



"McCrea, Deborah"
<mccrea@taftlaw.com>
10/22/2009 03:27 PM

To NCIC OPPT@EPA
cc "Bilott, Robert A." <bilott@taftlaw.com>

bcc

Subject 10/22/2009 Letter To EPA Docket Center

AR 226 - 3912

09 NOV -2 AM 11:48

RECEIVED

Taft /

Deborah McCrea / Legal Assistant
Taft Stettinius & Hollister LLP
425 Walnut Street, Suite 1800
Cincinnati, Ohio 45202-3957
Tel: 513.381.2838 • Fax: 513.381.0205
www.taftlaw.com / mccrea@taftlaw.com

Internal Revenue Service Circular 230 Disclosure: As provided for in Treasury regulations, advice (if any) relating to federal taxes that is contained in this communication (including attachments) is not intended or written to be used, and cannot be used, for the purpose of (1) avoiding penalties under the Internal Revenue Code or (2) promoting, marketing or recommending to another party any transaction or matter addressed herein.

This message may contain information that is attorney-client privileged, attorney work product or otherwise confidential. If you are not an intended recipient, use and disclosure of this message are prohibited. If you received this transmission in error, please notify the sender by reply e-mail and delete the message and any attachments.



1217_001.pdf

CONTAINS NO CBI

MR 322454

CIPS - AGE 34

CONTAINS NO CBI

CONFIDENTIAL

Taft/

Taft Stettinius & Hollister LLP

425 Walnut Street, Suite 1800 / Cincinnati, OH 45202-3957 / Tel: 513.381.2838 / Fax: 513.381.0205 / www.taftlaw.com
Cincinnati / Cleveland / Columbus / Dayton / Indianapolis / Northern Kentucky / Phoenix / Beijing

ROBERT A. BILOTT
513-357-9638
bilott@taftlaw.com

October 22, 2009

FEDERAL EXPRESS

EPA Docket Center, MC 2822T
U.S. Environmental Protection Agency
EPA West, Room 3334
1301 Constitution Avenue, NW
Washington, D.C. 20004

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

To IRIS Database for PFOA/PFOS:

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

1. Steenland, K., *et al.*, "Association of Perfluorooctanoic Acid and Perfluorooctane Sulfonate With Serum Lipids Among Adults Living Near a Chemical Plant," *Am. J. Epidemiol.* (online Oct. 21, 2009 (doi: 10.1093/aje/kwp279)).

Very truly yours,



Robert A. Bilott

RAB:mdm
Enclosure

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

American Journal of Epidemiology

- [Oxford Journals](#)
- [Medicine](#)
- [American Journal of Epidemiology](#)
- [American Journal of Epidemiology Advance Access](#)
- [10.1093/aje/kwp279](#)

American Journal of Epidemiology Advance Access published online on October 21, 2009
American Journal of Epidemiology, doi:10.1093/aje/kwp279

American Journal of Epidemiology © The Author 2009. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. All rights reserved. For permissions, please e-mail: journals.permissions@oxfordjournals.org.

Original Contribution

Association of Perfluorooctanoic Acid and Perfluorooctane Sulfonate With Serum Lipids Among Adults Living Near a Chemical Plant

Kyle Steenland*, Sarah Tinker, Stephanie Frisbee, Alan Ducatman and Viola Vaccarino

* Correspondence to: Dr. Kyle Steenland, Departments of Environmental and Occupational Health and of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322 (e-mail: nsteenl@sph.emory.edu).

Received for publication January 23, 2009. Accepted for publication August 11, 2009.

ABSTRACT

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are compounds that do not occur in nature but have been widely used since World War II and persist indefinitely in the environment. They are present in the serum of Americans with median levels of 4 ng/mL and 21 ng/mL, respectively. PFOA has been positively associated with cholesterol in several studies of workers. A cross-sectional study of lipids and PFOA and PFOS was conducted among 46,294 community residents aged 18 years or above, who drank water

This Article

- ▶ [Abstract](#) FREE
- ▶ [Full Text \(PDF\)](#)
- ▶ [Alert me when this article is cited](#)
- ▶ [Alert me if a correction is posted](#)

Services

- ▶ [Email this article to a friend](#)
- ▶ [Similar articles in this journal](#)
- ▶ [Similar articles in PubMed](#)
- ▶ [Alert me to new issues of the journal](#)
- ▶ [Add to My Personal Archive](#)
- ▶ [Download to citation manager](#)
- ▶ [Request Permissions](#)
- ▶ [Disclaimer](#)

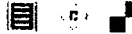
Google Scholar

- ▶ [Articles by Steenland, K.](#)
- ▶ [Articles by Vaccarino, V.](#)

PubMed

- ▶ [PubMed Citation](#)
- ▶ [Articles by Steenland, K.](#)
- ▶ [Articles by Vaccarino, V.](#)

Social Bookmarking

 What's this?

