland, K., et al., "Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with Uric Acid Among Adults with Elevated Community Exposure to PFOA," *Environ. Health Persp.* (online doi: 10.1289/ehp.0900940 (Oct. 22, 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)
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Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctanesulfonate (PFOS) with Uric Acid Among Adults with Elevated Community Exposure to PFOA

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Association of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA

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Running title: Serum perfluorinated compounds and uric acid

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Disclosures: We have no conflict of interests to disclose.

Key words: PFOA, PFOS, uric acid

This research was funded by the C8 Class Action Settlement Agreement (Circuit Court of Wood County, West Virginia) between DuPont and Plaintiffs, which resulted from releases into drinking water of the chemical perfluoro-octanoic acid (PFOA, or C8). Funds are administered by an agency which reports to the court. Our work and conclusions are independent of either party to the lawsuit.

Abstract

Background: Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) are compounds which do not occur in nature, have been widely used since WWII, and persist indefinitely in most environments. Median serum levels in the US are 4 ng/ml and 21 ng/ml, respectively. PFOA has been associated with elevated uric acid in two studies of workers. Uric acid is a risk factor for hypertension and possibly other cardiovascular outcomes.

Methods: We conducted a cross sectional study of PFOA and PFOS and uric acid among 54,951 adult community residents in Ohio and West Virginia, who lived or worked in six water districts contaminated with PFOA from a chemical plant. Analyses were conducted by linear and logistic regression, adjusted for confounders.

Results: Both PFOA and PFOS were significantly associated with uric acid. An increase of 0.2-0.3 mg/dl uric acid was associated with an increase from the lowest to highest decile of either PFOA or PFOS. Hyperuricemia risk increased modestly with increasing PFOA ; the odds ratios by quintile of PFOA were 1.00, 1.33 (95% CI 1.24-1.43), 1.35 (95% CI 1.26-1.45), 1.47 (95% CI 1.37-1.58), and 1.47 (95% CI 1.37-1.58)(test for trend, $p < 0.0001$). A less steep trend was seen for PFOS. Inclusion of both correlated fluorocarbons in the model indicated PFOA was a more important predictor than PFOS.

Conclusion: Higher serum levels of PFOA were associated with a higher prevalence of hyperuricemia, but the limitations of cross-sectional data and the possibility of non-causal mechanisms prohibit conclusions regarding causality.

Introduction

Both perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) are perfluorinated compounds which have been found in the blood of virtually all Americans tested over the last decade (Calafat et al. 2007). They do not occur naturally but were introduced in the environment after World War II.

PFOA is used as a polymerization aid in the manufacture of several types of fluoropolymers which have been used in a wide variety of industrial and consumer products, such as Teflon and Gore-tex. PFOA does not break down in most environment. The half-life of PFOA in humans is estimated to be 3.8 years (arithmetic mean 95% CI, 3.1-4.4) (Olsen et al. 2007a). The median level in the US population was 4 ng/ml in 2003 (Calafat et al. 2007). The origins of long-chain perfluorocarbon exposures stem from manufacture or use of industrial products, yet the routes of exposure and specific origins are rarely clear. PFOA is also widespread in the serum of inhabitants of many other countries (Lau et al. 2009).

PFOA has been found to be significantly associated with elevated uric acid in two cross-sectional studies of workers (n=160 and n=1024) (Sakr et al. 2007a; Costa et al. 2009). There is also evidence in the literature for an association of PFOA with cholesterol and diabetes in humans. A positive correlation of PFOA with cholesterol was observed in six occupational studies (Sakr et al. 2007a; Costa et al. 2009; Sakr et al. 2007b; Olsen et al. 2000; Olsen and Zobel 2007b; Olsen et al. 2003), and two community studies (Emmett et al. 2006; Steenland et al. 2009), although in one community study and two of occupational ones the relationship was not statistically significant. PFOA exposure was observed to be associated with a two-fold increase in diabetes mortality in one cohort study of highly-exposed workers when the exposed workers were compared to non-exposed workers, although no association was seen in another

cross-sectional study of diabetes prevalence (Leonard et al. 2008; McNeil et al. 2009). In addition, PFOA has been associated with a number of outcomes in animal data, particularly tumors and neo-natal loss (EPA 2005; Lau et al. 2007).

