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July 14, 2009

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TSCA Confidential Business Information Center (7407M)
EPA East - Room 6428, Attn: Section 8(e) & FYI
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Submission To TSCA 8(e)/FYI Database Re: PFOA/PFOS

To TSCA 8(e)/FYI Database:

We are hereby providing the following information for inclusion in the TSCA 8(e)/FYI databases with respect to PFOA/PFOS:

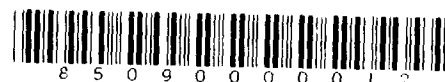
1. Steenland, K., *et al.*, "Predictors of PFOA Levels in a Community Surrounding a Chemical Plant," 117 *Environ. Health Perspectives* 1083-88 (July 2009);
2. Frisbee, S.J., *et al.*, "The C8 Health Project: Design, Methods, and Participants," *Environ. Health Perspectives* (Online edition) (doi: 10.1289/ehp.0800379)(online July 13, 2009); and
3. C8 Science Panel, Study Summary/Status Report (July 8, 2009).

Very truly yours,

Robert A. Bilott

RAB:mdm
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Predictors of PFOA Levels in a Community Surrounding a Chemical Plant

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BACKGROUND: Perfluorooctanoic acid (PFOA) is considered a probable human carcinogen by the U.S. Environmental Protection Agency. It does not exist in nature but has been used widely since World War II. It is present in the serum of most Americans at about 4–5 ng/mL, although the routes of exposure remain unknown.

OBJECTIVES: We examined predictors of PFOA in mid-Ohio Valley residents living near a chemical plant that until recently released large quantities of PFOA into the environment, contaminating drinking water.

METHODS: We studied 69,030 residents in six contaminated water districts who participated in a 2005–2006 survey involving a questionnaire and blood tests. Of these, 64,251 had complete data on PFOA and covariates. We also analyzed a subset (71%) for whom we had occupational history. We ran linear regression models to determine serum PFOA predictors.

RESULTS: Mean PFOA serum level was 83.0 ng/mL (median, 28.2). The most important predictors were current (median for all districts, 38.4; highest district, 224.1) and past (median, 18.6) residence in contaminated water districts, and current (median, 147.8) and past (median, 74.9) employment at the chemical plant (R^2 model = 0.55). PFOA was higher for males, those consuming local vegetables, and those using well water rather than public water, and lower for those using bottled water. PFOA was higher at younger and older ages.

CONCLUSIONS: PFOA levels in this population varied with distance of residence from the plant and employment at the plant. Effects of age and sex reflected prior findings. Effects of other demographic and lifestyle covariates were relatively weak.

KEY WORDS: PFOA, serum levels, water contamination. *Environ Health Perspect* 117:1083–1088 (2009). doi:10.1289/ehp.0800294 available via <http://dx.doi.org/> [Online 23 March 2009]

Perfluorooctanoic acid (PFOA, or C8) does not occur in nature. It is used as a polymerization aid in the manufacture of several types of fluoropolymers, which are used in a wide variety of industrial and consumer products, including extensive use in the manufacture of Teflon. PFOA does not break down once in the environment, leading to widespread buildup and bioaccumulation. The half-life of PFOA in human serum has been estimated to be about 4 years (Olsen et al. 2007). Most people in the United States have measurable PFOA in their serum, with a median of 4 ng/mL in 2003–2004 (Calafat et al. 2007b), although the exact sources of this exposure are not clear.

PFOA causes cancer of the testicles, liver, and pancreas in rodents, and there is some evidence that it also causes breast cancer in rodents [U.S. Environmental Protection Agency (EPA) 2005]. It also causes fetal loss and low birth weight in mice and immunotoxic and hepatotoxic effects in rodents (U.S. EPA 2005). Health effects in humans are not well established. There have been some reports of associations with lower birth weight (Apelberg et al. 2007; Fei et al. 2007), higher cholesterol (Sakr et al. 2007a, 2007b), and impaired liver function (Olsen et al. 2007), but these effects are usually modest, and the literature is sparse. Mortality studies of workers have shown increases in some causes of death but have

not been consistent and have been based on relatively small numbers of deaths (Gilliland and Mandel 1993; Leonard et al. 2007).

PFOA has been used in the manufacturing of fluoropolymers at a chemical plant in Washington, West Virginia, since 1951, with use peaking in the late 1990s. PFOA is used as a surfactant in the polymerization of trifluoroethylene to make Teflon. It entered the groundwater via both air emissions, which were deposited on the soil around the plant and leached downward, and emissions into the Ohio River, which then entered the groundwater that communicates with the river. Public drinking water comes from wells pumping from the groundwater, which are located close to the river. Some local landfill sites may have also contributed to groundwater contamination. Emissions have been sharply reduced in the past few years. There is evidence that drinking water is the primary route of exposure for the population living in these districts (Emmett et al. 2006).

In 2001, a group of residents from the Ohio and West Virginia communities in the vicinity of the plant filed a class-action lawsuit alleging health damage due to contamination of human drinking water supplies with PFOA. The settlement of the class action lawsuit led to a baseline survey, called the C8 Health Project, which was conducted

in 2005–2006 and gathered data from 69,000 Ohio and West Virginia residents who lived in six contaminated water districts surrounding the chemical plant. The C8 Health Project included blood draws and subsequent measurement of serum PFOA (West Virginia University 2009). The present study is an analysis of these data to study factors associated with PFOA levels.

Materials and Methods

Study participants. The C8 Health Project, conducted by Brookmar Inc., began data collection in August 2005 and completed it in August 2006. Its purpose was to collect health data from class members through questionnaires and a battery of blood tests, including a test to ascertain the concentration of PFOA in the serum. Subjects were eligible to participate in the C8 Health Project if they had consumed drinking water for at least 1 year before 3 December 2004 supplied by Little Hocking Water Association (Ohio), City of Belpre (Ohio), Tupper Plains Chester Water District (Ohio), Village of Pomeroy (Ohio), Lubeck Public Service District (West Virginia), Mason County Public Service District (West Virginia), or private water sources within these areas that were contaminated with PFOA. Subjects were also eligible if they could document that they had either worked in a contaminated water district or went to school there for at least 1 year. Figure 1 shows the six water districts. Subjects were compensated \$400 if they filled out the extensive questionnaire and came to local survey stations to donate a blood sample.

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The authors declare they have no competing financial interests.

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A full description of the C8 Health Project is in preparation.

The C8 Health Project collected data on 69,030 subjects. It is not known what percentage of the eligible population participated, because the eligible population was not enumerated (the past populations of the water districts are not known, nor are the number of eligible people who lived outside the water districts but went to school or worked there). Nonetheless, it is believed that most participated, given the widespread public interest and the financial incentive. We have estimated the participation rate among current residents in 2005–2006 among adults ≥ 20 years of age using census data (the population ≥ 18 years of age, as studied here, was not available from the census). 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 this number (33,001 residents) by the population (40,721 residents) to find an estimated participation rate of 81% among current residents ≥ 20 years of age.

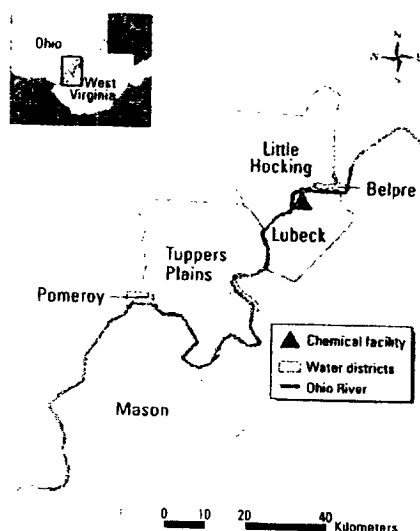


Figure 1. Six contaminated water districts of the C8 Health Project.

Statistical analysis. It was expected *a priori* that water districts would play an important role in predicting exposure, with subjects in water districts more distant from the plant likely to have lower serum levels. Subjects in the C8 Health Project were required to document past or present consumption of contaminated public water from one of the six contaminated water districts (either via living in the water district for at least 1 year, or by working or going to school there for at least 1 year; $n = 68,873$), or having drunk from private wells with documented contamination ($n = 157$). This documented water district of exposure is called the “qualifying” water district. Sixty-three percent of the population reported currently drinking public water (as their main water source) in one of the six water districts. We classified water district into 12 groups: six for currently (2005–2006) drinking public water in one of the six contaminated water districts, and six for not currently drinking public water but having previously been exposed by drinking water in one of the six water districts. Among those classified by their qualifying water district,

73% of these had a record of having lived or worked in the past in their qualifying water district, with the remainder presumably having gone to school there (no data were available on school history). Hereafter, we loosely describe these variables as “current” (2005–2006) and “past” exposure, because most of those not currently drinking contaminated public water qualified for the study because of having drunk contaminated water in the past.

Besides age, race, sex, and water district, other *a priori* variables of interest were having worked at the chemical plant, growing your own vegetables, and drinking bottled water (Emmett et al. 2006). Detailed employment history was available for only adult study subjects who consented to make available identifiable information to the authors as part of future follow-up studies (71%). We restricted analyses using a variable for current or past employment at the chemical plant to that subset. Our initial model was based on including these *a priori* variables found to be important in previous studies, as well as the variables for water district. The initial model then included current or past water district, occupational

Table 1. Descriptive statistics of mid-Ohio Valley residents exposed to PFOA ($n = 69,030$).

Variable*	No. (%)	Median PFOA (ng/mL)	Variable*	No. (%)	Median PFOA (ng/mL)
Blood PFOA in 2005–2006	69,030 (100)	28.2 ^b	Previously resided or worked in water district		
Age (years)			Belpre	3,387 (4.9)	17.3
0–9	4,915 (7.1)	32.8	Tupper Plains	4,359 (6.3)	13.6
10–19	9,658 (14.0)	26.6	Little Hocking	4,465 (6.5)	33.7
20–29	10,073 (14.6)	21.0	Lubeck	8,552 (12.4)	28.4
30–39	10,547 (15.3)	22.7	Mason County	2,711 (3.9)	10.5
40–49	12,113 (17.6)	28.0	Pomeroy	2,016 (2.9)	11.0
50–59	10,515 (15.2)	33.6	Vegetarian		
60–69	6,881 (10.0)	42.9	Yes	502 (0.7)	24.5
≥ 70	4,328 (6.3)	40.1	No	68,528 (99.3)	28.2
Sex			Consumed alcohol in last 3 days		
Male	33,242 (48.2)	33.7	Yes	8,883 (13.1)	33.4
Female	35,788 (51.8)	23.7	No	59,029 (86.9)	27.6
Race			Current smoking		
White	66,989 (97)	28.1	Yes	14,847 (21.5)	25.3
Nonwhite	2,041 (3)	29.5	No	54,088 (78.5)	29.3
BMI			Former smoking		
< 24	18,849 (28.1)	27.9	Yes	14,697 (21.3)	31.2
24–26	12,501 (18.6)	29.1	No	54,280 (78.7)	27.5
27–29	11,800 (17.6)	30.8	Regular exercise		
≥ 30	24,005 (35.8)	26.1	Yes	22,072 (32.0)	30.3
Worked at chemical plant ^c			No	46,958 (68.0)	27.3
Yes, current	1,171 (2.4)	147.8	Bottled water		
Yes, previous	1,447 (2.9)	74.9	Yes	3,728 (5.4)	31.3
No	45,276 (94.9)	24.3	No	65,302 (94.6)	28.0
Grow own vegetables			Well water		
Yes	16,015 (23.2)	34.1	Yes	4,434 (6.4)	21.7
No	53,015 (76.8)	26.7	No	64,596 (93.6)	28.7
Currently resident in water district			Date of testing		
Belpre	5,388 (7.8)	35.0	First 2 months	10,284 (14.9)	48.9
Tupper Plains	9,703 (14.1)	37.2	Second 2 months	14,046 (20.4)	39.9
Little Hocking	8,390 (12.2)	224.1	Third 2 months	15,524 (22.4)	28.8
Lubeck	8,289 (12.0)	66.9	Fourth 2 months	14,948 (21.7)	23.8
Mason County	10,066 (14.6)	12.4	Fifth 2 months	8,756 (12.7)	17.8
Pomeroy	1,560 (2.3)	12.1	Last 2 months	5,472 (7.9)	14.7

*A total of 2,120 subjects were missing PFOA values, 1,875 subjects BMI, 1,118 subjects alcohol use, 95 subjects current smoking, 53 subjects former smoking, 8,649 subjects household income, and 144 subjects water district. ^bMean 83.6 ng/mL, geometric mean 32.9 ng/mL. ^cData on working at chemical plant were available for only 71% of the population.

exposure (for the subset with available data), eating local vegetables, use of bottled water, age, sex, and race (white vs. nonwhite).