- ▶ [TOP](#)
- ▶ [ABSTRACT](#)
- ▶ [INTRODUCTION](#)
- ▶ [MATERIALS AND METHODS](#)
- ▶ [RESULTS](#)
- ▶ [DISCUSSION](#)
- ▶ [References](#)

contaminated with PFOA from a chemical plant in West Virginia. The mean levels of serum PFOA and PFOS in 2005–2006 were 80 ng/mL (median, 27 ng/mL) and 22 ng/mL (median, 20 ng/mL), respectively. All lipid outcomes except high density lipoprotein cholesterol showed significant increasing trends by increasing decile of either compound; high density lipoprotein cholesterol showed no association. The predicted increase in cholesterol from lowest to highest decile for either compound was 11–12 mg/dL. The odds ratios for high cholesterol (≥ 240 mg/dL), by increasing quartile of PFOA, were 1.00, 1.21 (95% confidence interval (CI): 1.12, 1.31), 1.33 (95% CI: 1.23, 1.43), and 1.40 (95% CI: 1.29, 1.51) and were similar for PFOS quartiles. Because these data are cross-sectional, causal inference is limited. Nonetheless, the associations between these compounds and lipids raise concerns, given their common presence in the general population.

cholesterol; fluorocarbons; lipids; triglycerides; water supply

Abbreviations: CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein; PFHxS, perfluorohexanysulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate



INTRODUCTION

Both perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are perfluorinated compounds that have been found in the blood of virtually all tested Americans over the last decade (1). They do not occur naturally but were introduced in the environment after World War II.

▲	TOP
▲	ABSTRACT
■	INTRODUCTION
▼	MATERIALS AND METHODS
▼	RESULTS
▼	DISCUSSION
▼	References

PFOA is used to polymerize several types of fluoropolymers, which are used in a wide variety of industrial and consumer products. It has been used extensively as a surfactant in the manufacture of Teflon (DuPont, Wilmington, Delaware). PFOA does not break down once in the environment, leading to widespread buildup and bioaccumulation. The half-life of PFOA in humans is estimated to be about 3.8 years (2). PFOA is not metabolized in the body; its tissue distribution in humans is unknown but, on the basis of experiments with rats, it is likely to be present primarily in the liver, kidney, and blood (3). It is not lipophilic, unlike chlorinated hydrocarbons. Most people tested in the United States have measurable PFOA in their serum, with a median level of 4 ng/mL (1), but PFOA is not formed naturally and the industrial or product routes 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 (4). It also causes fetal loss and low birth weight in mice (4) and has been shown to be weakly associated with lower birth weight in humans (5, 6). It has been shown to be associated with increased liver enzymes in 3 occupational studies of workers (7–9) but not in 1 study of community residents exposed via contaminated drinking water (10). It has also been found to be positively correlated with cholesterol in 5 occupational studies (7–9, 11, 12) and 1 community study (10), although in several of these the relation was not statistically significant at the 0.05 level.

A putative mechanism by which PFOA might affect cholesterol in humans is not clear. However, as noted, there is evidence that PFOA is associated with increased liver enzymes, and the liver is an important site of cholesterol synthesis. It is also possible that an increase in fatty acids in the serum leads indirectly to higher cholesterol levels, with no impact on cholesterol production.

PFOS is another fluorocarbon that is widespread in the serum of US residents, with a median serum level of 21 ng/mL, although as with PFOA the source of this exposure is not known (1). Until recently, PFOS has been used in the manufacture of Scotchgard (3M Company, St. Paul, Minnesota), among other products. Its half-life has been estimated at 5.4 years (2). PFOS is also considered an animal carcinogen by the Environmental Protection Agency (4). There is only 1 study of PFOS and cholesterol (13), which found a significant (at the 0.05 level) positive association in a cross-sectional study of workers at 1 plant but not at another plant.

PFOA has been used in the manufacture of fluoropolymers at a chemical plant in Washington, West Virginia, since 1951. In 2001, a group of residents from the Ohio and West Virginia communities in the vicinity of the Washington Works plant filed a class-action lawsuit, alleging health damage due to contamination of human drinking water supplies with PFOA. The pretrial settlement of this lawsuit led to a baseline survey, called the C8 Health Project. This survey was conducted in 2005–2006 and gathered data from 69,000 Ohio and West Virginia residents or former residents who had lived, worked, or gone to school in 6 contaminated water districts surrounding the chemical plant. The C8 Health Project included blood draws and subsequent measurement of serum PFOA and serum PFOS, as well as clinical chemistry including lipids. PFOS has not been used at or emitted by the chemical plant.

The current study is an analysis of these data in adults aged 18 years or older who were not taking cholesterol-lowering medication, with a goal of determining whether there are associations between PFOA or PFOS and lipids. The exposure metric in this study is serum PFOA or PFOS measured in 2005–2006, and the outcomes are concurrent levels of lipids.

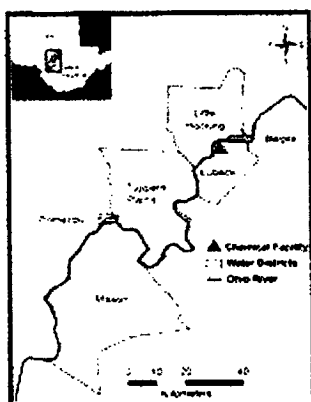
MATERIALS AND METHODS

Study participants

Study subjects participated in the C8 Health Project (2005–2006). The purpose of the C8 Health Project was to collect health data from residents covered under the legal settlement of a class action lawsuit, via written questionnaires and a battery of blood tests, including measurement of serum levels of PFOA and PFOS. Subjects were eligible to participate in the C8 Health Project if they had consumed public drinking water for at least 1 year before December 3, 2004, supplied by any of 6 contaminated water districts, or from a small number of private wells known to be contaminated. The 6 water districts all had documented PFOA contamination of public water at ≥ 0.05 ng/mL. Subjects were eligible if they could document that they had lived, worked, or gone to school in a contaminated water district for at least 1 year. Figure 1 shows the 6 water districts. Subjects were compensated \$400 if they filled out the extensive questionnaire and came to local survey stations to donate a blood sample (30–35 mL). The C8 Health Project collected data on 69,030 subjects, of whom 46,494 were 18 years or older and not taking cholesterol-lowering medication (19% of adults were taking such medication). It is not known what percentage of the eligible population participated, but it is believed to be the majority, given the high interest and the financial incentive. Using census data from 2005, we estimate that 81% of current residents aged 20 years or older participated in the C8 Health Project (14).