Perfluorooctanesulfonate (PFOS) is another perfluorocarbon which is widespread in the serum of US residents, with a median serum level of 21 ng/ml in 2003 (Calafat et al. 2003). While PFOA is found at much higher levels among our study subjects than the US general population, PFOS levels were similar to US general population levels, suggesting that the nearby industrial facility was not a significant source of PFOS. Until recently PFOS was used in the manufacture of Scotchgard, among other products. Its half-life in people has been estimated at 5.4 years (arithmetic mean, 95% CI 3.9-6.9) (Olsen et al. 2007a). In one cross-sectional study of PFOS and cholesterol, a statistically significant positive association was observed among workers at one plant, but not at a second plant (Olsen et al. 1999). There are no data of which we are aware regarding an association of PFOS and uric acid.

Uric acid is a natural product of purine metabolism and has both oxidant and anti-oxidant properties. There is considerable epidemiologic evidence from longitudinal studies, supported by animal evidence, that elevated uric acid is a risk factor for hypertension (Feig et al. 2006; Sundström et al. 2005; Mellen et al. 2006; Shankar et al. 2006; Symala et al. 2007). A recent randomized trial found that lowering uric acid resulted in lowering blood pressure in adolescents (Feig et al. 2008). On the other hand, there is debate about whether uric acid is a predictor of cardiovascular disease, independent of other known risk factors, and independent of its role as a marker of kidney disease (Shankar et al. 2006; Johnson et al. 2003; Wannamethee 2005; Hakoda et al. 2005; Fang et al. 2000). There is also some evidence that uric acid is an independent risk

factor for stroke, diabetes, and metabolic syndrome (Dimitroula et al. 2008; Hayden et al. 2004), while it protects against Parkinson's disease (Chen et al. 2009).

PFOA has been used in the manufacturing of fluoropolymers at a chemical plant in Washington, West Virginia since 1951. In 2001, a group of residents from the Ohio and West Virginia communities in the vicinity of the Washington Works plant filed a class-action lawsuit against the plant, alleging health damage due to contamination of human drinking water supplies with PFOA. The settlement of this lawsuit led to a baseline survey, called the C8 Health Project. This survey was conducted in 2005-2006 and gathered data from 69,000 current and former residents of Ohio and West Virginia who had lived, worked, or attended school in six contaminated water districts surrounding the chemical plant. The C8 Health Project included blood draws and subsequent measurement of serum PFOA and serum PFOS, as well as clinical chemistries including uric acid.

The current study is an analysis of these data in adults age 20 and older with a goal of determining whether there are associations between PFOA or PFOS and uric acid in this population. The exposure metrics in this study are serum PFOA and PFOS measured in 2005-2006, and the outcome is concurrent uric acid level.

Methods

Study population

Study subjects participated in the C8 Health Project (Steenland et al. 2009; Frisbee et al. 2009). The purpose of the C8 Health Project was to collect health data from residents covered under the legal settlement of a class action lawsuit, including a battery of blood tests and measurement of serum levels of PFOA and PFOS. The C8 Health Project began in August 2005

and completed enrolling subjects in August 2006. Subjects were eligible to participate in the C8 Health Project if they had consumed public drinking water for at least one year before December 3, 2004, supplied by any of six contaminated water districts, or from a small number of private wells known to be contaminated. The six water districts all had documented PFOA contamination of public water (≥ 0.05 ng/ml). Subjects were eligible if they could document that they had either lived, worked or attended school in a contaminated water district for at least one year. Figure 1 shows the approximate boundaries of the six water districts. Subjects filled out an extensive questionnaire and came to local survey stations to donate a blood sample.