We included the entire population ($n = 69,030$) in analyses using the above regression model (absent occupational exposure, available on a subset), to which we added a large number of other potentially important variables, ultimately retaining those that had a significant association (at $p \leq 0.05$) with PFOA. Because the population is so large and any variable only slightly associated with PFOA may be statistically significant, this strategy of model building led to inclusion in the final model of variables statistically associated with PFOA levels but without any important contribution to explaining the overall variance of PFOA. We adopted this strategy partly because of the exploratory nature of this analysis and the minimal prior data on factors associated with PFOA in the general population. Results from regression models in which the log of PFOA was the outcome were transformed back to the original unlogged scale, resulting in multiplicative effects for predictor variables. All predictor variables in the regression were categorical. Predicted values were reported as a percent change compared with baseline values for each categorical variable in the regression.

All regression models used the natural log transformation of PFOA because the log transform was more normally distributed; we checked residuals for normality.

Laboratory method for PFOA. Analyses were conducted by a large commercial lab (Exygen, State College, PA, USA). PFOA is customarily measured in the serum, where virtually all PFOA in whole blood may be found (Ehresman et al. 2007). The analytical method for measurement of PFOA in the serum, which was used in this study, has been described in detail previously (Flaherty et al. 2005; Longnecker et al. 2008). Briefly, the method uses liquid chromatography separation with detection by tandem mass spectrometry. The approach allows for rapid throughput using a 96-well plate and can handle large numbers of samples. Extraction of the serum or plasma samples was done using acetonitrile. Chromatography on the extract was done using a quaternary pump and vacuum degasser. The mobile phases consisted of two systems: a 2 mM ammonium acetate solution, and methanol with gradients set up to ensure both rapid and complete separation. The lab used ^{13}C -PFOA at a concentration of 1 ng/mL as its internal standard. Mass spectrometry was done in selected reaction monitoring mode with $m/z = 413 \rightarrow 369$ as the principal ion monitored for PFOA ($m/z = 370$ for the ^{13}C internal standard). Fortification recoveries using rabbit serum or plasma as the matrix for PFOA were generally within 90–110%. The

coefficient of variation based on multiple samples between batches was generally ≤ 0.10 over the range of 0.5–40 ng/mL, with a more precise relative coefficient of variation of approximately 0.01 for highly fortified (10,000 ng/mL) samples (Flaherty et al. 2005).

The limit of detection for PFOA was 0.5 ng/mL. Only 0.06% of observations were below the limit of detection, and we assigned these a value of 0.25 ng/mL.

Results

Table 1 provides descriptive data for the population. Figure 2 shows the distribution of PFOA. The log of PFOA is more normally distributed than PFOA, and use of it in the regression model for the full population led to residuals that were approximately normally distributed (Figure 3). The theoretical 2.5% tails

of the distribution of the studentized residuals (> 1.96 or < -1.96) contained 2.76% and 2.60% of the data, respectively, conforming reasonably to expectations.

Table 2 shows the results of the final model for the entire population, without inclusion of a variable for working at the chemical plant (model R^2 , 0.55). We added five additional variables (date of testing divided into bimonthly intervals, alcohol consumption in the last 3 days, being a vegetarian, body mass index (BMI), and regular exercise) to variables of *a priori* interest in the initial model, based on each being significantly associated with PFOA ($p < 0.05$) when added to the initial model.

Table 2 shows strong effects of water district, with current residence in water districts closest to the plant having the highest

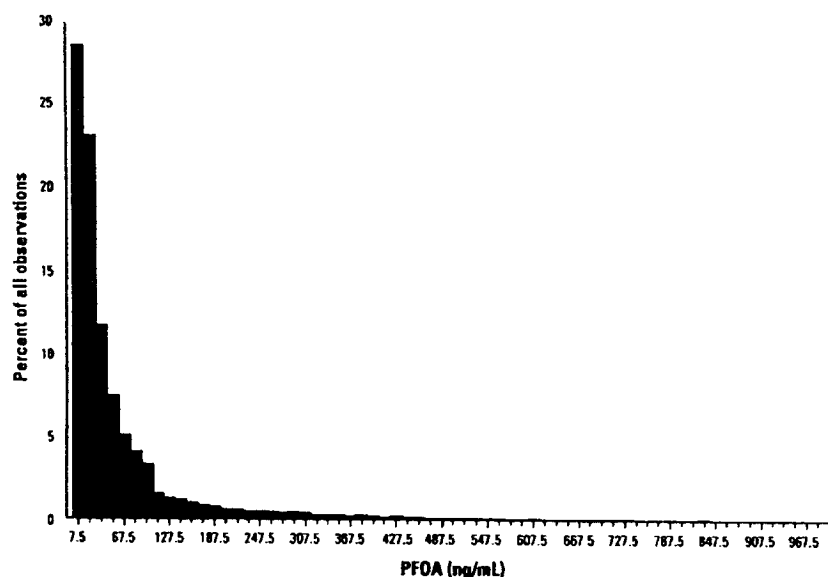


Figure 2. Distribution of PFOA (C8; 405 observations $> 1,000$ ng/mL not shown).

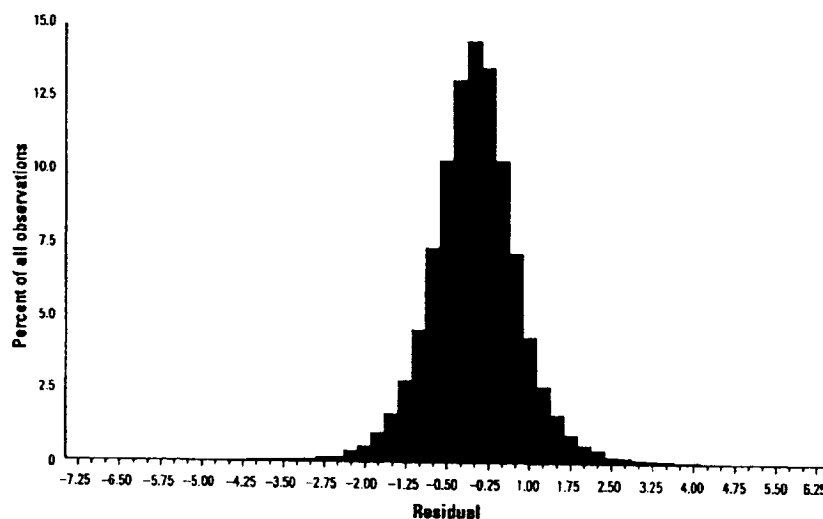


Figure 3. Distribution of residuals from regression model (Table 2).

PFOA levels. Figure 4 shows the data graphically. Currently drinking public water in Little Hocking or Lubeck is associated with the highest levels of PFOA. The well field for Little Hocking public water is located directly across the river from the plant, and the plant itself is

located in Lubeck. Current residence in Belpre and Tupper Plains water districts had the next highest levels. These districts are slightly farther away (Belpre is also upstream). Residents of districts farthest away (Mason, Pomeroy) had the lowest levels. Past consumption of water

in Little Hocking or Lubeck was also associated with elevated levels, although less than for those currently residing in these water districts. The median level for current residents of any water district was 38.4 ng/mL, whereas the median for past residents was 18.6 ng/mL.

Figure 5 indicates that PFOA levels listed in Table 2 show a J-shaped curve with age. Male sex was also strongly associated with increased PFOA levels. Variables other than water district, age, and sex explained less of the variation in PFOA level.

Growing one's own vegetables was associated with increased PFOA, whereas drinking bottled water was associated with decreased PFOA. Drinking well water, current smoking, and drinking alcohol in the last 3 days were positively associated with an increase in PFOA. The alcohol finding could reflect some unknown aspect of increased liver activity (protein and lipid production).

Table 2 shows an approximate 30% decrease in levels over the year of testing (2005–2006), which results largely from residents outside the six water districts (37%) who were no longer exposed and whose blood levels dropped as they excreted PFOA. Note that the 34% decrease over time contrasts with the much sharper decrease seen in the unadjusted

Table 2. Multiple linear regression model for the log of PFOA level in all six water districts (model $R^2 = 0.55$, $n = 64,251$).

Variable	Predicted change (%) in PFOA vs. referent group	Regression coefficient [change in log PFOA (95% CI)]	p-Value	Variance (%) in PFOA (partial R^2)
Age (years)				
0–9	Referent			
10–19	–15	–0.16 (–0.20 to –0.12)	< 0.0001	< 1
20–29	–24	–0.28 (–0.32 to –0.24)	< 0.0001	< 1
30–39	–16	–0.17 (–0.21 to –0.13)	< 0.0001	< 1
40–49	–2	–0.02 (–0.06 to 0.02)	0.24	< 1
50–59	12	0.11 (0.07 to 0.15)	< 0.0001	< 1
60–69	23	0.21 (0.17 to 0.25)	< 0.0001	< 1
≥ 70	26	0.19 (0.11 to 0.27)	< 0.0001	< 1
Sex				
Female	Referent			
Male	35	0.30 (0.29 to 0.31)	< 0.0001	2.9
BMI				
< 24	Referent			
24–26	2	0.02 (–0.01 to 0.03)	0.13	< 1
27–29	2	0.02 (–0.01 to 0.03)	0.18	< 1
≥ 30	–4	–0.04 (–0.05 to –0.01)	< 0.0001	< 1
Grow vegetables				
No	Referent			
Yes	11	0.10 (0.08 to 0.12)	< 0.0001	< 1
Currently resident in water district				
Belpre	203	1.11 (1.07 to 1.15)	< 0.0001	3.7
Tupper Plains	200	1.10 (1.06 to 1.14)	< 0.0001	4.1
Little Hocking	1,612	2.84 (2.80 to 2.88)	< 0.0001	21.5
Lubeck	421	1.61 (1.61 to 1.69)	< 0.0001	8.2
Mason County	9	0.09 (0.05 to 0.13)	< 0.0001	< 1
Pomeroy	3	0.03 (–0.03 to 0.09)	0.27	< 1
Previously lived or worked in water district				
Prior Belpre	62	0.48 (0.44 to 0.52)	0.005	< 1
Prior Tupper Plains	36	0.29 (0.25 to 0.33)	< 0.0001	< 1
Prior Little Hocking	246	1.22 (1.18 to 1.26)	< 0.0001	4.3
Prior Lubeck	169	0.88 (0.84 to 0.92)	< 0.0001	3.2
Prior Mason County	–2	–0.01 (–0.05 to 0.04)	0.57	< 1
Prior Pomeroy	Referent			
Vegetarian				
No	Referent			
Yes	–10	–0.10 (–0.18 to –0.02)	0.01	< 1
Consumed alcohol in last 3 days				
No	Referent			
Yes	7	0.06 (0.04 to 0.08)	< 0.001	< 1
Smoking				
Never	Referent			
Current	6	0.06 (0.04 to 0.08)	< 0.0001	< 1
Former	–1	–0.01 (–0.03 to 0.01)	0.18	< 1
Bottled water				
No	Referent			
Yes	–6	–0.06 (–0.08 to –0.04)	< 0.0001	< 1
Well water				
No	Referent			
Yes	12	0.11 (0.09 to 0.13)	< 0.0001	< 1
Race				
Nonwhite	Referent			
White	2	0.02 (–0.02 to 0.06)	0.31	< 1
Time of blood draw				
First 2 months	Referent			
Months 3–4	6	0.06 (0.04 to 0.08)	< 0.0001	< 1
Months 5–6	–11	–0.12 (–0.14 to –0.10)	< 0.0001	< 1
Months 7–8	–14	–0.15 (–0.17 to –0.13)	< 0.0001	< 1
Months 9–10	–22	–0.25 (–0.27 to –0.23)	< 0.0001	< 1
Months 11–12	–29	–0.34 (–0.38 to –0.30)	< 0.0001	< 1

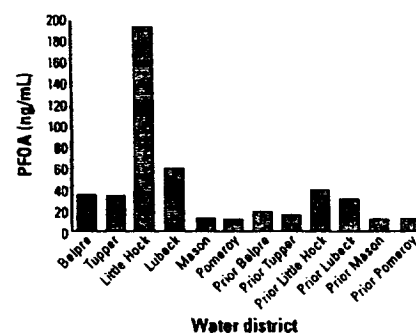


Figure 4. PFOA level (geometric mean) by current and former water district. Current water district refers to living in exposed water district in 2005–2006 at time of blood draw. Prior water district refers to having either lived, worked, or gone to school for at least 1 year in one of the six exposed water districts. Model prediction compared with observed median value of 11.50 ng/mL for Prior Pomeroy.