- ▲ [TOP](#)
- ▲ [ABSTRACT](#)
- ▲ [INTRODUCTION](#)
- [MATERIALS AND METHODS](#)
- ▼ [RESULTS](#)
- ▼ [DISCUSSION](#)
- ▼ [References](#)

Figure 1. Study area, Ohio and West Virginia, 2005–2006.



View larger version (38K):

[\[in this window\]](#)

[\[in a new window\]](#)

[\[Download PowerPoint slide\]](#)

The Emory University Institutional Review Board approved this study.

Laboratory methods

The analytical method for PFOA and PFOS used in this study has been described in detail previously (15, 16). Briefly, the method utilizes liquid chromatography separation with detection by tandem mass spectrometry. Extraction of the serum samples is done by using acetonitrile. Estimates of precision for PFOA were generally within $\pm 10\%$ for multiple replicates over the range of 0.5–40 ng/mL with a more precise relative precision measure of approximately 1% for highly fortified (10,000 ng/mL) samples. Relative precision estimates for PFOS were similar.

Blood samples were not required to be fasting and were obtained at any time that the participants came to the study site, that is, throughout the course of the day. Serum was separated from red cells, placed in transport tubes, and refrigerated for shipment to the lab. Total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides were measured enzymatically at a large commercial accredited laboratory. Low density lipoprotein (LDL) cholesterol was calculated by the Friedewald equation when triglycerides were less than 400 mg/dL (94% of triglycerides).

Statistical analysis

Analyses were conducted by linear regression in which the outcomes were total cholesterol, LDL cholesterol, HDL cholesterol, the ratio of total cholesterol to HDL cholesterol, triglycerides, and non-HDL cholesterol (equal to total cholesterol – HDL cholesterol). We used (natural) log-transformed values of these variables for all outcomes, which tended to normalize residuals and led to a better goodness of fit as measured by the *R*-square. The improvement was particularly notable for the ratio of total cholesterol to HDL cholesterol and for triglycerides, which had the least normal distributions. For other outcomes, there was only a slight improvement, but we log transformed all outcomes for consistency. The log-transform model, when transformed back to the original scale, results in a multiplicative model in which the effects of PFOA and other covariates multiply the background cholesterol level.

Covariates in the model were chosen because of their established relation to 1 or more lipids (independent of whether they were associated with PFOA), such that they were potentially confounding variables. Covariates included age (8

categories), gender, body mass index (by quartile), education as a measure of socioeconomic status (less than high school, high school, more than high school), smoking (current, former, never), regular exercise (yes/no), and current alcohol consumption (yes/no). For simplicity, we retained the same set of covariates in all models. Covariates chosen in this manner were generally statistically significant predictors of most lipid outcomes, in the anticipated direction. We also considered a variable for fasting in the 6 hours prior to the blood sample (42% had not eaten in the prior 6 hours). This variable had little effect on any outcome other than triglycerides, where fasters had markedly lower triglyceride levels than did nonfasters. Hence, we included this variable in the triglyceride model. We also ran models separately for fasters and nonfasters to determine if the effects of PFOA and PFOS on outcomes differed by fasting status. Finally, we ran models for non-HDL cholesterol as this measure is less susceptible to postprandial effects (17). PFOA and PFOS in all these analyses were considered as categorical (deciles) or continuous (sometimes (natural) log transformed) variables.

In addition to the linear regressions described above, we also ran a logistic model for the dichotomous outcome hypercholesterolemia, which was defined as a cholesterol level of ≥ 240 mg/dL (15% of the population had hypercholesterolemia). In these models, we used quartiles of PFOA (0–13.1, 13.2–26.5, 26.6–66.9, ≥ 67.0 ng/mL) or PFOS (0–13.2, 13.3–19.5, 19.6–28.0, ≥ 28.1 ng/mL), as well as models in which the exposures were continuous.

Graphical representation of the linear regression results focused on the predicted trend in lipids by decile (using the medians of the deciles) of either PFOA or PFOS, given a covariate profile for an average subject. Confidence intervals for predicted values were calculated for the expected population mean cholesterol level (SAS PROC REG, CML option; SAS Institute, Inc., Cary, North Carolina). Tests for linear trend in decile analyses were conducted on the basis of the *P* value for a single unlogged term for either PFOA or PFOS.

RESULTS

Descriptive results

Table 1 provides descriptive statistics on PFOA, PFOS, and outcome variables. As expected, PFOA was highly skewed, with some very high levels, while PFOS was not. Among the outcome variables, triglycerides were the most skewed. Missing data were minimal with the exception of LDL cholesterol for which 7% of subjects were missing, largely because of the exclusion of subjects with high triglycerides (>400 mg/dL). PFOA and PFOS were moderately correlated, with a Spearman correlation coefficient of 0.32.