The C8 Health Project collected data on 69,030 subjects, of whom 54,591 were 20 years and older and are included in this study. We have estimated the participation rate among current residents in 2005-2006 among adults age 20 and older using census data. Estimates of the population of the six water districts were made based on population estimates for census block groups in 2005. Block groups are smaller than census tracts but larger than census blocks. To find the population of each water district, we determined which block groups were entirely within the water district. We then determined which block groups intersected the boundaries of the water districts. For those which intersected, we then calculated the ratio of water district area to block group area within each block group and multiplied the ratio by the block group population. We then summed the populations for the entire water district and then summed across all six water districts. Finally we determined the numbers of current residents (63% of total participants) in the water districts who participated in the C8 Health Project in 2005-2006, and divided these residents (33,001) by the population (40,721) to find a participation rate of 81% among current residents age 20 and older.

Statistical Analysis

All analyses were done using the SAS statistical package. Analyses were conducted using linear regression with uric acid as the outcome. Residuals were checked for normality. The exposure variables were serum PFOA or PFOS. Most analyses used categorical exposure variables (deciles, lowest decile as reference), to avoid any assumptions about the shape of a parametric model, taking advantage of the large sample size which permitted adequately precise estimates across multiple categories. As a test for linear trend, we used the p-value of the parameters for PFOA or PFOS as continuous variables. We also conducted some analyses using the log transform of the exposure variables (PFOA and PFOS), as the log transform appeared to fit the data well. Covariates in the model were chosen *a priori* because of their established relationship to uric acid, such that they were potentially confounding variables. Covariates included age (18-39, 40-49, 50-59, 60-69, 70-79, 80+), gender, body mass index (BMI), education as a measure of socio-economic status (less than high school, high school, some college, college plus), smoking (never, current, former), current alcohol consumption, and serum creatinine as a marker of kidney function. The log of creatinine was used because it provided a better fit to the data (higher likelihood) than either untransformed continuous or categorical variables for creatinine. All covariates were statistically significant predictors of uric acid, in the predicted direction.

In addition to the linear regressions described above, we also ran logistic regression models for the dichotomous outcome hyperuricemia, which was defined as serum uric acid >6 mg/dl for women and >6.8 mg/dl for men (Johnson et al. 2003). In these models we used quintiles of PFOA (0-11.4, 11.5-20.6, 20.7-38.9, 39.1-88.6, 88.7+ ng/ml) or PFOS (0-12.1, 12.2-

17.4, 17.5-23.2, 23.2-31.8, 31.90+ ng/ml). These analyses were adjusted for the same covariates used in linear regression.

We provided graphical representation of the linear regression results by showing the predicted trend in uric acid by decile of either PFOA or PFOS, given a covariate profile for an average subject. We used the median of each decile for graphing the x-axis.

Laboratory methods

The analytical method for perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS) used in this study has been described in detail previously (Flaherty et al. 2005; Longnecker et al. 2008). Both fluorocarbons are found in the serum fraction of the blood; they are not lipophilic (but rather proteinophilic) and no adjustment is made for lipid fractions. Briefly, the method utilizes liquid chromatography separation with detection by tandem mass spectrometry. Extraction of the serum samples was done using acetonitrile. Estimates of precision for PFOA were generally within $\pm 10\%$ for multiple replicates of individual samples over the range of 0.5 ng/mL to 40 ng/mL with a more precise relative precision measure of approximately 1% for highly fortified (10,000 ng/mL) samples. Relative precision estimates for PFOS were similar. The limit of detection for both chemicals is 0.5 ng/ml. Less than one percent of values of each chemical were less than the limit of detection, and these were assigned 0.25 ng/ml.

Blood samples were not required to be fasting, and were obtained at any time that the participants came to the study site, i.e., throughout the course of the day. Serum was separated from red cells and placed in transport tubes, and refrigerated for shipment to the lab. Uric acid was measured in serum via the enzymatic uricase method. Uric acid is oxidized by uricase to

allantoin and hydrogen peroxide. DHBS (3-5 Dichloro-2-hydroxybenzenesulfate) coupled with 4-aminoantipyrine and hydrogen peroxide, in the presence of peroxidase, forms a colored complex that is measured at 520 nm. The color intensity is proportional to the concentration of uric acid in the sample.

