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12/14/2009 03:38 PM

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

Subject 12/14/2009 Letter To EPA Docket Center

A1226-3921

09 DEC 14 11:06 AM

Taft /

Deborah McCrea / Legal Assistant
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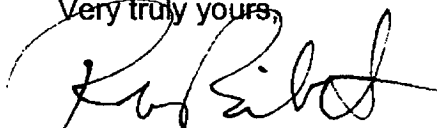
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December 14, 2009
Page 2

5. 10/30/09 Letter from Perry Cohn, Ph.D., MPH, to ATSDR with New Jersey Department of Health and Senior Services' "Comments on Draft Perfluoroalkyls Toxicological Profile";
6. 10/27/09 Letter from David G. Gray, Ph.D., Tetra Tech Inc., to ATSDR with "Comments on Draft Toxicological Profile for Perfluoroalkyls";
7. 10/30/09 Comments of Olga V. Naidenko, Ph.D., Environmental Working Group, on ATSDR draft Toxicological Profile for Perfluoroalkyls; and
8. 10/30/09 and 11/3/09 Letters from Robert A. Bilott to ATSDR with Comments on Draft Toxicological Profile for Perfluoroalkyls.

Very truly yours,

A handwritten signature in black ink, appearing to read "R. Bilott", written over the closing text.

Robert A. Bilott

RAB:mdm

Enclosures

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)

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ROBERT A. BILOTT
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December 14, 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. 10/30/09 Letter from James Kelly, M.S., to ATSDR with Minnesota Department of Health's "Comments on Draft Toxicological Profile for Perfluoroalkyls";
2. 8/31/09 Letter from Henry A. Spiller, MS, D.ABAT, to ATSDR with Kentucky Regional Poison Center's "Comments on Toxicological Profile for Perfluoroalkyls";
3. 10/29/09 Letter from Suzanne E. Fenton, Ph.D., of U.S. Department of Health & Human Services, Public Health Service, National Institutes of Health, National Institute of Environmental Health Sciences, to ATSDR Re: "Comments on ATSDR Draft Toxicological Profile on Perfluoroalkyls";
4. 10/30/09 and 11/2/09 Letters from Gloria B. Post, Ph.D., DABT, to ATSDR with New Jersey Department of Environmental Protection's "Comments on Draft Toxicological Profile for Perfluoroalkyls";



Protecting, maintaining and improving the health of all Minnesotans

October 30, 2009

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mail Stop F-62
Atlanta, Georgia 30333

RE: Comments on Draft Toxicological Profile for Perfluoroalkyls

Dear Sir/Madam:

The Minnesota Department of Health (MDH) is pleased to provide the attached comments on the Agency for Toxic Substances and Disease Registry's (ATSDR) Draft Toxicological Profile for Perfluoroalkyls, dated May 2009. MDH has had extensive experience with perfluoroalkyls (a.k.a. perfluorochemicals, or PFCs) due to 3M's long history of PFC manufacture and waste disposal in Minnesota. These activities have resulted in contamination of groundwater, drinking water, biota, and other environmental media. In response, MDH has developed health-based exposure limits, conducted health assessments documented in ATSDR-approved Health Consultations and Public Health Assessments, and conducted other relevant studies.

If you have any questions regarding these comments, please contact Helen Goeden (651-201-4904; helen.goeden@state.mn.us) or myself at 651-201-4910 or james.kelly@state.mn.us.

Sincerely,

A handwritten signature in black ink, appearing to read "James Kelly", is written over a horizontal line.

James Kelly, M.S.
Research Scientist
Site Assessment and Consultation Unit
Environmental Health Division

Encl.

General Comments:

- 1) The draft document represents a good attempt at compiling a large amount of information. However, interpretation of the data (i.e., what does this potentially mean for human health) is limited and needs to be expanded.
- 2) Since multiple chemicals are contained within this review it can be rather confusing. Authors should consider including a subheading for each PFC, as appropriate, under each health effect section.
- 3) The draft document needs to be updated to include numerous papers that have been published since the literature review for this draft was conducted. In particular, the recently published results from the human C8 Study regarding cholesterol, uric acid and immunological effects need to be included. In addition, an updated study of mortality in PFC workers was recently published (Lundin et al 2009).