▲	TOP
▲	ABSTRACT
▲	INTRODUCTION
▲	MATERIALS AND METHODS
•	RESULTS
▼	DISCUSSION
▼	References

View this table: Table 1. Descriptive Statistics and PFOA, PFOS, and Outcome Variables ($n = 46,294$), Ohio
[\[in this window\]](#) and West Virginia, 2005–2006
[\[in a new window\]](#)

Table 2 gives descriptive statistics for other variables in the model, along with the percentage of missing data for each variable.

View this table: Table 2. Descriptive Statistics on Covariates, Ohio and West Virginia, 2005–2006

[\[in this window\]](#)

[\[in a new window\]](#)

Linear regression results; categorical exposure

A largely monotonic increase in log cholesterol with each decile of PFOA or PFOS was observed (Table 3; Figures 2 and 3). For both perfluorinated compounds, the exposure-response slope appears to decrease somewhat after about 40 ng/mL, although for PFOS this tendency is driven by only the last data point. The models each explained 14% of the variance of log cholesterol. Tests for linear trend were highly significant (Table 4).

View this table: Table 3. Regression Results for Total Cholesterol With Deciles of PFOA, Ohio and West

[\[in this window\]](#)

[\[in a new window\]](#)

Virginia, 2005–2006^a

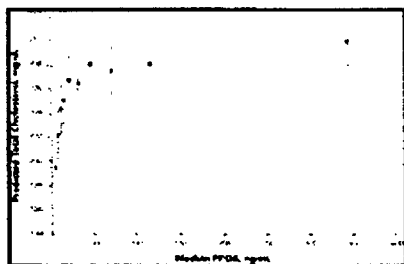


Figure 2. Total cholesterol by decile of perfluorooctanoic acid (PFOA), with 95% confidence intervals, Ohio and West Virginia, 2005–2006. The model was adjusted for covariates. The x-axis uses medians of PFOA deciles. Predicted cholesterol levels are based on an "average" subject with the following characteristics: age 60–69 years, male gender, not taking cholesterol-lowering medication, never smoked, high school diploma, does not participate in regular exercise, does not drink alcohol, and body mass index between 24 and 27 kg/m². Confidence intervals are based on the predicted population mean given those covariate levels.

View larger version (6K):

[\[in this window\]](#)

[\[in a new window\]](#)

[\[Download PowerPoint slide\]](#)

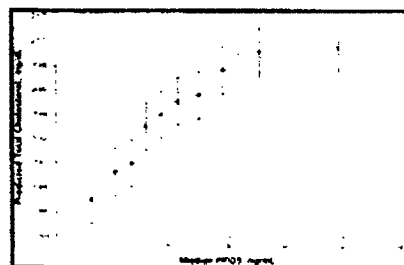


Figure 3. Total cholesterol by decile of perfluorooctane sulfonate (PFOS), with 95% confidence intervals, Ohio and West Virginia, 2005–2006. The model was adjusted for covariates. The x-axis uses medians of PFOS deciles. Predicted cholesterol levels are based on an "average" subject with the following characteristics: age 60–69 years, male gender, not taking cholesterol-lowering medication, never smoked, high school diploma, does not participate in regular exercise, does not drink alcohol, and body mass index between 24 and 27 kg/m². Confidence intervals are based on the predicted population mean given those covariate levels.

View larger version (6K):

[\[in this window\]](#)

[\[in a new window\]](#)

[\[Download PowerPoint slide\]](#)

perfluorohexanysulfonate (PFHxS), for which we had almost complete data. These compounds are also present in the environment; they are not metabolites of PFOA and PFOS in the body. Both compounds were present at low levels in 99% of our population (mean PFNA, 1.6 ng/mL (standard deviation, 0.8); mean PFHxS, 5.1 ng/mL (standard deviation, 10.0)). Like PFOA and PFOS, both showed a monotonic increase in cholesterol by increasing decile of each perfluorinated compound. In part, a parallel exposure-response pattern would be expected because both PFNA and PFHxS are, in turn, correlated with PFOA and PFOS (PFNA Spearman correlations = 0.31 and 0.55 with PFOA and PFOS, respectively; PFNA Spearman correlations = 0.31 and 0.47 with PFOA and PFOS, respectively), making it difficult to sort out the role of each specific perfluorinated compound.

We conducted supplementary analyses to explore possible interactions with gender and age, as well as the possible role of body mass index as an intermediate variable. We ran separate models for men and women for total cholesterol and PFOA or PFOS. Both sexes show monotonic increases in cholesterol with increases in both perfluorinated compounds, similar to the combined analyses. A test of interaction between gender and both log PFOA and log PFOS was not significant ($P = 0.16$ and $P = 0.44$, respectively). Similarly, we modeled interaction terms for categorical age and log PFOA and PFOS. An F test comparing the full model with interaction terms with a reduced model without them was not significant for either exposure ($P = 0.14$ for both PFOA and PFOS), indicating slight interaction with age. We also ran models with or without body mass index in the model, under the hypothesis that body mass index might be an intermediate variable that should not be included in the model. Models without body mass index reduced the exposure coefficient for log PFOA by 8% and that for log PFOS by 2%.