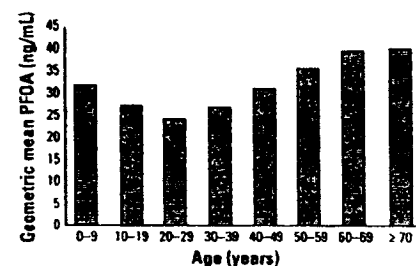


Figure 5. Predicted PFOA serum level (geometric mean) by age: model prediction compared with observed median value of 32.0 ng/mL for age group 0–9 years.

much less than those living there currently, again consistent with the gradual excretion of PFOA once high exposure ceases. This analysis via distance of water district from the plant is crude; a more comprehensive analysis using geocoding of past and present addresses, as well as estimates of annual emissions from the plant, is under way.

Demographic and other environmental factors played much less important roles. Male sex was the most important demographic factor associated with higher levels. Age showed a J-shaped relationship with serum PFOA, with higher levels in the young and the old, similar to what has been found previously by Emmett et al. (2006) and Calafat et al. (personal communication, 2008). The reasons for these demographic patterns are not known. We also found a trend of decreasing levels of PFOA over time during this 1-year study, which was primarily due to decreasing levels among people no longer living in the six water districts and therefore no longer exposed.

In conclusion, PFOA levels are far above background in this population that has consumed contaminated drinking water. Further studies are under way to determine whether PFOA is associated with health effects in this population.

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ENVIRONMENTAL HEALTH PERSPECTIVES

The C8 Health Project: Design, Methods, and Participants

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The C8 Health Project: Design, Methods, and Participants

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COMPETING INTERESTS DECLARATION:

For SJF, AS, SSK, CP, JAH, CJ, KML, AMD:

These authors were engaged in the Project pursuant to a contractual relationship between Brookmar, Inc. and West Virginia University. These authors have no current or prior competing financial or non-financial interests to disclose. These authors declare that their ability to design, conduct, interpret, or publish this research was unimpeded and fully independent of the Court and/or settling parties.

For APBJr, AM, PF, SA:

As described in the paper, Brookmar, Inc. was a for-profit company created solely to carry out the C8 Health Project component of the Court-directed settlement, and remained an active entity throughout the course of and until the closure of this study. APBJr and AM were the sole owners of Brookmar, Inc. PF and SA were employees of Brookmar, Inc. Brookmar, Inc. received funding exclusively from the Settlement, administered through the Health Project Administrator, to conduct the Project. As described in the paper, the design of the Project was developed in consultation with, though not subject to, the wishes of the settling parties. However, these authors declare that the study was performed, and their ability to interpret, and publish this research was unimpeded and fully independent of the Court and/or settling parties.

For TF, KS, VMV:

These authors are members or contractors of the Court-approved C8 Science Panel. As such, they are in receipt of funding from the C8 Class Action Settlement Agreement between DuPont and Plaintiffs, resulting from releases of chemical perfluorooctanoic acid (PFOA or C8) into drinking water, and approved by the Circuit Court of Wood County, West Virginia. These authors declare that their ability to design, conduct, interpret, or publish research was unimpeded and fully independent of the Court and/or settling parties. In addition, they declare no non-financial competing interests.

ABBREVIATIONS:

Abbreviation	Full Definition
APFO	Ammonium perfluorooctanoate
C5 / PFPeA	Perfluoropentanoic acid
C6 / PFHxA	Perfluorohexanoic acid
C6S / C6 Sulfonate / PFHS	Ammonium perfluorohexane sulfonate
C7 / PFHpA	Perfluoroheptanoic acid
C8 / PFOA	Perfluorooctanoic acid
C8S / C8 Sulfonate / PFOS	Perfluorooctanesulfonic acid
C9 / PFNA	Perfluorononanoic acid
C10 / PFDA	Perfluorodecanoic acid
C11 / PFUnA	Perfluoroundecanoic acid
C12 / PFDoA	Perfluorododecanoic acid
PFC	Perfluorocarbon
PFO	Perfluorooctanoate
LOD	Limit of Detection

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ABSTRACT

Background: The C8 Health Project was created, authorized, and funded as part of the Settlement Agreement reached in the case of *Jack Leach, et al. v E. I. duPont de Nemours and Company* (No. 01C-608 W. Va., Wood County Circuit Court filed April 10, 2002). The settlement stemmed from the perfluorooctanoic acid (PFOA or C8) contamination of drinking water in six water districts in two states near the DuPont Washington Works facility near Parkersburg, West Virginia. **Objectives:** This study reports on the methods and results from the C8 Health Project, a population study created to gather data which would allow class members to know their own PFOA levels and permit subsequent epidemiologic investigations. **Methods:** Final study participation was 69,030, enrolled over a 13-month period in 2005-2006. Extensive data were collected including demographic data, medical diagnoses (both self-report and medical records review), clinical laboratory testing, and determination of serum concentrations of 10 perfluorocarbons. Here we describe the processes used to collect, validate, and store these health data. We also describe survey participants and their serum perfluorocarbon levels. **Results:** The population geometric mean for serum PFOA was 32.91 ng/mL, 500% higher than previously reported for a representative American population. Serum concentrations for PFHS and PFNA were elevated 39% and 73% respectively, while concentrations of PFOS was present at levels similar to the US population. **Conclusions:** This largest known population study of community perfluorocarbon exposure permits new evaluations of associations between PFOA, in particular, and a range of health parameters. These will contribute to understanding of the biology of perfluorocarbon exposure. The C8 Health Project also represents an unprecedented effort to gather basic data on an exposed population; its achievements and limitations can inform future legal settlements for populations exposed to environmental contaminants.

INTRODUCTION

Perfluorocarbons

Perfluorooctanoic acid (PFOA or C8), is one member of the class of man-made perfluorocarbon (PFC) compounds. PFOA exists as an alkyl acid (PFOA), an ammonium salt (ammonium perfluorooctanoate, APFO), or as a dissociated conjugate base (perfluorooctanoate, PFO). A closely related PFC is perfluorooctanesulfonate (PFOS, C8 sulfonate, or C8S). Additional, related PFCs include: C5 (perfluoropentanoic acid, PFPeA), C6 (perfluorohexanoic acid, PFHxA), C6 sulfonate (ammonium perfluorohexane sulfonate, PFHS), C7 (perfluoroheptanoic acid, PFHpA), C9 (perfluorononanoic acid, PFNA), C10 (perfluorodecanoic acid, PFDA), C11 (perfluoroundecanoic acid, PFUnA), and C12 (perfluorododecanoic acid, PFDoA). PFCs are used as plasticizers, wetting agents, and as emulsifiers during the manufacture of fluoropolymers including products that impart nonstick heat resistance to cookware, or breathable yet waterproof properties to fabrics. PFCs may also result from the metabolism or environmental breakdown of fluorinated telomers, including chemicals used to coat commercial food packaging, and for stain-resistant treatment for fabrics and clothing. PFOA may also be a residual impurity in personal care products.

PFCs and Health

PFOA and other PFCs persist in the environment, and are found in ground and surface water globally (Yamashita et al., 2008). They are present in blood and other tissues of animal species worldwide, including remote regions (Tao et al., 2006). Recent publications have extensively reviewed and summarized the known toxicological properties, environmental distribution, and potential health concerns related to PFOA (Kennedy et al., 2004; Kudo et al., 2003; Lau et al., 2007). Animal toxicology studies have suggested potential suppression of humoral immunity, neuroendocrine effects, and exposure-related gestational and developmental effects. Cumulative evidence from mammalian animal studies has suggested

that the liver is an important target organ. Reported hepatotoxic effects include liver enlargement, hepatocellular adenomas, and peroxisome proliferation (specifically PPAR- α), possibly suggesting a possible non-genotoxic carcinogenic mechanism for PFCs.

Additionally, combined evidence supports that PFCs generally, and PFOA and PFOS specifically, are present in the sera of diverse human populations (Lau et al., 2007). In the US, analysis of NHANES samples reported detection of these chemicals in almost all samples, with a US-population median of 5 ppb PFOA. Both PFOA and PFOS concentrations were higher in the serum of men and those with higher education (Calafat et al., 2007a, Calafat et al., 2007b). While potential sources of human exposure continue to be investigated, current, known sources of PFOA exposure generally include drinking water, household dust, and food or migration from food packaging (in particular commercial and fast-food/take out packages) and cookware (Lau et al., 2007). Occupational studies have shown elevated worker exposures in manufacturing processes that use PFOA or PFOS (Emmet et al., 2006; Olsen et al., 2003).

Human population studies, predominately medical surveillance studies of male American workers exposed occupationally to PFOA or PFOS, have reported inconsistent findings (Lau et al., 2007). While some studies have reported associations between exposure and cancer (bladder and prostate in particular), lipids, liver enzymes, and some thyroid hormones, other or follow-up studies have either contradicted earlier findings, or found evidence suggesting explanation through confounding parameters (Lau et al., 2007). Maternal serum or neonatal cord blood studies have implicated an association of PFOA or PFOS with birth weight (Apelberg et al., 2007; Washino et al., 2009), but there are also contradictory findings in high-exposure populations (Nolan et al., 2008). The half-life of PFOS and PFOA in human sera has been reported as approximately 5 and 3.5 years respectively (Olsen et al., 2007).

In a review process that remains ongoing, the United States Environmental Protection Agency (EPA) is considering evidence and classification of PFOA as a likely human carcinogen (EPA-SAB-06-006). The PFOA Stewardship Program proscribes PFOA, PFOA precursors, and related, higher homologue chemicals from emissions and products by 2015. In the European Union, the use of PFOS and derivatives was stopped in 2000 and banned in 2008, though PFOA use remains largely unregulated (Jensen et al., 2008).

Origin of the C8 Health Project

The C8 Health Project can be traced to legal actions taken by a local family. A portion of this family's farmland was sold to DuPont in 1984, who subsequently converted the land parcel into a site to dispose of waste products from PFC manufacturing from their Washington Works plant. The family alleged that [the then unknown] chemicals from the landfill were responsible for family illness, wildlife death, and the death of almost 300 head of their cattle (see Supplemental File, Note 1). The family agreed to a confidential settlement with DuPont in 2001; associated legal activities, including independently commissioned studies and reports filed by government agencies, served to provide environmental data and to heighten local awareness of the exposure, coincident with an emerging scientific literature.