It is also not clear why some papers, while contained within the reference list, were not cited within the document. For example, in the Mechanism of Toxicity section reviews from 1998 - 2003 are cited as the major source of information but the more recent review by Lau et al 2007 is not. Studies examining humanized PPAR α receptors *in vitro* and *in vivo* should be included (e.g., Wolf et al 2008 and Foreman et al 2009). More recently publications regarding mechanism(s) of action and other sensitive health effects (e.g., alterations in serum thyroid hormone levels, immunotoxicity) have expanded the discussion well beyond liver and PPAR α .

- 4) There is a general consensus that serum levels are a better dose metric for dose-response and for comparison across species than administered dose. Wherever possible serum levels should be provided, including tables and figures 3-1 through 3-5. In addition, a discussion of human equivalent doses should be presented to allow a more accurate comparison of effect levels.
- 5) The draft document includes statements that the lack of reported significant exposure-related adverse effects in humans precludes the derivation of MRLs. We are not aware of another chemical in which the absence of clear exposure-related adverse effects in humans was utilized as the major rationale for not deriving guidance. Guidance values, such as MRLs, are rarely based on human evidence but on evidence gathered in laboratory animals. Evidence of adverse effects has been clearly demonstrated in a wide range of laboratory species, including nonhuman primates. While there is limited evidence that some of the endpoints observed in rodents (enlarged livers) may not directly relevant to humans there currently is no evidence that the other health effects in rodents or the health effects in nonhuman primates are not relevant to humans.

A secondary rationale, the uncertainty regarding animal-to-human extrapolation, is also given. Typically across species toxicokinetic information for chemicals is not available and therefore the differences are unknown. For several of the PFCs we have this information - it is not an unknown but a known quantitative difference. These differences can be addressed by utilizing serum levels as the dose metric or by adjusting the administered dose to account for differences in elimination half-life.

- 6) The summary of Regulations, Advisories and Guidelines is incomplete. Several other countries (e.g., Germany, Canada) as well as states have derived health-based guidance. Some of these values are listed below:
- North Carolina's Public Health Goal for PFOA (June 2007) is 0.63 ug/L;
 - German Ministry of Health, Drinking Water Commission (July 2006) has several values. The Precautionary Action Values for composite PFOA and PFOS are: 5.0 ug/L immediate action to reduce adult intake; > 1.5 – 5.0 ug/L (1 yr tolerable max.); > 0.6 – 1.5 ug/L (3 yr tolerable max.); and > 0.1 – 0.6 ug/L (10 yr tolerable max.). The Provisional toxicological assessment lifelong health based guide value is 0.3 ug/L (applies to composite of PFOA & PFOS).
 - Health Canada has developed a draft Drinking Water Guidance Value of 0.7 ug/L for PFOA and 0.3 ug/L for PFOS.
 - United Kingdom, Drinking Water Inspectorate 2007 has a Tier 2 value of 10 ug/l for PFOA and of 1 ug/L for PFOS.
 - In addition to the values for PFOA and PFOS the Minnesota Department of Health has health-based guidance for PFBA (see <http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfba.pdf>) and PFBS (see <http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfbs.pdf>).

Specific Comments:

- Comparisons of administered dose and dose duration do not provide an accurate picture of species sensitivity. On page 119 the comparison of monkeys, rats and mice regarding sensitivity to the hepatic effects of PFOA would appear quite different if BMDL serum levels for hepatic effects are compared. The BMDL in Cynomolgus monkeys in the 26 week study (Butenhoff et al 2002) was ~23 ug/mL, in rats exposed for 70 - 90 days (Butenhoff et al 2004) it was ~ 25 ug/mL, in mice exposed throughout gestation it was ~ 29 ug/mL.
- Half-life of PFBA in humans. The correct units (hours) is listed in Table 3-8, however, throughout the text the units are reported as days.
- Maternal-infant transfer. It is incorrectly stated that no data regarding concentrations of PFCs in human milk in the US population are available. At least two studies have been conducted: Perfluorinated compounds in human milk from Massachusetts, U.S.A. Tao L et al. Environ Sci Technol. 2008, Apr 15; 42(8):3096-101 and Polyfluoroalkyl chemicals in the serum and milk of breastfeeding women. von Ehrenstein OS et al. Reprod Toxicol. 2009, Jun; 27(3-4):239-45. In fact, Tao et al 2008 is cited in Section 6 of the draft document.
- Discussion contained in Section 3.10 Populations that are unusually susceptible and Section 6.7 Populations with potentially high exposures should also include issues such as conditions that could impact the ability to eliminate PFCs and health effects beyond liver effects (immunological and thyroid hormone effects).
- 3M has reported that information on the import and export of PFCs from the United States is available from the U.S. Customs Service databases.
- Section 6.2 – PFOS is still in use in specific applications exempted by EPA. For example, some chrome platers use surfactants containing PFOS to limit hexavalent chromium emissions. MDH summarized Minnesota's experience with this use in a Health Consultation (<http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/pfosdetectbrainerd.pdf>). The U.S.