Results

Table 1 provides descriptive statistics on uric acid, PFOA, PFOS, and covariates in the model. The distribution of PFOA is highly elevated compared to that of the general US population and highly skewed, while the distribution of PFOS generally conforms to that expected based on the US population. Uric acid levels conform to what would be expected in an adult population. There are few missing data, so that the final model included 97% of the adult participants.

Table 2 shows results of the model for PFOA and uric acid, while Table 3 shows the results for PFOS and uric acid. A test for linear trend (using untransformed PFOA and PFOS) was highly significant (coefficient PFOA 0.00011, s.e. 0.00002, coefficient PFOS 0.00070, s.e. 0.00006), $p < 0.0001$) in both cases. Figure 2 shows the actual observed mean values of uric acid with deciles of PFOA and PFOS, without covariate adjustment. Figures 3 and 4 display the model's predicted values for uric acid by decile of PFOA and PFOS, respectively, adjusted for covariates. The model-predicted values have the same pattern as the observed data, although they are slightly higher because they are the predicted values for males, which have slightly higher levels than the entire population which is the basis for Figure 2. Both Tables 2 and 3, and Figures 2-4, indicate a close to monotonic increase in uric acid with an increase in either PFOA or PFOS. There is an increase in uric acid of 0.2-0.3 ug/dl from lowest to highest decile for both

PFOA and PFOS. The exposure-response for PFOA appears to tail off at the highest exposures, whereas for increasing PFOS, uric acid increases approximately linearly. The uppermost exposure levels of PFOA in this population were far above expected US levels; this was not the case for PFOS.

PFOA and PFOS were correlated in our data (Spearman correlation coefficient 0.31). When both PFOA and PFOS were included in the linear regression model, both variables continued to show a positive linear trend; the trend for PFOA was slightly diminished but the one for PFOS was notably diminished, suggesting that PFOA was the more important of the two variables. The trend for PFOA peaked at a 0.25 ug/dl increase for uric acid at the highest decile of PFOA (vs. 0.28 ug/dl without PFOS in the model), while the trend for PFOS peaked at 0.13 ug/dl uric acid increase for the highest decile of PFOA (compared to 0.22 without PFOA in the model).

Analyses of hyperuricemia as an outcome (>6.0 mg/dl for women, >6.8 mg/dl for men) by quintile of PFOA yielded odds ratios of 1.00, 1.33 (95% CI 1.24-1.43), 1.35 (95% CI 1.26-1.45), 1.47 (95% CI 1.37-1.58), and 1.47 (95% CI 1.37-1.58). The test for linear trend, via determining the statistical significance of the coefficient for a continuous variable PFOA, was significant (coefficient 0.00023, s.e. .00004, $p<0.0001$), although the trend in odds ratio appeared to plateau rather than increase in a strictly linear fashion. The corresponding odds ratios for PFOS were lower, 1.00, 1.02 (95% CI 0.95-1.10), 1.11 (95% CI 1.04-1.20), 1.19 (95% CI 1.11-1.27), and 1.26 (95% CI 1.17-1.35) (test for trend, coefficient continuous variable PFOS 0.0050, s.e. 0.0007, $p<0.0001$). When both PFOA and PFOS were entered into the logistic model for hyperuricemia, the same pattern of results was observed, with a slightly less steep

trend (OR for top quintile PFOA was 1.42 (95% CI 1.32-1.53), while it was 1.13 (95% CI 1.05-1.22) for PFOS. No significant interaction between PFOA and PFOS was observed.

Only 119 people (0.2%) had creatinine > 2.50 mg/dl, suggesting kidney disease which can affect uric acid, and their exclusion did not change results. A broader exclusion cutpoint of 1.50 mg/dl excluded 739 and again had no effect on results. Inclusion of a variable for taking cholesterol medication (15% took medication) was not a significant predictor of uric acid; among those not taking such medication, measured total cholesterol was a significant positive predictor of higher uric acid, but had little effect on the odds ratios for PFOA or PFOS.