The following points summarize key events in the almost two-decade time-line leading to the C8 Health Project:

- Cumulative evidence detected PFOA contamination of water supplies along the mid-Ohio River valley. Water pollution was attributed to direct industrial releases from DuPont's Washington Works plant into the Ohio River, a principal source of public drinking water, and airborne pollution more broadly contaminating water tables and aquifer systems, with subsequent well contamination, an important drinking water source in a rural community (See Supplemental File, Note 2).

- August 2001-April 2002: Thirteen plaintiffs filed a lawsuit against DuPont, which was subsequently certified as a Class Action, *Leach v. E.I. DuPont de Nemours & Co., Civil Action No. 01-C-608*, filed in Wood County, West Virginia Circuit Court. The “Class” was defined as individuals, in West Virginia or Ohio, whose drinking water had been contaminated by quantifiable levels of PFOA.
- November 2004: A multi-component \$107 million pre-trial settlement between the Class and DuPont was reached. Complete settlement terms are part of the public record.

Key provisions included:

- A \$70 million award for Class members, of which \$20 million was required to be used for health and education projects;
- Provision of water treatment technologies to remove PFOA from the water supply of the six affected water districts;
- Formation of an independent panel of three scientific experts to carry out a community study and determine if there is a “probable link” (see Supplemental File, Note 3) between PFOA exposure and human disease.

The settlement broadly outlined terms of agreement but did not detail how they were to be satisfied. Post hoc negotiations between settling parties resolved that the health and education projects and Class payments would be achieved through a population-wide health study of the Class, initially known as the “Settlement Class Health & Education Project” and later the “C8 Health Project” (the Project). An independent company, Brookmar, Inc. (Brookmar), was created to design, publicize, and implement the Project under court supervision. Three epidemiologists (the C8 Science Panel) were appointed to determine the presence or absence of what the court termed a “probable link” between PFOA exposure and human disease (see Supplemental File, Note 3). In addition to Project data, the C8 Science

Panel is to include data from de novo, prospective community studies that they proposed and are conducting.

The Project faced significant implementation challenges, including court and population expectations for rapid timelines, and absence of precedent for the likely scale of the community project. Project participation was the established route for Class members to benefit from the settlement, but neither Class size nor participation was known a priori. Accordingly, Brookmar developed procedures to accommodate: rurality; shift workers; eligible Class members no longer living in the area; wide range in participant age and mobility; a deliberately short survey period; expressed community apprehension regarding data privacy and concern about adverse effects on insurability and even employability; and the desire for participants to receive personalized information about laboratory results and general information about Project findings. The data collection methodology implemented by Brookmar, agreed to implicitly or explicitly by counsel for the settling parties, is described below.

C8 HEALTH PROJECT METHODS

Eligibility

Class eligibility was defined by exposure to contaminated water, a combination of geographic and concentration criteria, and exposure duration. Key criteria included:

- Exposure to contaminated water from any of six public water districts (2 in West Virginia, 4 in Ohio; see Supplemental File, Figure 1) or from private water sources within the geographical boundaries of the public water sources which contained ≥ 0.05 ppb PFOA.
- The ability to document a minimum 12 months of exposure to contaminated water between 1950 and December 3, 2004, at either primary residence, place of employment, or school.

Participants supplied documentation demonstrating both their identity and exposure using a combination of Court-defined acceptable documents. Brookmar independently verified the authenticity of documents with the issuing agency, and identity documentation was examined to ensure that participants were enrolled only once. Scanned document copies became part of the participant's Project electronic data record.

Data Components

Four types of data were collected: a) health survey; b) self-reported anthropometric measurements; c) blood sample; and d) medical chart review to validate selected self-reported diagnoses. In identifying clinical laboratory tests and selecting diagnoses for validation, priority was given to those with potential associations to PFC exposure as reported in the scientific literature. Clinical laboratory tests included: serum lipid, immune and inflammatory markers; liver, kidney, and thyroid function; complete blood count; serum electrolytes and protein; and endocrine function, including insulin and glucose (see Supplemental File, Note 4). Validated medical diagnoses included: heart disease; cancers; thyroid disease; neurologic disorders;

inflammatory and autoimmune disorders; and pregnancy complications (see Supplemental File, Note 5).

The health survey gathered: demographic data; current and historic residential and employment information, including water source and use; personal medical diagnoses, treatments including medications, and physical symptoms; family medical history; pregnancy history and pregnancy-related outcomes for women; and information about lifestyle and health behaviors. Participants also self-reported their own height, weight, and blood pressure. Brookmar contracted with a separate company to independently pilot test the survey, and revisions were made based on pilot-test findings. The final version of the survey was accepted by the settling parties. The survey, a list of the clinical laboratory tests, and the eighteen medical diagnoses verified by medical record review are publically available (WVU C8 Health Project Data Hosting Website).

Enrollment

An independent information technology (IT) company was contracted to build and manage informatics solutions that addressed Class security concerns and created a web-based mechanism for Project registration and health survey completion. Participants could alternatively register in person and use paper-based surveys. After registration and completion of the health survey, participants received instructions regarding requirements for demonstrating eligibility and making an appointment at a Project data-collection site. Standard data quality-assurance techniques for survey data, including a quota for data duplicate entry for paper-based surveys and electronic-based logic rules (e.g., limited-answer menus) for web-based surveys, were in place for the health survey.

Data Collection Procedures

Temporary modular office units were established in each water district, staffed with nurses, phlebotomists, and intake personnel, and equipped for venipuncture, blood

processing, and short-term record and blood sample storage. Participants could schedule appointments between 7:30 a.m. and 7:30 p.m. at the location of their convenience. Due to both feasibility and participant considerations, fasting was not required for phlebotomy, though self-reported fast duration was collected to facilitate interpretation of laboratory results.

At in-person appointments, participants submitted eligibility documentation and the water district indicated by the exposure documentation provided was recorded; this was usually but not always the source of greatest exposure. Project staff verified demographic data, current residential information, completion of the health survey, and asked participants to report their current height, weight, and blood pressure. Participants voluntarily submitted a blood sample.

Each verified participant received \$150 for completing the health survey and an additional \$250 for providing a blood sample (regardless of sample quantity or quality). The payment amount reflected the compensation intentions of the settlement and remuneration for Project participation expenses.

Blood Sample Processing and Laboratory Methods

Blood samples were obtained and processed at individual data collection sites. Samples were drawn into 4 tubes per participant, with a maximum 35 cc for adults and 26 cc for children. Tubes were spun, aliquotted, and refrigerated until shipping. For limited-volume samples, serum was aliquotted with priority for PFC analysis. Samples were shipped on dry ice daily from each data collection site to the laboratory retained to measure serum PFCs. The clinical laboratory contracted to perform the clinical chemistry analysis picked up samples daily from each data-collection site. Additionally, an aliquot of serum from each participant was frozen and subsequently stored in a Project tissue bank.

Clinical laboratory tests were performed at a large, independent, accredited clinical diagnostic laboratory (LabCorp, Inc, Burlington, NC, USA). A customized HL7-interface generated immediate, on-site laboratory-specific identification numbers and tube labels, and

permitted subsequent electronic transfer of clinical laboratory results directly into the Project data system. Clinical laboratory tests and quality assurance were performed in accordance with the accreditation standards required of this laboratory.

The primary laboratory performing PFC analysis (Exygen Research Inc., State College, PA, USA) was selected based on its ability to meet FDA guidelines for bioanalytical method validation, a lower limit of quantification of 0.5 ng/mL, and 96-well-plate-based technology allowing for high throughput capability. This was the laboratory of record for a previously reported, independently performed study of residents in one water district included in the Project (Emmett et al., 2006). The PFOA quantification and validation methodology used by this laboratory has been previously detailed (Flaherty et al., 2005). The analytic protocol used for the Project was a modification of this methodology. Briefly, the technique used a protein precipitation extraction together with reverse-phase high-performance liquid chromatography/tandem mass spectrometry. Spectrometric detection was performed using a triple quadrupole mass spectrometer in selected reaction monitoring mode, monitoring for the individual m/z transitions for each of the 10 PFCs and the ^{13}C -PFOA surrogate. Results for the 10 PFCs measured were incorporated into the Project information system through a Windows-based program (See Supplemental File, Note 6).

PFC Quality Assurance

A two-tiered quality assurance program was implemented consisting of a) evaluation of test reliability in the primary lab (intra-lab) with the use of blank samples, samples spiked with a known PFC concentration, and participant duplicate samples, and b) use of a second, external laboratory (AXYS Analytical Services Ltd., Sidney, BC, Canada) to determine PFC concentrations for participant duplicate samples (inter-lab). This laboratory, with the ability to monitor 10 individual PFCs and a lower limit of quantification of 0.2 ng/mL, employed analytic methods previously described (Kuklenyik et al., 2004; Taniyasu et al., 2005). Briefly, the

technique used a solid phase extraction on a weak anion exchange column followed by reverse-phase high-performance liquid chromatography/mass spectrometry. Spectrometric detection was performed using a triple quadrupole mass spectrometer in selected reaction monitoring mode, monitoring individual m/z transitions for each of the target PFCs, the ^{13}C -PFOA, ^{13}C -PFOS, and ^{13}C -PFDA surrogates and the ^{13}C -PFOA and ^{13}C -FOUEA instrument internal standards.

To assess method performance at the primary lab, quality control samples in the form of two control serum blanks, two lab control spikes in control serum, and two sample duplicates, were performed with each batch of 90 samples analyzed. ^{13}C -PFOA (surrogate) was also added to every sample prior to extraction to assess lab preparation. Bulk control blanks and spikes were prepared at the primary lab and sent to the sampling sites. They were then blindly returned with every shipment of samples for analysis to assess storage, transport, and laboratory preparation effects. For these quality control samples, the Project IT system generated in-line dummy ID numbers and two sets of lab-ready, bar-coded phlebotomy tube labels). Site nurses aliquotted two sets of sample tubes, and both were included as part of the standard shipment to the primary laboratory. Based on a per-data collection site sampling plan, samples were also automatically identified by the Project IT system for the secondary lab. Labels and tubes were generated similarly, as were sample aliquots. Results from quality assurance samples were segregated from the main, participant database post hoc by the IT company, the only group unblinded to ID numbering.

During analysis of quality assurance results, a consistent difference between the primary and secondary laboratory was detected (approximately 30%) for samples obtained during the first four months of the Project. Investigation and additional, targeted intra- and inter-lab re-testing confirmed these directional (higher) differences. Per a court filing, Exygen discussed the cause as a problem of initially prepared samples used for internal calibration

(see Supplemental File, Note 7). Affected samples (approximately 25,000) were retested using serum stored in the Project tissue bank; quality assurance testing, including sample duplicates and replaced spiked and calibration samples, was also repeated. Retested results demonstrated a consistent decrease from initial results and increased consistency with the secondary lab. All analytic results presented here include only retested values for those affected serum samples.

For quantitative assessment of quality assurance test results, final test values were matched to participant quality assurance values for the primary or secondary lab. Results reported as less than the limit of detection (LOD) were treated conservatively and excluded from quality assurance analyses. Agreement between two measures was assessed with the absolute difference, percent difference (absolute difference between values divided by value means), and coefficient of variation (standard deviation divided by mean), which were then summarized (mean and median) across the matched-samples results.

Validation of Select Medical Diagnoses

Participants self-reporting one of the eighteen targeted diagnoses were asked to provide the time and location of diagnosis. After obtaining appropriate record release consent (described below), Brookmar requested a copy of supporting documentation from a medical record or pathology report from health care providers. Cooperating providers were compensated \$10 per necessary page. For approximately 36,000 validated diagnoses, the following was recorded: self-reported diagnosis; support (confirmation), non-support (negation), missing (records not obtained), or substitution (i.e., documentation supported a different diagnosis); the alternate diagnosis where appropriate; and type of documentation used for verification. Review of medical records and determination of diagnostic verification was performed by nurses employed by Brookmar.