We also ran an analysis including all subjects regardless of whether they were taking cholesterol medication, where the outcome was log PFOA (or log PFOS), and the predictor of interest was cholesterol medication. The motivation for this analysis was to assess whether taking cholesterol medication would be associated with lower PFOA, which might argue for "reverse causality" in that a decrease in cholesterol might lead to a decrease in PFOA. The model for log PFOA was taken from previous work (14) and included strong predictors including residential area and whether subjects worked at DuPont, as well as gender, age, body mass index, race, and other variables; this model explained 55% of the variance in log PFOA. Those taking cholesterol medication did, indeed, have a significantly lower log PFOA, but the effect was very modest (a decrease of only 4%), with statistical significance primarily a function of the large sample size. There was no difference in PFOS levels between those taking and not taking medication.

► DISCUSSION

PFOA has been found to be positively correlated with cholesterol in 5 occupational studies (7–9, 11, 12) and 1 community study (10), although in several of these the relation was not statistically significant at the 0.05 level. All of these studies except 1 were cross-sectional. Many showed a positive relation with other lipids, with the exception of HDL cholesterol.

- ▲ [TOP](#)
- ▲ [ABSTRACT](#)
- ▲ [INTRODUCTION](#)
- ▲ [MATERIALS AND METHODS](#)
- ▲ [RESULTS](#)
- [DISCUSSION](#)
- ▼ [References](#)

These findings of increased cholesterol in humans contradict what would be expected from animal studies. In animals, PFOA is a strong peroxisome proliferator-activated receptor- α in the liver, and this proliferation has been shown to alter lipid metabolism, resulting in decreases, not increases, in serum lipids (3, 18). However, it is not known if this mechanism is relevant to humans, where peroxisome proliferation is generally less apparent (19).

Our findings are broadly consistent with those from prior studies, using the largest data set to date. Both PFOA and PFOS showed largely consistent positive trends with all lipids except HDL cholesterol. The predicted increase in total cholesterol from lowest to highest decile of PFOA and PFOS was about 11–12 mg/dL. Analogously, the odds of high cholesterol (≥ 240 mg/dL) increased 40%–50% from the lowest to the highest quartile of PFOA and PFOS serum levels. These differences are important when considering the large populations potentially affected. For example, in the Framingham population, high cholesterol (> 240 mg/dL vs. < 200 mg/dL) resulted in a relative risk of coronary heart disease of about 1.8 (20). The finding that both PFOA (present at levels considerably above the US background) and PFOS (present at US background levels) were correlated independently with lipid levels suggests that perfluorinated compounds in general may show such associations.

The ratio of total cholesterol to HDL cholesterol also showed positive consistent trends in our data with both PFOS and PFOA. The ratio of total cholesterol to HDL cholesterol has been considered a better predictor of heart disease than total cholesterol itself, and there is continued evidence that this remains so (21). Recently, the ratio of LDL cholesterol to HDL cholesterol has been advocated as the best predictor of heart disease (22). The latter measure is highly correlated in our data to the ratio of total cholesterol to HDL cholesterol (Spearman correlation = 0.94).

Interpretation of these data is made difficult by our cross-sectional design, which prohibits knowing whether an increase in cholesterol followed an increase in PFOA or PFOS. The mechanism by which these perfluorinated compounds might be related to cholesterol in humans is not known. Perfluorinated compounds are not lipophilic. However, it is possible that both cholesterol and the perfluorinated compounds are correlated with a third unknown substance that increases with lipids, for example, and it is even possible that increased lipids could lead to increased retention of PFOA/PFOS in the serum, that is, exhibiting "reverse causality." Our analysis of PFOA levels in those taking cholesterol medications did not provide much evidence for reverse causality; while those on medication had lower PFOA, the decrease was only 4%. We will investigate further whether there is a casual relation between PFOA and cholesterol via a follow-up study of a subsample of this population in which we will retest subjects for cholesterol and PFOA/PFOS (refer to c8sciencepanel.org). PFOA levels are expected to have dropped because of filtration of the public water in 2005–2006. If cholesterol levels are unchanged when PFOA has decreased significantly, this would be evidence against causality, at least in terms of a short-term causal effect.

Another limitation of our analysis is the lack of a measure of cumulative exposure to PFOA or PFOS. We are in the process of estimating such measures in a separate project, using PFOA emissions from the plant over time, combined with residential history, data on wind patterns and groundwater flow, and pharmacokinetic modeling (refer to c8sciencepanel.org). Results from this project are not yet available.

It should be noted that, although PFOA and PFOS are highly significant predictors of lipid levels (our study had high power to detect statistically significant differences, compared with prior smaller studies), the perfluorinated compounds themselves did not explain a large portion of the variance in lipids. For total cholesterol, the most important predictors were age, gender, and body mass index, not serum levels of PFOA or PFOS.

Despite the caveats above, our findings are a cause for concern, given that both PFOA and PFOS are widespread in the serum of virtually all Americans and are common in many countries worldwide (23). If a causal relation between perfluorinated compound levels and cholesterol exists, there could be potentially serious consequences in the form of increased risk of cardiovascular disease. Published data to date are inadequate to establish whether PFOA increases the

risk of heart disease. Existing studies have been restricted to mortality studies of US worker populations (24, 25), with limited sample size and without clear results. We are conducting a longitudinal study of the population studied here to further investigate a possible relation between PFOA and PFOS and cardiovascular and other diseases (refer to c8sciencepanel.org for details).