EPA also recently completed a study of PFOS levels in wastewater from chrome platers in Region 5 (see <http://www.epa.gov/region5/water/npdestek/notices.htm>).

- 7) Section 6.4.2 – The statement attributed to Chang et al (2008) regarding PFBA levels is misleading and inappropriate. PFBA has been detected at a levels as high as 21 micrograms per liter (ug/L) in a single private well, and at levels of 1-3 ug/L in literally hundreds of other private wells in Washington County, Minnesota as documented in a Health Consultation (<http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/prwelldata.pdf>) and Public Health Assessment (<http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/pha/lakeelmooakdale/index.html>) reviewed and approved by ATSDR.
- 8) Section 6.4.4 – a recent study published by Guo et al (2009) describes PFC levels in articles of commerce, and should be included here.
- 9) Section 6.5. MDH recently published the results of a pilot biomonitoring study of Washington County residents exposed to PFOA and PFOS in drinking water (<http://www.health.state.mn.us/divs/eh/tracking/biomonitoringpilot.htm>). The results of this study should be included in this section.
- 10) A discussion of drinking water treatment may also be relevant. MDH has conducted a study of water treatment devices for removing PFCs from drinking water. The study can be found at <http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/water.html>.



KENTUCKY REGIONAL POISON CENTER
of Kosair Children's Hospital
 P.O. Box 35070
 Louisville, KY 40232-5070

PFAs Comment #1

Louisville (502) 589-8222 • Kentucky 1-800-222-1222 • Secretary 502-629-7264 • Administration 502-629-5326
 FAX 502-629-7277

August 31, 2009

Agency for Toxic Substances and Disease Registry
 Division of Toxicology and environmental Medicine
 1600 Clifton Rd, NE
 Mail Stop F-62
 Atlanta GA 30333

Re: Comments on Toxicological Profile for perfluoroalkyls

Dear Dr Frumpkin:

I recently received a copy of the ATSDR Toxicological Profile for PerfluoroAlkyls (Draft for Public Comment) and am concerned with what appears to be a very significant omission. These chemicals are used (as noted in this document) extensively in surface coating and protectant formulations. There have been numerous reports of human injury over the years (references attached) but there is no mention of this potential pulmonary injury in the "Profile". Additionally there have been a number of animal studies and these are also not mentioned or reviewed in the ATSDR "Profile".

Several statements bring about my concern. For example on page 15, "regardless of the route of exposure, the liver is the main target for perfluoroalkyl compounds". Our experience with these chemicals shows that significant injury to the lungs occurs when these chemicals are aerosolized in Spray Sealants (leather protectors grout sealers, etc). In all the references attached the primary target is the lungs, not the liver. Additionally on page 39 (Health Effect, Inhalation, Respiratory Effects, section 3.2.1.2) there is no mention of the potential pulmonary injury these chemical have caused or the potential for human exposure, while thousands of human cases have been reported over the years. The exposure and injury continues to be reported with published reports as recent as this year (2009, see reference 5)

I would ask that the authors for this profile consider the attached references when evaluating the potential for human effect after inhalation exposure to perfluoroalkyls and include this evidence in the profile.

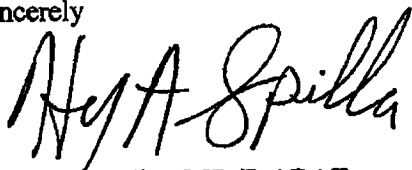


Designated as a Regional Poison Control Center by the
 American Association of Poison Control Centers



I believe the authors focus far too heavily on oral exposure, while the evidence for human injury after inhalation is nearly completely ignored.

Sincerely

A handwritten signature in black ink, appearing to read "H.A. Spiller". The signature is fluid and cursive, with the first name "H.A." and the last name "Spiller" clearly distinguishable.