Consenting Procedures

Brookmar required that participants read (and “check” affirmatively) an introductory section of the health survey that explained the purpose and procedures of the Project, and risks and benefits of participation. This language is publically available as part of the survey tool. All participants submitting a voluntary blood sample completed the standard consent and release forms of the clinical laboratory contracted for phlebotomy. Brookmar obtained a separate consent for the release of medical records necessary for diagnosis validation, which was subsequently mailed (along with a cover letter and specific documentation request) to the health care provider identified by the participant.

The Project group at West Virginia University and the C8 Science Panel obtained IRB approval, from their own institutions, permitting access to de-identified Project data. With assistance from Brookmar, the C8 Science Panel obtained an additional IRB approval allowing access to identified data, which facilitates contacting participants for enrollment in follow-up studies.

Implementation

Following input by the settling parties, Brookmar used multiple avenues to publicize the Project. Communications about Project eligibility requirements, enrollment, data collection procedures, timeline, and remuneration included a series of open meetings conducted in five of the six water districts, Project website messages, a phone bank, and press conferences with local media, an important source of information throughout the duration of the Project.

Brookmar also maintained communication with local health care providers. Meetings were conducted to inform the medical community about Project procedures, including medical record requests, as well as the information that participants would be provided pursuant to their Project participation.

Efforts to ensure full access for interested participants included multiple sites, 12-hour daily appointment availability, and disability accommodation including handicap access and

assistance completing the health survey. Brookmar also coordinated remote data collection for those otherwise eligible Class members unable to travel to a data collection site (e.g., those no longer living in the vicinity). For these participants, eligibility documentation was submitted via mail, followed by remote completion of the health survey and a personal telephone interview. These remote participants then completed phlebotomy at an identified, local, accredited laboratory. Of the total participants, approximately 600 participated via these procedures (personal communication, Brookmar).

Brookmar was unable to accommodate participants cognitively unable to complete the survey (or without a representative to accurately complete it on their behalf) or those physically unable to travel to a phlebotomy site. Thus these groups are likely underrepresented among Project participants.

Data Analysis and Reporting

Participants were mailed individualized results for clinical lab tests, including laboratory normal ranges and flags for abnormal findings. For severely abnormal values, emergency flags triggered a personal communication from Brookmar personnel with advice to seek prompt medical attention. Participants also received a report of their PFC values.

Upon completion of the Project, Brookmar filed an electronic dataset with the Wood County Court in May 2008. The dataset included the health survey, clinical laboratory and PFC values, an image of eligibility documents, and record of payment. To protect participant privacy, the presiding judge subsequently sealed the dataset. A mechanism is currently being sought wherein an agency, likely of the federal government, would maintain and make accessible a de-identified dataset for public research use.

The C8 Science Panel is conducting analyses using the Project cross-sectional data collected and is also conducting its own independent, environmental and population-based studies, also financed by the settlement. For consenting participants, the C8 Science Panel is

able to link Project-collected data with follow-up and longitudinal studies. A description of ongoing studies is available on the C8 Science Panel's website (C8 Science Panel Website).

A tissue bank of participant frozen serum was established at West Virginia University in which samples are stored, handled, and accessed in a manner consistent with the IRB protocol governing the Tissue Bank. The sera can be linked to de-identified Project data, and may be used for further studies related to human PFC physiology.

Brookmar contracted with the West Virginia University School of Medicine to report to the general public descriptive summaries of results from the Project. Summary data are reviewable at a website established for that purpose (WVU C8 Health Project Data Hosting Website).

The C8 Science Panel and the WVU Project group are preparing and submitting analyses of associations between PFCs and health outcomes, intended for peer-reviewed journals. These will form part of the evidence that will assist the C8 Science Panel in meeting their Court-appointed obligation to determine "probable links" (see Supplemental File, Note 3) between PFOA exposure and health outcomes.

Data Cleaning

In the first phase of data cleaning, the IT company ensured that question responses were consistent with question "skip patterns" and menu options, as well as ensuring consistent coding and formatting for question responses. For the de-identified dataset, text fields were scrubbed to eliminate potentially identifying information. In the second phase of data cleaning, completed collaboratively by the C8 Science Panel and WVU Project team, continuous variables were examined and decision rules were created for outliers and missing values. Lab-generated error messages for samples that could not be analyzed were deleted and results set to "null". For clinical lab results either lower or higher than the LOD, values were replaced with 50% below or above the lower or upper LOD, respectively.

Though serum samples were analyzed for 10 PFCs, not all PFCs were detectable in all samples tested. Four PFCs (PFHS, PFOA, PFOS, PFNA) were detectable in almost all (>97%) samples; for these PFCs, test results reported as less than the LOD were substituted with 0.25 ng/mL (50% of the lower LOD of 0.5 ng/mL). Three PFCs (PFHxA, PFHpA, PFDA) were detectable in approximately 50% of the samples; results for these PFCs are reported with and/or without substitution for values reported as less than the LOD. Three PFCs (PFPeA, PFUnA, and PFDoA) were detectable in only a negligible portion of the tested samples, and are not reported or included in further analyses. Thus, results reported here include 7 of the 10 tested PFCs (PFHS, PFOA, PFOS, PFNA, PFHxA, PFHpA, PFDA).

Estimation of Participation Rates

Total project participation was estimated by water district as the number of participating residents divided by the total contemporaneous population in that water district. Water district population was estimated using 2005-2006 Census population estimates for block groups, the smallest Census geographic unit that could be accurately identified. Block groups intersecting with water districts were determined, and the population of each block group was apportioned to the water district based on the ratio of water district area to block group area within each block group. The number of participants resident in each water district was based on the assigned water district, that for which the participant presented qualifying eligibility documents, and self-reported residence at the time of enrollment. Participation estimates for each water district was estimated for age and gender strata.

RESULTS

Project enrollment totaled 69,030. Approximately 80% completed registration and the health survey online (personal communication, Brookmar). PFC and clinical laboratory analyses were available for more than 65,000 participants. While children aged <10 years had highest proportion without available blood analyses (almost $\frac{1}{3}$), laboratory data were nevertheless available for more than 3,400 of these children. Consistent with regional demography, more than 97% of participants identified themselves as white and educational attainment and income levels were lower than national averages. Participants ranged in age from 1.5 years to older than 100, with an average age of 39.1 ± 19.9 (standard deviation). (See Supplemental File, Table 1.)

Twenty-six percent of adults (≥ 18 years at enrollment) reported current smoking, and an additional 26% reported former smoking. A substantial proportion of children (63.3%) and adults (69.1%) lacked a regular exercise program. Further, 39% of children were classified as being at-risk or already overweight based on BMI percentile, and 69% of adults were classified as overweight or obese based on BMI. However, as BMI calculations were completed using self-reported height and weight, they may underestimate actual population proportions. These demographic and health risk data are generally consistent with estimates for Appalachia from nationally representative data sources (Halverson et al., 2004). (See Supplemental File, Table 2.)

At the time of enrollment, most participants reported current residence in Ohio (52%) or West Virginia (45%); 63% of participants were resident in a qualifying water district at the time of their participation. Average monthly enrollment in the Project was 5,310, with enrollment peaking in January 2006 (8,003 participants). The largest proportion of participants qualified through Lubeck Public Service District (24.6%), followed by Tupper Plains (20.4%). (See Supplemental File, Table 3.)

As shown in Table 1, an estimated 80.3% of the population resident in the water districts during the enrollment period participated in the Project, with a slightly higher proportion of women compared to men participating. Participation by water district ranged from 70.3% of the resident population in Tupper's Plains to almost 95% in the Village of Pomeroy. The age groups with the lowest estimated participation were the elderly (>80 years of age) and young children (<4 years of age).

Serum analysis results for 10 PFCs (PFPeA, PFHxA, PFHS, PFHpA, PFOA, PFOS, PFNA, PFDA, PFUnA, PFDaA) were available for 66,899 participants. Table 2 summarizes the proportion of tested samples with a detectable PFC concentration and the number of samples for which 50% of the lower LOD was substituted.

Table 3 reports population summary statistics for the seven PFCs, stratified by gender and age groups. Due to population homogeneity (above), stratification by ethnicity was not performed. Patterns by age and gender in the 4 widely detectable PFCs are highlighted in Figure 1. For each, median concentrations were higher in males in most age groups. For PFOA and PFOS, population median concentrations demonstrated a J-shaped pattern, with higher values in younger age groups, lowest values in young- to middle-adult age groups, and highest population concentrations in older adult age groups. For PFHS and PFNA, the highest population median concentrations were observed in children.

Project results for four PFCs (PFHS, PFOA, PFOS, PFNA) are compared to results from the nationally representative NHANES sample in Figure 2. An important difference between NHANES and Project results is the inclusion of children <12 in the Project, although this Project age group is likely to have a minimal impact on overall population results in a sample size exceeding 65,000. For all PFCs except PFOS, serum concentrations reported for the Project exceeded NHANES results. The largest differences were observed for PFOA, where the Project population had more than a 500% (1999-2000) or 700% (2003-2004) larger

geometric mean. Smaller but still substantial differences were also observed for PFHS (57.1% [1999-2000] and 73.6% [2003-2004] larger) and PFNA (178% [1999-2000] and 39% [2003-2004] larger). In contrast, the Project population had a 36.8% (1999-2000) and 7.1% (2003-2004) lower geometric mean for PFOS.

Unadjusted, nonparametric Spearman's rho rank-order correlation analysis was performed for 21 pairings (7 PFCs) for the overall population. In general, correlations between the PFCs were low. Modest correlations (approximately 30%) were observed between the pairings of PFHS-PFOA, PFHS-PFNA, PFOA-PFOS, and PFOS-PFDA. Larger correlations were observed between PFHpA-PFOA (approximately 40%), PFHS-PFOS and PFOS-PFNA (approximately 50%), and PFNA-PFDA (approximately 60%). There were no discernable differences in correlations patterns between adults and children or between genders (not shown). (See Supplemental File, Figure 2.)

Table 4 reports serum PFC concentrations, weighted by age and gender, stratified by qualifying water district. Participants in Little Hocking Water Association had the highest levels of PFOA, more than 70% higher than the next group, participants with private wells. For all PFCs other than PFOA, the 157 participants qualifying through contaminated private wells had the highest serum concentrations. Participants in Lubeck Public Service District had the highest reported values for PFHxA, PFOS, PFNA, and PFDA. The highest values of PFHS were found in participants in the City of Belpre, OH.

Results for the quality assurance analysis are summarized in Table 5. The highest agreements, both intra-lab (within the primary lab) and inter-lab (between the primary and secondary lab), were observed for PFHS, PFOA, PFOS, and PFNA. The median intra-lab difference for PFOA and PFOS was 5.5% and 4.06% respectively, whereas the median inter-lab difference for PFOA and PFOS was 16.7% and 14.01% respectively. The least

agreement, either intra- or inter-lab agreement was observed for PFHxA. For PFHpA and PFDA, intra-lab but not inter-lab agreement was observed.

DISCUSSION

This unique and large survey resulted from the pretrial Settlement Agreement of a class action lawsuit and a Court-supervised health study of a population (n=69,030) exposed to sustained environmental contamination with PFOA. The demographic characteristics and health behaviors of the participants reflect that of the affected, mostly rural, Appalachian communities: predominately white, with lower-than-national-average levels of education and income, and higher rates of obesity and other health risk behaviors such as smoking and inactivity. Challenges posed by the definition of the Class, specifically the prolonged (50 year) exposure period and inclusion of residential, employment, and school-based exposure, preclude an exact determination of the total eligible population. However, a reasonable approximation suggests that 80% of the current population in affected water districts participated in the Project, though 37% of Project participants resided outside an affected water district at the time of their Project enrollment. It is probable that a combination of public concern about chemical contamination and monetary compensation contributed to participation. The high rates of population participation and the high rate (estimated at 80%) of online (versus paper survey) enrollment and completion of the health survey in a rural, poor area may provide useful lessons for future population surveys.