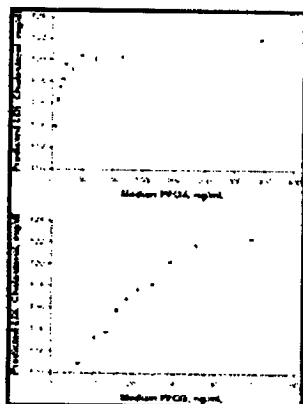


Figure 5. Increase in low density lipoprotein (LDL) cholesterol by perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), Ohio and West Virginia, 2005–2006. The model was adjusted for covariates. The x-axis uses medians of fluorocarbon deciles. Predicted cholesterol levels are based on an "average" subject with the following characteristics: age 60–69 years, male gender, not taking cholesterol-lowering medication, never smoked, high school diploma, does not participate in regular exercise, does not drink alcohol, and body mass index between 24 and 27 kg/m². Confidence intervals are based on the predicted population mean given those covariate levels.

View larger version (9K):

[\[in this window\]](#)

[\[in a new window\]](#)

[\[Download PowerPoint slide\]](#)

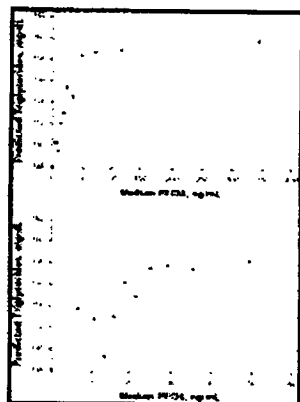


Figure 6. Increase in triglycerides by perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), Ohio and West Virginia, 2005–2006. The model was adjusted for covariates. The x-axis uses medians of fluorocarbon deciles. Predicted cholesterol levels are based on an "average" subject with the following characteristics: age 60–69 years, male gender, not taking cholesterol-lowering medication, never smoked, high school diploma, does not participate in regular exercise, does not drink alcohol, and body mass index between 24 and 27 kg/m². Confidence intervals are based on the predicted population mean given those covariate levels. This model contained an additional variable for not having eaten in the 6 hours before blood draw; the figure is for an "average" subject who had not eaten in the past 6 hours.

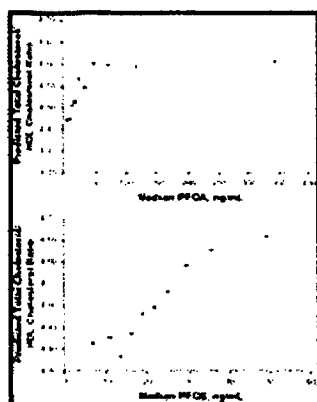
View larger version (9K):

[\[in this window\]](#)

[\[in a new window\]](#)

[\[Download PowerPoint slide\]](#)

Figure 7. Increase in total cholesterol/high density lipoprotein (HDL) cholesterol ratio by perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), Ohio



and West Virginia, 2005–2006. The model was adjusted for covariates. The x-axis uses medians of fluorocarbon deciles. Predicted cholesterol levels are based on an "average" subject with the following characteristics: age 60–69 years, male gender, not taking cholesterol-lowering medication, never smoked, high school diploma, does not participate in regular exercise, does not drink alcohol, and body mass index between 24 and 27 kg/m². Confidence intervals are based on the predicted population mean given those covariate levels.

[View larger version \(10K\):](#)

[\[in this window\]](#)

[\[in a new window\]](#)

[\[Download PowerPoint slide\]](#)

ACKNOWLEDGMENTS

Author affiliations: Rollins School of Public Health, Emory University, Atlanta, Georgia (Kyle Steenland, Sarah Tinker, Viola Vaccarino); Department of Community Medicine, West Virginia University School of Medicine, Parkersburg, West Virginia (Stephanie Frisbee, Alan Ducatman); and Cardiology Department, Emory School of Medicine, Emory University, Atlanta, Georgia (Viola Vaccarino).

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

The authors are grateful for helpful comments from Tony Fletcher and David Savitz.

Conflict of interest: none declared.

References

1. Calafat AM, Wong LY, Kuklenyik Z, et al. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. *Environ Health Perspect* (2007) 115(11):1596–1602. [\[Web of Science\]](#) [\[Medline\]](#)
2. Olsen GW, Burris JM, Ehresman DJ, et al. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect* (2007) 115(9):1298–1305. [\[Web of Science\]](#) [\[Medline\]](#)

[▲ TOP](#)
[▲ ABSTRACT](#)
[▲ INTRODUCTION](#)
[▲ MATERIALS AND METHODS](#)
[▲ RESULTS](#)
[▲ DISCUSSION](#)
[• References](#)