No significant interactions were found between PFOA and age, creatinine, or BMI. A significant interaction was found for gender; although both sexes had showed a significant positive exposure-response, it was more consistently linear for females than males. For hyperuricemia, the ORs for females were 1.20 (95% CI 1.08-1.33), 1.26 (95% CI 1.13-1.41), 1.35 (95% CI 1.21-1.51), and 1.42 (95% CI 1.26-1.58), while for males the corresponding ORs were 1.31 (95% CI 1.19-1.45), 1.26 (95% CI 1.15-1.39), 1.37 (95% CI 1.25-1.51), and 1.34 (95% CI 1.22-1.48).

We also analyzed a subset of participants who had a PFOA level ≤ 20 ng/ml, dividing them into quartiles of PFOA exposure, such that the referent group had levels similar to the US general population. Those with 5-9.9 ng/ml (n=2012), 10-14.9 ng/ml (n=6841), and 15-20 ng/ml (n=7387) had predicted increases in uric acid of 0.14 (95% CI 0.07-0.20), 0.21 (95% CI 0.15-0.27), and 0.24 mg/dl (95% CI 0.18-0.31) above those with PFOA levels below 5 ng/ml.

Discussion

We observed a positive association between PFOA and uric acid, although the absolute magnitude of the change in uric acid from lowest to highest decile was modest. A significant positive association was observed in two previous studies of workers exposed to high levels of PFOA. No details were given one of these studies (Sakr et al. 2007a), while in the other study of 160 workers the exposure-response coefficient was about twice as high as our own (per unit PFOA) (Costa et al. 2009).

We also observed an elevated risk of hyperuricemia among subjects in the top quartile of PFOA. PFOS showed a similar relationships with uric acid as did PFOA, but with less pronounced trends. PFOA appeared to be more strongly associated with uric acid than PFOS. The odds ratio for hyperuricemia were higher for PFOA than for PFOS (1.47 vs 1.26 for the top quintile vs. the lowest quintile. Inclusion of both fluorocarbons in the model hyperuricemia only slightly diminished positive trends with PFOA, but had more effect on trends with PFOS.

Serum PFOA levels were quite high overall in this community due to primarily to contamination of drinking water (although 5% of the population had worked at the chemical plant, and had high levels due to occupational exposure). However there were a large number of people with low levels, similar to the US population. Serum PFOS was present at levels similar to the US population. Restriction of the data to those with lower levels of PFOA suggested that even slight increases in PFOA above background were associated with significant increases in uric acid.

In linear regression analyses, the exposure-response curve for PFOA and uric acid appeared to attenuate at the highest exposures, possibly reflecting saturation of a biological mechanism at high doses, whereas the curve for PFOS did not.

The percentage of the variance (change in R-square) in uric acid attributable to PFOA (or PFOS) is small, only about 1%. However, many variables which are important predictors explain only a small amount of the variation of something else. For example, in our model predicting cholesterol in this population (Steenland et al. 2009), removal of significant (and well-established) cholesterol predictors for exercise, smoking, gender, alcohol, and SES combined reduces the R-square of our model less than 1% (the reduced model contains only BMI and age). Furthermore, if there is a causal relationship between PFOA and uric acid, we may have misclassified PFOA by using current levels as past levels may be the more relevant predictor. This would bias our findings toward the null, decreasing the amount of variance explained.

A mechanism by which PFOA (or PFOS) might lead to higher uric acid is unknown. However, some data suggests that PFOA can induce oxidative stress in human liver cells (Yao et al. 2005, Panararetakis et al. 2001). It is in turn possible that such oxidative stress may be associated with increased uric acid (Patterson et al. 2003).

A second possible mechanism by which PFOA and uric acid might be associated without being causally linked is via shared renal transport transporters governing excretion of each substance. Organic ion transporters 1 and 3 (OAT 1 and 3) are involved in tubular secretion. OAT 1 and 3 have high affinity for PFOA (Nakagawa et al. 2008). Recent studies also show that OAT 1 and 3 are involved in urate secretion (Early et al. 2008). So it is possible that if the levels of PFOA increase, the secretion of urate is decreased and therefore blood urate levels may secondarily increase. However, whether this shared transporter hypothesis is relevant in humans remains speculative at this point.