As anticipated, study serum concentrations of PFOA, the identified environmental contaminant, deviated markedly from those of a representative, national sample in all affected water districts. The unadjusted population geometric mean of 28.2 (median 32.91) ng/mL was 6- to 8-fold higher than nationally representative values from the NHANES study. However, observations regarding higher-than-national-sample serum concentrations of PFHS and PFNA, but lower-than-national-sample concentrations for PFOS, were not anticipated. The distribution and pattern of PFHS and PFNA concentrations is not similar to that of PFOA, suggesting a possible exposure source other than the facility identified as the source of PFOA

exposure. Comparisons between these two studies are interpreted within the context of possible differences in laboratory analytic techniques (though both studies used solid-phase extraction followed by high performance liquid chromatography-tandem mass spectrometry) and measurement accuracy across a broad spectrum of concentrations.

Discernible gender differences for PFOA serum levels in most age groups are consistent with national findings in less-exposed populations. The findings of higher serum concentrations of PFCs in children, particularly for PFHS and PFNA, warrant further study. While these findings are unadjusted for potential confounders, higher concentrations in the youngest age groups is counter to traditional expectations of biologic burden paralleling cumulative environmental exposure, and merit further study.

The observation that the highest population burden of PFOA was found in the Little Hocking Water Association district is consistent with water quality measurement reports from the affected water districts (many of which are publically available; also see Supplemental File, Note 2). However, the population PFOA results for Little Hocking are substantially lower than those previously reported in a smaller sample of Little Hocking residents (age and gender adjusted mean of 228 reported here vs. 448 ng/mL; Emmett et al., 2006). While the reasons for these differences are not clear, representativeness of the samples, and study time periods, are possible explanations. The same laboratory performed PFOA analysis in each study.

While the highest serum concentrations of PFOA were observed in Little Hocking, it is interesting that higher burdens of other PFCs were found in other water districts. Investigating the association between water PFC concentrations and serum PFC concentrations, and investigating the distributions of occupational contributions, are beyond the scope of the present report. Further work is underway to model occupational, temporal, spatial, and temporal-spatial variation in water PFC levels, including differences between public water supplies and private wells, and the association with serum PFC levels.

Correlations between the different PFCs were generally modest and without discernable age or gender patterns. Presently, the meaning of these correlations are unclear and will likely need to be interpreted later, within the context of a better understanding of patterns of cumulative exposure, environmental accumulation, and physiological metabolism of these chemicals across the lifespan.

Previous studies have reported on the complexity of PFC determination (van Leeuwen et al., 2006). While intra-lab measurements demonstrated reasonable stability, inter-lab measurements showed larger divergence. It is not surprising that measurements from the Project, which at times processed more than 7,000 samples per month, would not achieve the same level of accuracy as federally funded projects with smaller sample sizes and smaller ranges of exposure. Spearman testing of quality-assurance results demonstrates that rank order is highly preserved for intra- and inter-laboratory comparisons.

The large size of this cohort, together with the broad range of serum PFC values, provides unique opportunities for investigating associations between PFCs and human health. While the prevalence study design inherently limits causal inference, the Project remains the largest and broadest study to date of associations between PFC exposure and human health. Subcohorts from this population, to be followed over time, have been identified and the C8 Science Panel has already begun enrollment in longitudinal studies. A multivariable analysis of factors determining PFOA levels in the population has been conducted and submitted for publication (Steenland et al., in press 2009). Additional targeted analyses investigating associations between PFCs and specific clinical chemistries and disease endpoints are already underway and will be reported elsewhere.

CONCLUSION

The data from the 69,030 C8 Health Project participants provide valuable information on serum PFC concentration, demographic factors, clinical chemistry and self-reported disease in a population with a high participation rate. Ongoing work investigating the inter-relationships between them will provide clues about possible etiologic relationships, within the limitations of the prevalence study design. In addition, they provide a valuable baseline characterization of this population for subsequent, prospective studies.

The results, therefore, have the potential to improve the current understanding of the biology of PFC exposure and are unprecedented among toxic tort settlements, most of which simply provide compensation for the Class without attempting to generate useful health and exposure data or assess health effects. As an innovative effort to gather data on an exposed population, the C8 Health Project can also serve as a model for future legal settlements for populations exposed involuntarily to environmental contaminants.

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Table 2. Availability of Detectable Serum Concentrations for PFCs

	Number of Samples with Detectable Concentration		Number of Samples with Concentration <LOD		Numbers of Samples with Substitution of 50% of LOD (0.25 ng/mL)	
	N	% ^a	N	% ^a	N	% ^a
PFPeA	3247	4.9%	63652	95.2%	0	0.0%
PFHxA	35574	53.2%	31326	46.8%	0	0.0%
PFHS	65499	97.9%	1400	2.1%	1400	2.1%
PFHpA	25095	37.5%	41804	62.5%	0	0.0%
PFOA	66857	99.9%	42	0.1%	42	0.1%
PFOS	66600	99.6%	299	0.5%	299	0.5%
PFNA	65348	97.7%	1551	2.3%	1551	2.3%
PFDA	30996	46.3%	35903	53.7%	0	0.0%
PFUnA	5835	8.7%	61064	91.3%	0	0.0%
PFDoA	488	0.7%	66411	99.3%	0	0.0%

^a Denominator is total possible samples (66,899)

Table 3. Population Serum Concentrations for 7 PFCs (ng/mL)

Age	Gender	PFHxA ^a	PFHxA ^b	PFHS	PFHpA ^a	PFHpA ^b	PFOA	PFOS	PFNA	PFDA ^a	PFDA ^b
< 12 Years	Female	Mean	0.9	1.3	10.6	1.1	73.0	22.6	1.9	0.5	0.7
		Median	0.7	1.0	6.1	0.7	30.7	19.9	1.6	0.5	0.6
		Geometric Mean	0.7	1.1	6.5	0.7	34.8	19.7	1.7	0.4	0.7
		Std. Deviation	0.9	1.0	13.0	1.3	120.1	12.7	1.4	0.3	0.2
	Male	Mean	1.0	1.3	12.6	1.1	82.1	24.6	1.9	0.5	0.7
		Median	0.7	1.0	6.9	0.7	35.1	21.7	1.6	0.5	0.6
		Geometric Mean	0.7	1.1	7.4	0.7	39.1	21.5	1.7	0.4	0.7
		Std. Deviation	1.0	1.0	18.3	1.3	129.1	13.4	1.1	0.3	0.3
	Total	Mean	1.0	1.3	11.6	1.1	77.6	23.6	1.9	0.5	0.7
		Median	0.7	1.0	6.4	0.7	32.6	20.7	1.6	0.5	0.6
		Geometric Mean	0.7	1.1	7.0	0.7	36.9	20.6	1.7	0.4	0.7
		Std. Deviation	1.0	1.0	15.9	1.3	124.9	13.1	1.3	0.3	0.3
12 - 19 Years	Female	Mean	0.8	1.4	6.2	0.7	51.0	20.1	1.4	0.5	0.7
		Median	0.5	1.0	3.7	0.3	22.1	18.0	1.3	0.4	0.6
		Geometric Mean	0.5	1.1	4.0	0.5	25.1	17.6	1.3	0.3	0.7
		Std. Deviation	1.0	1.2	9.5	0.8	85.2	11.0	0.7	0.4	0.3
	Male	Mean	0.9	1.4	8.3	1.0	68.4	23.4	1.6	0.3	0.7
		Median	0.6	1.0	4.9	0.6	30.2	20.5	1.5	0.5	0.7
		Geometric Mean	0.6	1.1	5.3	0.6	33.9	20.6	1.5	0.3	0.7
		Std. Deviation	1.3	1.5	11.8	1.2	104.9	12.7	0.8	0.4	0.3
	Total	Mean	0.9	1.4	7.3	0.9	59.9	21.8	1.5	0.3	0.7
		Median	0.6	1.0	4.3	0.6	25.7	19.3	1.4	0.5	0.6
		Geometric Mean	0.6	1.1	4.6	0.6	29.3	19.1	1.4	0.3	0.7
		Std. Deviation	1.2	1.4	10.8	1.0	96.2	12.0	0.7	0.4	0.3
20 - 39 Years	Female	Mean	0.8	1.4	3.0	0.5	42.3	16.6	1.4	0.3	0.8
		Median	0.3	1.0	2.2	0.3	17.0	14.8	1.2	0.5	0.6
		Geometric Mean	0.5	1.1	2.2	0.4	19.8	14.0	1.2	0.3	0.7
		Std. Deviation	1.0	1.2	3.0	0.6	118.3	9.7	0.8	0.4	0.4
	Male	Mean	1.0	1.5	5.3	0.6	76.5	24.3	1.7	0.4	0.8
		Median	0.6	1.0	3.8	0.3	28.3	22.2	1.6	0.5	0.7
		Geometric Mean	0.6	1.2	3.8	0.4	33.4	20.7	1.6	0.5	0.7
		Std. Deviation	1.4	1.6	7.6	0.7	208.1	12.8	0.8	0.4	0.8
	Total	Mean	0.9	1.4	4.0	0.5	58.1	20.1	1.5	0.6	0.8
		Median	0.5	1.0	2.9	0.3	21.8	18.1	1.4	0.5	0.7
		Geometric Mean	0.6	1.2	2.9	0.4	25.2	16.8	1.4	0.3	0.7
		Std. Deviation	1.2	1.4	5.7	0.7	166.6	11.9	0.8	0.4	0.6
40 - 59 Years	Female	Mean	0.8	1.4	3.3	0.5	80.2	20.8	1.5	0.5	0.8
		Median	0.5	1.0	2.4	0.3	25.7	17.7	1.3	0.3	0.7
		Geometric Mean	0.5	1.1	2.3	0.4	30.4	16.9	1.3	0.4	0.7
		Std. Deviation	1.0	1.1	3.7	0.8	260.7	14.2	0.8	0.4	0.4

Age	Gender		PFHxA ^a	PFHxA ^b	PFHS	PFHpA ^a	PFHpA ^b	PFOA	PFOS	PFNA	PFDA ^a	PFDA ^b
≥ 60 Years	Male	Mean	0.9	1.4	4.7	0.6	1.2	120.4	26.6	1.6	0.5	0.8
		Median	0.5	1.0	3.4	0.3	0.8	37.7	23.5	1.5	0.3	0.7
		Geometric Mean	0.6	1.2	3.5	0.4	1.0	43.8	22.3	1.5	0.4	0.7
		Std. Deviation	1.1	1.2	16.8	0.8	1.2	339.0	16.7	0.9	0.8	1.1
	Total	Mean	0.9	1.4	4.0	0.5	1.2	99.4	23.6	1.6	0.5	0.8
		Median	0.5	1.0	2.9	0.3	0.8	30.7	20.5	1.4	0.3	0.7
		Geometric Mean	0.6	1.1	2.8	0.4	0.9	36.2	19.3	1.4	0.4	0.7
		Std. Deviation	1.0	1.2	11.9	0.8	1.2	301.4	15.7	0.9	0.6	0.9
	Female	Mean	0.8	1.3	4.7	0.7	1.4	107.0	28.2	1.5	0.5	0.8
		Median	0.3	1.0	3.3	0.3	0.9	41.0	24.2	1.3	0.3	0.7
		Geometric Mean	0.5	1.1	3.4	0.4	1.0	44.2	22.9	1.3	0.4	0.7
		Std. Deviation	0.9	1.0	5.3	1.1	1.6	199.9	19.7	0.8	0.4	0.4
Total Population	Male	Mean	0.9	1.5	4.6	0.6	1.3	120.8	30.3	1.5	0.5	0.8
		Median	0.3	1.0	3.4	0.3	0.9	42.8	26.1	1.4	0.3	0.7
		Geometric Mean	0.5	1.2	3.4	0.4	1.0	47.2	24.7	1.3	0.4	0.7
		Std. Deviation	1.1	1.4	5.3	0.9	1.3	394.1	23.2	0.9	0.4	0.5
	Total	Mean	0.8	1.4	4.7	0.6	1.3	113.8	29.2	1.5	0.5	0.8
		Median	0.3	1.0	3.3	0.3	0.9	41.9	25.1	1.4	0.3	0.7
		Geometric Mean	0.5	1.1	3.4	0.4	1.0	45.7	23.7	1.3	0.4	0.7
		Std. Deviation	1.0	1.2	5.3	1.0	1.4	311.7	21.5	0.8	0.4	0.5
	Female	Mean	0.8	1.4	4.3	0.6	1.2	68.8	20.7	1.5	0.5	0.8
		Median	0.5	1.0	2.7	0.3	0.8	23.6	17.6	1.3	0.3	0.7
		Geometric Mean	0.5	1.1	2.8	0.4	1.0	27.9	17.0	1.3	0.4	0.7
		Std. Deviation	1.0	1.1	6.2	0.8	1.2	190.6	14.1	0.8	0.4	0.4
Total Population	Male	Mean	0.9	1.4	5.9	0.7	1.3	98.2	26.0	1.7	0.5	0.8
		Median	0.6	1.0	3.8	0.3	0.9	33.7	22.9	1.5	0.3	0.7
		Geometric Mean	0.6	1.2	4.0	0.4	1.0	39.4	21.9	1.5	0.4	0.7
		Std. Deviation	1.2	1.4	12.8	0.9	1.3	284.3	16.5	0.9	0.6	0.8
	Total	Mean	0.9	1.4	5.1	0.6	1.2	82.9	23.3	1.6	0.5	0.8
		Median	0.5	1.0	3.2	0.3	0.9	28.2	20.2	1.4	0.3	0.7
		Geometric Mean	0.6	1.1	3.3	0.4	1.0	32.9	19.2	1.4	0.4	0.7
		Std. Deviation	1.1	1.3	10.0	0.9	1.2	240.8	15.6	0.9	0.5	0.7