3. Kennedy GL Jr, Butenhoff JL, Olsen GW, et al. The toxicology of perfluorooctanoate. *Crit Rev Toxicol* (2004) 34(4):351–384.[CrossRef][Web of Science][Medline]
4. Draft risk assessment of the potential human health effects associated with exposure to perfluorooctanoic acid and its salts. (2005) Washington, DC: Risk Assessment Division, Office of Pollution Prevention and Toxics, Environmental Protection Agency. (www.epa.gov/oppt/pfoa/pubs/pfoarisk.pdf).
5. Fei C, McLaughlin JK, Tarone RE, et al. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environ Health Perspect* (2007) 115(11):1677–1682.[Web of Science][Medline]
6. Apelberg BJ, Witter FR, Herbstman JB, et al. Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environ Health Perspect* (2007) 115(11):1670–1676.[Web of Science][Medline]
7. Sakr CJ, Kreckmann KH, Green JW, et al. Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonium perfluorooctanoate or APFO) as part of a general health survey in a cohort of occupationally exposed workers. *J Occup Environ Med* (2007) 49(10):1086–1096.[Web of Science][Medline]
8. Sakr CJ, Leonard RC, Kreckmann KH, et al. Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. *J Occup Environ Med* (2007) 49(8):872–879.[CrossRef][Web of Science][Medline]
9. Olsen GW, Zobel LR. Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical production workers. *Int Arch Occup Environ Health* (2007) 81(7):231–246.[CrossRef][Web of Science][Medline]
10. Emmett EA, Zhang H, Shofer FS, et al. Community exposure to perfluorooctanoate: relationships between serum levels and certain health parameters. *J Occup Environ Med* (2006) 48(8):771–779.[CrossRef][Web of Science][Medline]
11. Olsen GW, Burris JM, Burlew MM, et al. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. *Drug Chem Toxicol* (2000) 23(4):603–620.[CrossRef][Web of Science][Medline]
12. Costa G, Sartori S, Consonni D. Thirty years of medical surveillance in perfluorooctanoic acid production workers. *J Occup Environ Med* (2009) 51(3):364–372.[CrossRef][Web of Science][Medline]
13. Olsen GW, Burris JM, Mandel JH, et al. Serum perfluorooctane sulfonate and hepatic and lipid clinical chemistry tests in fluorochemical production employees. *J Occup Environ Med* (1999) 41(9):799–806.[Web of Science][Medline]
14. Steenland K, Jin C, MacNeil J, et al. Predictors of PFOA levels in a community surrounding a chemical plant. *Environ Health Perspect* (2009) 117(7):1083–1088.[Web of Science][Medline]
15. Flaherty JM, Connolly PD, Decker ER, et al. Quantitative determination of perfluorooctanoic acid in serum and plasma by liquid chromatography tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. (2005) 819(2):329–338.[CrossRef][Web of Science][Medline]
16. Longnecker MP, Smith CS, Kissling GE, et al. An interlaboratory study of perfluorinated alkyl compound levels in human plasma. *Environ Res*. (2008) 107(2):152–159.[Medline]
17. Frost PH, Havel RJ. Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol* (1998) 81(4A):26B–31B.[CrossRef][Web of Science][Medline]
18. Loveless SE, Finlay C, Everds NE, et al. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). *Toxicology* (2006) 220(2-3):203–217.[CrossRef][Web of Science][Medline]
19. DeWitt JC, Shnyra A, Badr MZ, et al. Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator-activated receptor alpha. *Crit Rev Toxicol* (2009) 39(1):76–94.[CrossRef][Web of Science][Medline]
20. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation* (1998) 97(18):1837–1847.[Abstract/Free Full Text]
21. Kastelein JJ, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation* (2008) 117(23):3002–3009.[Abstract/Free Full Text]
22. Fernandez ML, Webb D. The LDL to HDL cholesterol ratio as a valuable tool to evaluate coronary heart disease

- risk. *J Am Coll Nutr* (2008) 27(1):1–5. [[Abstract/Free Full Text](#)]
23. Kannan K, Corsolini S, Falandysz J, et al. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. *Environ Sci Technol* (2004) 38(17):4489–4495. [[Medline](#)]
 24. Leonard RC, Kreckmann KH, Sakr CJ, et al. Retrospective cohort mortality study of workers in a polymer production plant including a reference population of regional workers. *Ann Epidemiol* (2008) 18(1):15–22. [[CrossRef](#)][[Web of Science](#)][[Medline](#)]
 25. Gilliland FD, Mandel JS. Mortality among employees of a perfluorooctanoic acid production plant. *J Occup Med* (1993) 35(9):950–954. [[CrossRef](#)][[Web of Science](#)][[Medline](#)]

 [CiteULike](#)  [Connotea](#)  [Del.icio.us](#) [What's this?](#)

This Article

- ▶ [Abstract](#) FREE
- ▶ [Full Text \(PDF\)](#)
- ▶ [Alert me when this article is cited](#)
- ▶ [Alert me if a correction is posted](#)

Services

- ▶ [Email this article to a friend](#)
- ▶ [Similar articles in this journal](#)
- ▶ [Similar articles in PubMed](#)
- ▶ [Alert me to new issues of the journal](#)
- ▶ [Add to My Personal Archive](#)
- ▶ [Download to citation manager](#)
- ▶ [Request Permissions](#)
- ▶ [Disclaimer](#)

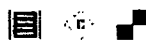
Google Scholar

- ▶ [Articles by Steenland, K.](#)
- ▶ [Articles by Vaccarino, V.](#)

PubMed

- ▶ [PubMed Citation](#)
- ▶ [Articles by Steenland, K.](#)
- ▶ [Articles by Vaccarino, V.](#)

Social Bookmarking


[What's this?](#)

Online ISSN 1476-6256 - Print ISSN 0002-9262
Copyright © 2009 Johns Hopkins Bloomberg School of Public Health
Oxford Journals Oxford University Press

- [Site Map](#)
- [Privacy Policy](#)

- [Frequently Asked Questions](#)

Other Oxford University Press sites: [Oxford University Press](#)



American Journal of Epidemiology

- [Oxford Journals](#)
- [Medicine](#)
- [American Journal of Epidemiology](#)
- [American Journal of Epidemiology Advance Access](#)
- Pp. kwp279v1-kwp279

[Return to article](#)

Table 1. Descriptive Statistics and PFOA, PFOS, and Outcome Variables ($n = 46,294$), Ohio and West Virginia, 2005–2006

Variable	Mean (SD)	Median	Range	% Missing
PFOA, ng/mL	80.3 (236.1)	26.6	0.25–17,556.6	<1
PFOS, ng/mL	22.4 (14.8)	19.6	0.25–759.2	<1
Total cholesterol, mg/dL	199.0 (41.9)	196.0	35–685	<1
HDL cholesterol, mg/dL	50.1 (14.6)	48.0	6–172	<1
LDL cholesterol, mg/dL	114.7 (34.3)	112.0	0–458	6.5
Triglycerides, mg/dL	179.8 (144.6)	143.0	19–4,560	<1
Total cholesterol/HDL cholesterol ratio	4.3 (1.5)	4.0	1–69	<1
Non-HDL-C, mg/dL	148.9 (42.4)	146	28–587	<1

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; non-HDL-C, total cholesterol – HDL cholesterol; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; SD, standard deviation.