Our findings are of interest because uric acid itself has been linked to hypertension and possibly other cardiovascular outcomes. A strength of our study is the large population and the

fact that the participation rate in the community was high, lessening concern about chance findings and about potential selection biases. A limitation is that we did not have data on blood pressure for our population, making it impossible to directly assess a possible fluorocarbon-blood pressure relationship. Perhaps the principal limitation of our study is that, despite the associations we observed, causal inference is limited by the cross-sectional nature of the data. We cannot know whether the rise in PFOA or PFOS preceded the rise in uric acid. It is also possible that both perfluorinated compounds rise with increased uric acid because all three are related to some other as yet unknown biologic mechanism, an interpretation consistent with the parallel effects of both PFOA and PFOS, assuming this mechanism was related to perfluorinated compounds in general.

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Table 1. Descriptive statistics (n=54,951) for adults age $\geq$ 20 in the mid-Ohio valley in 2005-2006*

Continuous variables	Mean (std dev)(inter-quartile range)	Median	Percent
Uric acid (mg/dl)	5.58 (1.55)(4.5-6.6)	5.50	n.a.
PFOA (ng/ml)	86.4 (261.3)(13.5-71.4)	27.9	n.a.
PFOS(ng/ml)	23.4 (16.1)(13.6-29.3)	20.2	n.a.
Age	45.0 (15.9)(33-57)	44.0	n.a.
BMI	28.7 (6.5)(24.2-32.0)	27.5	n.a.
Creatinine (mg/dl)	0.95 (0.28)(0.8-1.1)	0.90	n.a.
Categorical variables used in model			
BMI $\leq$ 24	21.5 (1.7)(19.1-23.7)	21.9	25%
BMI 24-27.4	25.8 (1.0)(25.0-26.6)	25.8	25%
BMI 27.5-31.9	29.5 (1.26)(28.4-30.6)	29.4	25%
BMI 31.9+	37.3(6.35)(33.5-39.5)	35.6	25%
Age 18-39	28.6(6.42)(23-34)	29	39.8%
Age 40-49	44.8(2.9)(42-47)	45	21.0%
Age 50-59	54.3(2.9)(52-57)	54	18.7%
Age 60-69	64.1(2.8)(62-66)	64	12.3%
Age 70-79	73.7(2.8)(71-78)	73	6.2%
Age 80+	83.8(3.7)(81-86)	83	1.9%
Never smoker	n.a.	n.a.	48%
Current smoker	n.a.	n.a.	26%

Former smoker	n.a.	n.a.	26%
Current alcohol	n.a.	n.a.	48%
Male	n.a.	n.a.	48%
Less than high school	n.a.	n.a.	13%
High school	n.a.	n.a.	42%
Some college	n.a.	n.a.	32%
College +	n.a.	n.a.	18%
High uric acid (>6.0 for women, >6.8 men)	n.a.	n.a.	24%

*Maximum percent missing for any variable was 1.1%

Table 2. Results from model with PFOA and uric acid*

Parameter	Estimate	Std err
PFOA 0-7.8 ng/ml (referent)	0	
PFOA 7.9-11.4 ng/ml	0.09	0.02
PFOA 11.5-15.4 ng/ml	0.16	0.02
PFOA 15.5-20.6 ng/ml	0.18	0.02
PFOA 20.6-27.8 ng/ml	0.21	0.02
PFOA 27.9-38.9 ng/ml	0.21	0.02
PFOA 39.0-56.9 ng/ml	0.22	0.02
PFOA 57.0-88.6 ng/ml	0.22	0.02
PFOA 88.7-188.6 ng/ml	0.25	0.02
PFOA 188.7+ ng/ml	0.28	0.02

*Model R-square 0.40, n=53,458 (3% of data lost due to missing values). Adjusted for age, creatinine, gender, smoking, education, BMI, and current alcohol consumption. All covariates significant at $p < 0.0001$ in expected directions.