^a Substitution with 50% of LOD for values reported as <LOD^b No substitution for values reported as <LOD

Table 4. Age and Gender Adjusted Serum PFC Concentrations by Water Districts

Water District	Mean (ng/mL)		PFHxA ^a	PFHxA ^b	PFHS	PFHpA ^a	PFHpA ^b	PFOA	PFOS	PFNA	PFDA ^a	PFDA ^b
	Mean (ng/mL)	Std. Error										
City of Belpre (OH)	Mean (ng/mL)	Std. Error	0.86	1.41	5.82	0.64	1.10	42.96	23.18	1.50	0.47	0.73
			0.01	0.02	0.11	0.01	0.02	2.48	0.16	0.01	0.01	0.01
Little Hocking Water Association (OH)	Mean (ng/mL)	Std. Error	0.85	1.39	5.70	1.15	1.86	227.59	23.47	1.60	0.50	0.77
			0.01	0.02	0.09	0.01	0.01	2.03	0.14	0.01	0.01	0.01
Lubeck Public Service District (WV)	Mean (ng/mL)	Std. Error	1.02	1.51	5.58	0.61	1.05	92.36	24.96	1.64	0.55	0.82
			0.01	0.01	0.08	0.01	0.01	1.78	0.12	0.01	0.00	0.01
Mason County (WV)	Mean (ng/mL)	Std. Error	0.72	1.28	4.15	0.38	0.83	16.00	23.01	1.59	0.45	0.72
			0.01	0.02	0.09	0.01	0.02	2.06	0.14	0.01	0.01	0.01
Tuppers Plains (OH)	Mean (ng/mL)	Std. Error	0.84	1.38	4.48	0.43	0.91	42.07	22.29	1.50	0.53	0.74
			0.01	0.02	0.08	0.01	0.02	1.96	0.13	0.01	0.04	0.01
Village of Pomeroy (OH)	Mean (ng/mL)	Std. Error	0.83	1.38	4.25	0.38	0.83	15.96	20.97	1.46	0.47	0.69
			0.02	0.03	0.17	0.01	0.04	3.83	0.25	0.02	0.00	0.02
Private Well (WV or OH)	Mean (ng/mL)	Std. Error	0.65	1.88	9.27	0.82	1.48	132.56	26.15	1.67	0.40	0.81
			0.09	0.16	0.79	0.07	0.14	18.41	1.22	0.07	0.01	0.08

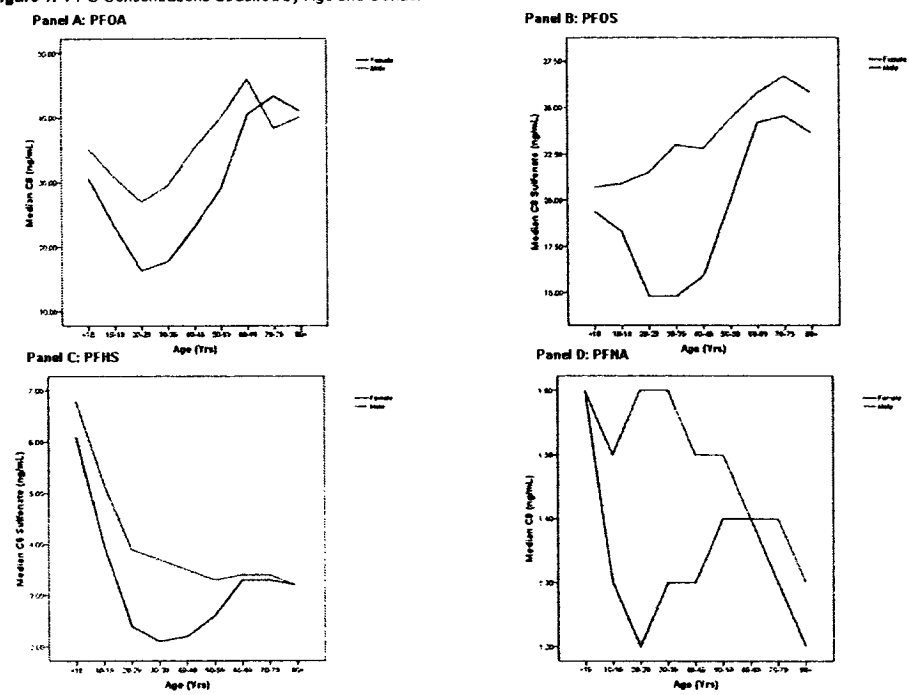
^a Substitution with 50% of LOD for values reported as <LOD^b No substitution for values reported as <LOD

Table 5. Summary of Intra- and Inter-Lab Quality Assurance

		Intra-Lab Comparisons ^a					Inter-Lab Comparisons ^b				
		Primary Lab Test Results (ng/mL)	Primary Lab QA Sample (ng/mL)	Absolute Difference	Percent Difference	Coefficient of Variation	Primary Lab Test Results (ng/mL)	Secondary Lab QA Sample (ng/mL)	Absolute Difference	Percent Difference	Coefficient of Variation
PFHxA	N	664	612	574	574	574	1180	All values reported as <LOD	2316	N/A	2316
	Mean	1.3	1.3	0.3	18.3%	0.1	1.2				
	Median	1.0	0.9	0.1	11.8%	0.1	0.9				
PFHS	N	1236	1241	1234	1234	1234	2561	2319	2316	2316	2316
	Mean	4.6	4.6	0.4	9.4%	0.1	4.9				
	Median	3.1	3.1	0.2	4.9%	0.0	3.5				
PFHpA	N	446	434	410	410	410	1074	583	572	572	572
	Mean	1.2	1.2	0.1	8.5%	0.1	1.5				
	Median	0.9	0.9	0.1	4.2%	0.0	1.0				
PFOA	N	1269	1269	1269	1269	1269	2603	2599	2599	2599	2599
	Mean	77.3	80.4	9.7	10.1%	0.1	134.5				
	Median	25.3	25.3	1.4	5.2%	0.0	43.9				
PFOS	N	1261	1261	1260	1260	1260	2594	2588	2588	2588	2588
	Mean	22.9	23.2	2.0	8.4%	0.1	22.3				
	Median	19.5	19.8	0.7	4.1%	0.0	19.4				
PFNA	N	1246	1243	1240	1240	1240	2539	2329	2314	2314	2314
	Mean	1.6	1.6	0.2	9.0%	0.1	1.6				
	Median	1.4	1.4	0.1	6.5%	0.1	1.4				
PFDA	N	566	570	516	516	516	1200	409	371	371	371
	Mean	0.8	0.8	0.1	6.9%	0.1	0.8				
	Median	0.7	0.7	0.0	0.0%	0.0	0.7				

^a Comparison between matched samples for main test results and blinded, duplicate QA samples sent to the primary lab^b Comparison between matched samples for main test results and blinded, duplicate QA samples sent to the secondary lab

Figure 1. PFC Concentrations Stratified by Age and Gender



254x190mm (96 x 96 DPI)



C8 Science Panel

C8 Science Panel Studies

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Summary of the C8 Science Panel Studies

No single epidemiologic study is sufficient to determine whether C8 damages health. The Science Panel has designed a series of different kinds of studies which are described briefly below. These studies began in late 2006 and are currently ongoing, with results already coming out of them (follow link at left to C8 study results). Results from these studies take from one year to five years from starting. Some of these studies are based on already collected information, while others require collection of new information, including interviews and blood samples. Any information gathered on individuals will be kept confidential by the Science Panel. In many cases a study requires a team of investigators, but in all studies a member of the Science Panel is overseeing the conduct of each specific study.

Choose from the list below to jump to a specific study:

1. [Cholesterol, diabetes, uric acid, and C8 levels among participants in the C8 Health Project](#)
2. [Cross Sectional Study of C8 and Immune Function, Hematopoietic Function, Liver, Kidney, and Endocrine Disorders and Cancer Prevalence - a Prevalence study among participants in the C8 Health Project.](#)
3. [Community follow-up study](#)
4. [Worker follow-up study](#)
5. [The Study of Birth Outcomes in the Mid-Ohio Valley](#)
6. [The Study of Birth Outcomes among the C8 Health Project Participants](#)
7. [The Geographic Patterns of Cancer Study](#)
8. [Short Term Follow-up Study of C8 and Immune, Liver, Kidney and Endocrine Function](#)
9. [Exposure study](#)

10. Half-life study
 11. Study of C8 and Neurobehavioral Development among children from the C8 Health Project
-

1. Cholesterol, diabetes, uric acid, and C8 levels among participants in the C8 Health Project (study completed)

Investigator: Kyle Steenland

Outline of study

The C8 Health Project carried out by Brookmar gathered information from August 2005 to July 2006 and analyzed blood for C8 level, cholesterol and uric acid. Information on self-reported diabetes was also recorded. In three different reports we have looked at the data collected from approximately 55,000 participants over age 20 to determine whether cholesterol and uric acid increased with C8 levels in the blood, and whether those with higher C8 levels in the blood had more diabetes. Analyses were adjusted for other variables which could affect the outcomes, such as age, gender, obesity, and smoking. More detailed results of these studies can be found elsewhere on this website ([link](#)). Briefly, higher C8 was linked to higher cholesterol. Those in the highest 25% of C8 had a 50% increased risk of having high cholesterol (>240 mg/dl) compared to those in the lowest 25% of C8. Higher C8 was also associated with high uric acid, although less dramatically, with about a 30% increased risk of high uric acid for those in the top 25% of C8 vs. the lowest 25%. Higher levels of C8S (C8 with a sulfur group attached - this chemical was not used by Dupont nor released into the environment) was also associated with higher levels of cholesterol and uric acid. Neither self-reported nor medically validated diabetes (adult onset, Type II diabetes) were associated with higher levels of C8.

Study status (June 2009)

These three reports were completed in early 2009. Results of these studies are available [here](#). Briefly, higher C8 was associated with higher cholesterol and higher uric acid, while self-reported diabetes was not linked to C8.

However, these reports do not provide conclusive evidence

exposure to C8 in the past. Comparisons are adjusted for other variables of importance such as age, sex, smoking and weight.