[Return to article](#)

Online ISSN 1476-6256 - Print ISSN 0002-9262

Copyright © 2009 Johns Hopkins Bloomberg School of Public Health

Oxford Journals Oxford University Press

- [Site Map](#)
- [Privacy Policy](#)

American Journal of Epidemiology

- [Oxford Journals](#)
- [Medicine](#)
- [American Journal of Epidemiology](#)
- [American Journal of Epidemiology Advance Access](#)
- Pp. kwp279v1-kwp279

► [Return to article](#)

Table 2. Descriptive Statistics on Covariates, Ohio and West Virginia, 2005–2006

Variable	No.	% of Total
Age, years		
18–29	12,067	26.1
30–39	10,058	21.7
40–49	10,493	22.7
50–59	7,527	16.3
60–69	3,801	8.2
70–79	1,728	3.7
≥80	620	1.3
Gender		
Female	24,968	53.9
Male	21,326	46.1
Smoking		
Current smoker	12,720	27.5
Former smoker	10,677	23.1
Nonsmoker	22,787	49.2
Missing	110	0.2
Education		
Less than 12 years	5,470	11.8
High school diploma or GED certificate	18,960	41.0
Some college	15,450	33.4

Bachelor's degree or higher	6,171	13.3
Missing	243	0.5
Regular exerciser		
Yes	14,345	31.0
No	31,949	69.0
Alcohol consumption		
Current drinker	23,591	51.0
No current drinking	22,703	49.0
Body mass index, kg/m ²		
<24.02	12,685	27.4
24.02–27.45	11,612	25.1
27.46–31.90	10,892	23.5
≥31.91	10,604	22.9
Missing	501	1.1

Abbreviation: GED, General Educational Development.

▶ [Return to article](#)

Online ISSN 1476-6256 - Print ISSN 0002-9262

Copyright © 2009 Johns Hopkins Bloomberg School of Public Health

Oxford Journals Oxford University Press

- [Site Map](#)
- [Privacy Policy](#)
- [Frequently Asked Questions](#)

Other Oxford University Press sites: Oxford University Press



American Journal of Epidemiology

- [Oxford Journals](#)
- [Medicine](#)
- [American Journal of Epidemiology](#)
- [American Journal of Epidemiology Advance Access](#)
- Pp. kwp279v1-kwp279

► [Return to article](#)

Table 3. Regression Results for Total Cholesterol With Deciles of PFOA, Ohio and West Virginia, 2005–2006^a

Variable	Regression Coefficient ^b (SE)	P Value
PFOA decile		
1	Referent	
2	0.01 (0.004)	0.0026
3	0.02 (0.004)	<0.0001
4	0.03 (0.004)	<0.0001
5	0.04 (0.004)	<0.0001
6	0.03 (0.004)	<0.0001
7	0.04 (0.004)	<0.0001
8	0.04 (0.004)	<0.0001
9	0.04 (0.004)	<0.0001
10	0.05 (0.004)	<0.0001
Age, years		
18–29	Referent	
30–39	0.08 (0.003)	<0.0001
40–49	0.13 (0.003)	<0.0001
50–59	0.16 (0.003)	<0.0001
60–69	0.16 (0.004)	<0.0001
70–79	0.13 (0.005)	<0.0001
≥80	0.11 (0.008)	<0.0001
Male gender	–0.03 (0.002)	<0.0001

Smoking		
Never smoked	Referent	
Former smoker	0.002 (0.002)	0.3785
Current smoker	0.01 (0.002)	<0.0001
Less than 12 years	Referent	
Education		
High school diploma or GED certificate	0.01 (0.003)	0.0079
Some college	0.002 (0.003)	0.4429
Bachelor's degree or higher	0.03	0.4791
Participates in regular exercise	-0.01 (0.002)	<0.0001
Currently drinks alcohol	0.01 (0.002)	<0.0001
Body mass index, kg/m²		
<24.02	Referent	
24.02–27.45	0.06 (0.003)	<0.0001
27.46–31.90	0.08 (0.003)	<0.0001
≥31.91	0.07 (0.003)	<0.0001

Abbreviations: GED, General Educational Development; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; SE, standard error.

^a Coefficients for PFOS by decile in an analogous model were 0.01, 0.01, 0.03, 0.03, 0.04, 0.04, 0.05, 0.06, 0.06.

^b Change in natural log of total cholesterol.

▶ [Return to article](#)

Online ISSN 1476-6256 - Print ISSN 0002-9262
 Copyright © 2009 Johns Hopkins Bloomberg School of Public Health
 Oxford Journals Oxford University Press

- [Site Map](#)
- [Privacy Policy](#)
- [Frequently Asked Questions](#)