Table 3. Results from model with PFOS and uric acid*

Parameter	Estimate	Std. err.
PFOS 0-9.0 ng/ml (referent)	0	
PFOS 9.1-12.1 ng/ml	0.00	0.02
PFOS 12.2-14.9 ng/ml	0.01	0.02
PFOS 15.0-17.4 ng/ml	0.06	0.02
PFOS 17.5-20.1 ng/ml	0.08	0.02
PFOS 20.2-23.1 ng/ml	0.09	0.02
PFOS 23.1-26.8 ng/ml	0.12	0.02
PFOS 26.9-31.8 ng/ml	0.12	0.02
PFOS 31.9-40.4 ng/ml	0.12	0.02
PFOS 40.5+ ng/ml	0.22	0.02

*** Model R-square 0.40, n=53,458 (3% of data lost due to missing values). Adjusted for age, creatinine, gender, smoking, education, BMI, and current alcohol consumption. All covariates significant at $p<0.0001$ in expected directions.**

Figure Legends

Figure 1. Six water districts contaminated with PFOA

Figure 2. Observed uric acid with increasing PFOA and PFOS*

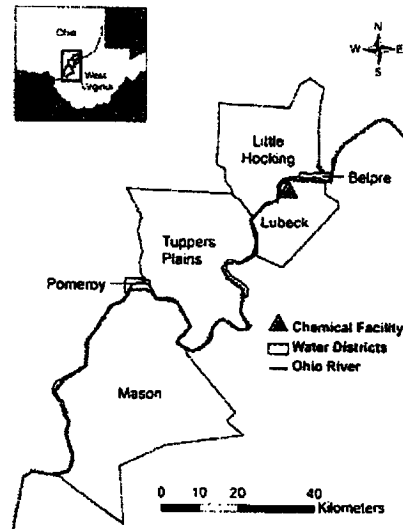
*unadjusted for covariates

Figure 3. Predicted uric acid with increasing PFOA*

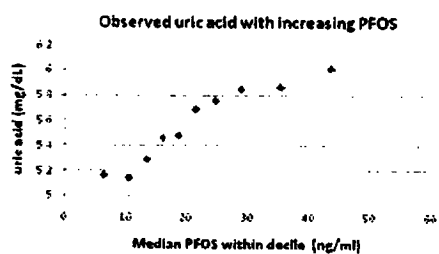
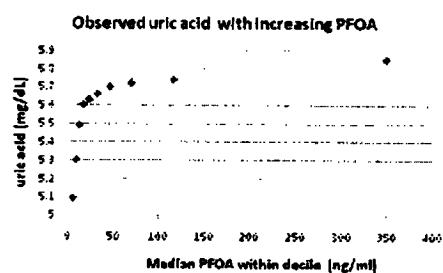
*Predicted value from regression model for an average participant, ie, age 45, creatinine 0.95, high school education, male, BMI 28.55, non smoker, non drinker. 95% CIs are for population means.

Figure 4. Predicted uric acid with increasing PFOS*

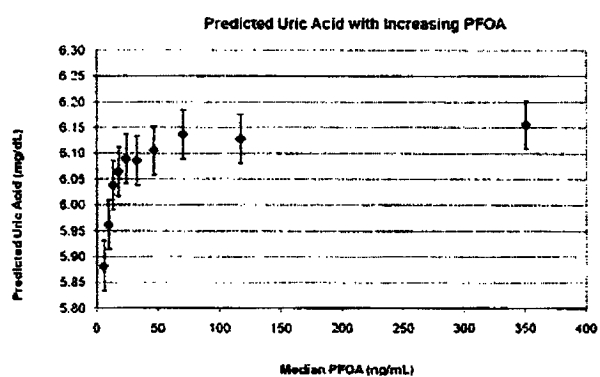
*Predicted value from regression model for an average participant, ie, age 45, creatinine 0.95, high school education, male, BMI 28.55, non smoker, non drinker. 95% CIs are for population means.



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