The first phase of analyses uses the C8 concentrations measured at the time of the C8 Health Project. The second phase will allow rates of disease to be analyzed in relation to estimated past C8 exposure. This will focus on diseases including kidney, liver, autoimmune and thyroid diseases and will take place in 2010 once we have integrated historic exposure data and date of disease onset.

Study status (June 2009)

A report on immune biomarkers was submitted to the court in March 2009 and is available [here](#). Results suggested that there may be a relation between immune function and PFOA exposure in exposed persons. However as noted in the report, these results cannot be directly interpreted as indicating an increase in disease risk in this population, but they warrant further investigation which is underway in study #8 "Short Term Follow-up Study of C8 and Immune, Liver, Kidney and Endocrine Function". Other analyses and reports are being prepared and several will be made public during 2009. This work is being done in collaboration with WVU researchers who also hold a copy of the data from the C8 Health Project.

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3. Community follow-up study

Investigator: Kyle Steenland, Emory University

Outline of study

This study is a 4 year follow-up study exploring disease occurrence among adult participants in the C8 Health Project, a survey of about 70,000 community residents (of which 55,00 were above age 20) residing in six water districts conducted from July 2005 - August 2006. Among these, about 40,000 have agreed to participate in the community follow-up study. We are interviewing these 40,000, asking about disease occurrence over time. There are two interviews - one in 2009 and another in 2010.

data from Brookmar's C8 Health Project. Initial data suggests that for approximately half of the currently reported medical conditions, a prior verification exists from Brookmar. We are now seeking medical records from the first several thousand people who have completed interviews.

This study is anticipated to provide important evidence regarding whether there is a probable link between C8 and disease because they are follow-up studies in which it is clear that C8 exposure preceded disease. Taken together with all the other evidence, it will provide the basis for a judgment about a probable link for chronic diseases such as cancer, heart disease, diabetes.

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4. Worker follow-up study

Investigator: Kyle Steenland, Emory University

Outline of study

C8 has been used in the manufacturing of Teflon and other products by DuPont in its West Virginia Washington Works plant. Many workers in the plant have been exposed to C8 over time, at levels higher than the surrounding community. We will conduct a study of disease occurrence among workers at the plant.

DuPont has already assembled a group of approximately 6,000 workers who worked at the Washington Works plant at any time between 1 Jan 1952 and 31 Dec 2001. DuPont has studied the mortality of these workers to determine whether they died of certain diseases at a higher rate than expected. However, studies of death patterns may be less revealing than studies of disease occurrence (fatal and non-fatal disease). We are following these same workers to determine what diseases they have had, including non-fatal as well as fatal disease. We are interested in major diseases such as cancer, heart disease, diabetes.

Workers are currently being interviewed in 2009, and will be interviewed once more with a shorter second interview in 2010. All workers will be free to participate or not. This study will be conducted independently of DuPont, and all information will be kept confidential. No information collected

on any individual worker will be given to DuPont or anyone else. We estimate that about 2/3 of the 6,000 workers are no longer working.

DuPont has developed a way to estimate C8 exposure depending on where a worker has worked, based on C8 blood measurements for approximately 1,000 workers in 2004. DuPont has classified plant jobs into three groups of low, medium, and high exposure to C8. We plan to develop this work further, in order to take into account changes in exposure level over time. We may also create additional exposure categories beyond the low, medium, and high categories.

Interviews are done either via a telephone interview or website interview, and take approximately 30 minutes in length. Interviews cover medical history and other descriptive information such as years of schooling, marital status, smoking history, alcohol history, height, and weight, and medications. Subjects are paid for their time as in the community study.

As part of our study we will determine whether workers have died and if so, cause of death. In addition, we will check the records of the West Virginia and Ohio cancer registries to see who has developed cancer. For those workers who report having had a disease, we will ask permission to review their medical records to confirm this information. For workers who have died we will interview their relatives to find out what diseases they had.

Once all this information has been collected in 2009-2010, we will then compare the rate of new disease occurrence among the workers to that expected based on comparable Americans who had minimal or no exposure to C8. If C8 is related to any health damage, then disease rates among the workers will be higher than those in comparable Americans without exposure. Otherwise they will not.

We will also make some comparisons within the workers based on their level of exposure to C8. We will compare rate of new disease occurrence among those with higher levels of C8 over time to rate among workers with low levels of exposure.

Timeline: data collection now to 2010, results in 2011

Study Status (June 2009)

As of June 2009 approximately 50% of workers had

will help to determine whether mothers with higher estimated C8 exposure had a higher risk of having poor birth outcomes. If exposure to C8 increases the risk of a poor birth outcome, we expect to see worse birth outcomes in women with more C8 exposure. We will make adjustments for other influences on pregnancy health, including mother's age, race, education, marital status, number of previous births, and smoking habits. These characteristics about the mother are listed on the birth certificate. We will also take into account information from the U.S. Census about community characteristics, such as average income, proportion below the poverty level, and average housing value.

Study Status (June 2009)

We have received birth records for selected areas of Ohio and West Virginia from the State Health Departments. For Ohio, we have live birth records for the period from 1989 - 2004. For West Virginia, we have live birth and stillbirth records for the period 1980 - 2004. The mother's residence at the time of birth has been assigned to a location using either address or Zip Code. We are tabulating the U.S. Census data about the community characteristics. Once the data from the Exposure Study are available, we will continue with the analyses. This project has begun and is expected to be completed in 2010 once the estimates of C8 exposure are available from the Exposure Study.

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6. The Study of Birth Outcomes among the C8 Health Project Participants

Investigator: David Savitz

Study Overview

This study will evaluate whether C8 exposure is related to birth outcomes, including miscarriage (pregnancy loss before 20 weeks), preterm birth (early delivery), low birth-weight, average birth-weight, preeclampsia (pregnancy complication with high blood pressure), and birth defects.

The primary data source for this study is the C8 Health Project questionnaire. Women who enrolled in the C8 Health Project in 2005 - 2006 were asked questions about any

pregnancies they had. Because women may not remember exactly how long the pregnancy lasted before the baby was born (important to define preterm birth) or exactly how much a baby weighed at birth (important to define low birth-weight births), we will also use data from birth records kept by the Ohio and West Virginia Health Departments. The birth records are helpful because they have an exact measurement of gestational age and birth-weight. However, we will only be able to use the extra information from the birth certificates for the 70% of women who consented to participate in Science Panel research linking data sources. For all women in the C8 Health Project reporting one or more pregnancies, we will estimate their blood levels at the time of their pregnancies based on where she lived, her water consumption patterns, and her C8 blood level measured at the time of her enrollment. We will get this estimate from another Science Panel study (see the Exposure Study).

The Study of Birth Outcomes among the C8 Health Project Participants will help to determine whether mothers with higher estimated C8 exposure had a higher risk of having poor birth outcomes. If exposure to C8 increases the risk of a poor birth outcome, we expect to see worse birth outcomes in women with more C8 exposure. We will make adjustments for other influences on the health of pregnancy, such as mother's age, race, education, marital status, number of previous births, and smoking habits.

Study Status (June 2009)

An initial analysis of C8 Health Project participants' births was completed and submitted to the court in March 2009. You can view the status report [here](#). For this initial analysis, we restricted to births in the 5 years before the Health Project and used the C8 blood measurement as the measure of exposure. This analysis used only data from the C8 Health Project questionnaire. For the 70% of the women who provided consent, we are linking the women's pregnancies to the Ohio and West Virginia State Health Department birth records for births from 1980-2004. Once the exposure data are available from the Exposure study we will conduct additional analyses that include more births to more women over longer periods of time.

This project has begun and is expected to be completed in 2010 once the estimates of C8 exposure are available from the Exposure Study.

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Virginia has been somewhat delayed by temporary freeze on recruiting staff in the state. Detailed Exposure data are anticipated by February 2010 to allow completion of the analyses.

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8. Short Term Follow-up Study of C8 and Immune, Liver, Kidney and Endocrine Function

Investigator: Tony Fletcher

Outline of study

This study will primarily assess changes of some clinical markers in relation to changes in C8, and detailed indicators of immune status, in a population of 800 of the C8 Health Project participants who agreed to participate in Science Panel studies. We will also assess the risk of common infectious disease and urinary markers indicative of kidney disease.

These participants will be recalled and invited to participate in a second interview and provide a second blood sample, and a urine sample. Statistical analyses will focus on the relationship between trends in C8 serum levels and trends in various clinical markers: of immune, cancer, thyroid, endocrine, kidney and liver function; both C8 and the biomarkers will then have been measured on two occasions. An extended panel of tests for assessing immune function will be given and the association with C8 investigated. In a subset of 400 of these participants, the extent to which C8 modifies the protection afforded by influenza vaccination will be assessed. The incidence of infectious disease in relation to C8 will be assessed by both questionnaire data on self reported disease, including infectious diseases and serological tests of recent latent viral infections, specifically herpes simplex virus (HSV) infection.

The study will provide important new information because of its longitudinal nature; it will consider change in biomarkers over time in relation to changes in C8 levels in the blood. Particular attention will be given to markers of liver, kidney, endocrine and immune function. Additional, more specific immune screening tests will allow the assessment of the

This will let us estimate how much C8 was in the drinking water over time at different locations around the plant.

Taken together with residential histories available from the C8 Health Project, we will be able to estimate how much C8 participants in the C8 Health Project have taken into their bodies from drinking water over time. We will also consider what happens to C8 in the body in order to estimate what C8 levels have been in the blood over time for participants in the C8 Health Project.

Timeline: data collection and analysis 2007-8, results 2009

Study Status (June 2009)

Two unforeseen issues have arisen of importance, namely the way the groundwater flows (speed, direction) and the size of particles emitted from the plant. The groundwater flow is important because we need to understand how long C8 is likely to be present in the groundwater and where it will be in relation to the public wells which pump groundwater. The particle size is important because we need to know how fast the C8 particles emitted into the air will settle on the ground. Both of these have important implications on the amount of C8 expected to be in public water systems.

New data for particle size distributions have been obtained from DuPont. Although the particle size data are sparse, we are using them to develop a better understanding of how C8 is dispersed in the air. With regard to groundwater, we are making significant progress both with regard to groundwater movement and understanding how the Ohio River surface water interacts with the groundwater.

This study is to be completed in early 2010.

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10. Half-life study

Investigators: Kyle Steenland and Barry Ryan, Scott Bartell, Emory University

Outline of study

This project will examine the blood C8 levels of about 70,000 people who live near the Washington Works plant in West

life using these data is 2.3 years. Individual estimated half-lives varied widely in our study; most were between 1.5 and 4.6 years. At this rate about 95% of PFOA would be removed from the body 10 years after exposure ended. However, data from only one year are not sufficient to accurately estimate half-life. We will have a better estimate as time goes on.

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11. Study of C8 and Neurobehavioral Development among children from the C8 Health Project

Investigator: David Savitz

Outline of study

This study will evaluate whether neurobehavioral development is related to C8 exposure among children who participated in the C8 Health Project.

Neurobehavioral development refers to how children learn and behave compared to other children the same age. Some of the children who participated in the C8 Health Project and who will be 6-11 years old during the data collection period will be invited to participate in the Neurobehavioral Development Study. We will use data from the C8 Health Project to identify eligible children, and expect to enroll approximately 550 of them. Only one child per family will be allowed to participate. We will enroll only children who were born and lived their entire lives in one of the affected water districts, and provided consent to participate in Science Panel research. By restricting the study to children who spent their entire lives in only one water district we will have a better idea of how much C8 a child was exposed to over his/her lifetime.

A mobile study van will visit eligible families at their home. Children will be weighed and measured, asked questions, and play reading, word, and number games with a specially trained research assistant to assess their skills. At the same time, the child's mother will be interviewed. The mother will be asked questions about the child's health, behavior, and home environment. Additionally, the mother will take a short standardized test on vocabulary, similarities and block design. With the mother's permission, we will contact the