Henry A. Spiller, MS, D.ABAT
Director
Kentucky Regional Poison Center
PO Box 35070
Louisville, KY 40232-5070

Office – 502-629-5326

Email henry.spiller@nortonhealthcare.org

Waterproofing/sealant References

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3.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709

Date: October 29, 2009

From: Suzanne E. Fenton, PhD
Laboratory Head, Reproductive Endocrinology
Cellular and Molecular Pathology Branch
National Toxicology Program, MD E1-08
919-541-4141
fentonse@niehs.nih.gov

Subject: Comments on ATSDR Draft Toxicological Profile on Perfluoroalkyls

To: ATSDR Division of Toxicology and Environmental Medicine
Applied Toxicology Branch
1600 Clifton Rd NE
Mailstop F-62
Atlanta, GA 30333

Draft Writers and Reviewers:

I have read your draft on the perfluoroalkyls and wanted to take this opportunity to make some constructive comments on both the content and the interpretation of what is presented. Since my expertise in the general area of health effects, that is where I will focus my comments. I was actually quite impressed with your peer review panel and believe that they were able to give you some good guidance, and will continue to do the same following the next round of edits to the document.

In general, this document is outdated. That is no fault of yours, but the science on this family of chemicals has moved forward so quickly this calendar year that this document is no longer current and many statements are incorrect. A review and inclusion of the many documents in the May 2009 *Reproductive Toxicology* issue 27(3-4) is needed. This is needed to update the toxicokinetic and health effects information available on compounds other than PFOA and PFOS, to provide important information on the disposition of PFOA in the pregnant and lactating mouse and her offspring over the nursing period, compare and contrast PFOS and PFOA in their ability to induce PPAR- α and the requirement for this signaling pathway for more than liver effects, and update some of the information on human exposure and early life end points in humans. Other epidemiological studies should also be added (these are just some examples) – Hamm et al., *JESEE* advance online publication, 28 October 2009, doi:10.1038/jes.2009.57; Lundin et al., *Epidemiology*, 2009 Nov;20(6):921-8; MacNeil et al., *Environ Res.* 2009 Nov, 109(8):997-1003; Stein et al., *Am J Epidemiol.* 2009 Oct 1;170(7):837-46; Joensen et al.,

Environ Health Perspect. 2009 Jun;117(6):923-7; an update of exposure levels in the USA by Steenland et al., Environ Health Perspect. 2009 Jul;117(7):1083-8; and comparisons of these data with 2009 data that is accumulating from other areas of the globe, such as Japan, China, Australia, and Denmark should be made.

Many of the interpretations of the data presented in the Public Health Statements are too basic – the large majority of the human data to date had not considered early life exposure to this family of compounds and that should be stated. Just because these epidemiological studies had no significant associations of current serum levels or even those 10 yr ago (in an adult) does not mean that if early life exposure accumulation was taken into consideration, that the results would be the same. The current animal studies agree that developmental exposure to these compounds is important in manifestation of effects. An example of this is the paper by Hines et al, Mol Cell Endocrinol. 2009 May 25;304(1-2):97-105. In this paper, the investigators demonstrate that the increased weight gain effects in adult mice exposed prenatally to PFOA do not occur when adult mice are exposed to the compound for similar lengths of time and dose. This paper specifically shows a low dose effect of PFOA on end points that are of importance to human health and are not likely related to PPAR- α signaling.

There are also discussions in Tardiff et al., Food Chem Toxicol. 2009 Oct;47(10):2557-89; Post et al., Environ Sci Technol. 2009 Jun 15;43(12):4547-54; and the Repro Toxicol issue mentioned above that need to be included in this document for your discussion of MRLs. Furthermore, there is now more information on human milk as a source of exposure to PFAs, not that it would change your presentation of the data much. This area should be updated, however. I also think it is important to point out that the human data that you refer to for comparison of PFAA in serum:milk is from very limited information (1 study) with no comparison over time or parity and based on our work in mice (Fenton et al., 2009 Reprod Toxicol) the time of lactation that the sample is collected can have a fair influence on the ratio of PFOA in serum and milk.

Although there are many updates needed in the document, there are also a few places where care must be taken to present the actual state of the science. Most of the epidemiological studies that have been published to date have been careful to state that they found associations of PFAA levels with a certain health outcome, but in your document in several places phrases like “..perfluoroalkyl compounds produce cancer..” and “causality” discussions should be carefully considered and possibly rewritten to reflect the interpretations of the authors of that work. Causality is hard to prove, but significant associations are easy to cite.

Finally, I would like to add that the mammary gland tumors that were found in female rats in the 2 yr study (work by Beigel et al., and cited in the PFOA SAB report) should not be brushed under the rug. Because female rats do excrete PFOA nearly as fast as they take it in, the very low circulating levels that may have been in those rats did cause an increased incidence of mammary tumors. Work by my lab, in addition to independent work by Sandra Haslam (in 2009 Reprod Toxicol) has indicated altered mammary gland development in at least two mouse strains and our current work will determine the NOAEL and LOAEL for those end points. The effects of this perturbation of early life development is not fully understood, but other endocrine disrupting compounds demonstrating similar shifts in timing of mammary gland maturity have

demonstrated increased risk for mammary hyperplasia, spontaneous adenocarcinoma, and carcinogen-induced tumor development (i.e, dioxin and bisphenol A). With this in mind, expansion of the primary health discussion on liver effects is recommended. Diabetes (and altered growth patterns, leptin, insulin in animal models) is another area to consider when defining the health effects of interest for PFOA and/or a mixture of exposures in this family of compounds.

I hope you find these comments helpful and if I can clarify any of my statements or provide further assistance, please feel free to contact me at the address given.

4.



Jon S. Corzine
Governor

State of New Jersey
Department of Environmental Protection

Mark N. Mauriello
Acting Commissioner

Office of Science
PO Box 409
Trenton, NJ 08625

October 30, 2009 (Corrected 11/2/09)

Ms. Nickolette Roney
Division of Toxicology and Environmental Medicine, ATSDR
Mailstop F-62, 1600 Clifton Road, NE
Atlanta, Georgia 30333

RE: Comments on Draft Toxicological Profile for Perfluoroalkyls, Docket Control
Number ATSDR-253

Dear Ms. Roney,

As requested in the Federal Register notice of July 23, 2009, I am submitting comments on the ATSDR Draft Toxicological Profile for Perfluoroalkyls. I am the toxicologist with the New Jersey Department of Environmental Protection (NJDEP) with responsibility for developing the human health basis for New Jersey drinking water standards and guidance. I was responsible for the development of the current NJ health-based drinking water guidance for PFOA (NJDEP, 2007); the basis for this guidance has recently been published in a peer-reviewed journal (Post et al., 2009, as referenced in the attached comments). Currently, the New Jersey Drinking Water Quality Institute (DWQI), an advisory body to the Commissioner of NJDEP, is developing a recommendation for a New Jersey drinking water standard (MCL) for PFOA. I am one of the scientists involved with updating the 2007 guidance based on review of recent studies in order to develop a recommended human health basis for this MCL.

My comments focus on PFOA since I am most familiar with the literature on that compound. Additional detailed comments focusing on the epidemiological studies of PFOA are being submitted by Dr. Perry Cohn of the New Jersey Department of Health and Senior Services. Like me, Dr. Cohn is part of the effort to develop a recommendation for the health basis for the New Jersey drinking water standard for PFOA.

Additionally, I am aware of an important new PFOA study which will be published next week. I will submit an addendum to my comments discussing this study after it becomes available.

Thank you for the opportunity to comment on the Draft Toxicological Profile for Perfluoroalkyls. Please feel free to contact me at gloria.post@dep.state.nj.us if you have any questions or need further information.

Sincerely,

Gloria B. Post, Ph.D., DABT
Research Scientist

cc: Judy Louis, NJDEP
Perry Cohn, NJ DHSS

Gloria B. Post, NJDEP
Comments on Draft Toxicological Profile for Perfluoroalkyls

General Comments

I have several overall comments about the material presented in the document.

First, there is often a lack of synthesis and critical analysis of the conclusions made by the authors of the studies described in the document. Instead, the conclusions are given as stated by the authors of the studies, even if they contradict the conclusions of other studies presented in the same section or in other sections, without an attempt to synthesize and draw conclusions from the whole body of information. Some specific examples of where this problem occurs are discussed below.

Second, some important literature, both recent and older, is not included in the document. In other cases, key studies that are listed in the Reference section, but are not discussed in the text, should be discussed in the text. Below, I discuss the studies which I consider most important and which I recommend including in the document, and I provide the citations for those studies which are not already cited. It should be noted that there are many additional recent studies on health effects in humans and animals, environmental occurrence, human exposure, and fate and transport of PFOA that I am not including in these comments.

Finally, and most importantly, I strongly disagree both with the conclusion that there is insufficient information and too much uncertainty to develop a chronic oral MRL for PFOA and with the reasons given in the draft document to support this conclusion. I believe that there is currently enough information to develop a chronic oral MRL for PFOA and that there is less uncertainty for the chronic risk assessment of PFOA than many of the other contaminants for which chronic MRLs have been developed by ATSDR. This is discussed in detail below.

My specific comments follow. The citations for all studies mentioned in the comments which are not already cited in the draft document are provided at the end of the comments.

Section 1 – Public Health Statement

Please note: Some of the information suggested for inclusion in the comments below may be too detailed for the Public Health Statement. This information could be summarized in this section and then discussed in more detail in the relevant sections later in the document.

p. 3 Section 1.3

Water and Soil

PFOA and PFOS have been detected in drinking water not impacted by known sources such as fluorochemical facilities (Post et al., 2009a, Ericson et al., 2009, Jin et al, 2009, Rumsby et al., 2009, Mak et al., 2009, Takagi et al., 2009). The contribution of exposure to the relatively low concentrations commonly detected in drinking water is substantial compared to the total exposure in the general population (Post et al., 2009).

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An important source of perfluoroalkyls in surface water and drinking water is discharge from wastewater treatment plants (Kelly and Solem, 2008, Yu et al, 2009, Clara et al, 2008). Precursor compounds (fluorotelomer alcohols) found in wastewater are transformed to PFOA and other perfluoroalkyls through biodegradation which occur during wastewater treatment (Sinclair et al, 2006, Loganathan et al, 2007). The sludge from wastewater treatment plants has been applied to agricultural land. Perfluoroalkyls from the land-applied sludge can contaminate groundwater and soil. These chemicals may then potentially enter the food chain (milk, meat) through grazing of cattle or other animals (Renner, 2009, USEPA Region 4, 2009).

Perfluoroalkyls have recently been shown to be taken up into crops from soil (Stahl et al., 2009).

Recent research (Washington et al., 2009) suggests that an acrylate-linked fluorotelomer polymer can degrade to PFOA in soil.

Consumer Products

Fluorotelomer alcohols and larger molecules containing fluorotelomer alcohols (e.g. mono- and diphosphates) are widely used in consumer products such as greaseproof food packaging. These have been shown to break down to PFOA and related compounds both through metabolic transformation in the body and through biodegradation and atmospheric reactions in the environment (D'eon et al., 2009, Martin et al., 2005, Sinclair et al., 2007, Ellis et al., 2004, Henderson and Smith, 2007, Kudo et al., 2005, D'eon and Mabury, 2007, Mahmoud et al., 2008). Exposure to these precursors in consumer products may be a major source of human exposure to PFCs, and should be mentioned here.

p. 4 Section 1.5

Workers

"Inhalation/dermal—Long-term exposure to perfluoroalkyls at work has not been associated with significant adverse health effects, but two studies in workers found changes in sex hormones and cholesterol associated with the levels of PFOA in blood." Comment: I agree with the comment submitted by Dr. Perry Cohn: "This statement falls short of describing the published observations and those from the docket. There is reasonable evidence (see above and below), given that most of the investigations are based on death certificates, that exposed workers are indeed affected."

General Population

The C8 Health Study is an ongoing study of almost 70,000 people in Ohio and West Virginia who were exposed for one year or longer to PFOA in drinking water at concentrations ranging from approximately 0.05 ug/L to approximately 3 ug/L or higher. Data collected for each subject in this very large study includes serum PFOA levels, drinking water exposure history (e.g. PFOA concentration, current vs. former residence), levels of many parameters which can be measured in blood, and the subjects' medical histories. Additionally, there are other planned segments of this study which are described under Ongoing Studies on p. 224 of the document. It includes the community

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studied by Emmett et al. (2006a, 2006b), referred to here, but includes many more people and many more parameters than did Emmett et al. (2006a, 2006b).

The currently available data and the data which will later become available from this major study provide crucial information on the relationship in humans between external dose (exposure through drinking water), internal dose (serum level), and biological endpoints and adverse health effects. The median serum levels in the first and second deciles, 6 and 9.8 µg/L are within the range prevalent in the U.S. general population, where, for the 2003-2004 National Health and Nutrition Evaluation Survey (NHANES), the 75th and 95th percentile levels were 5.8 and 9.8 µg/L (Calafat et al., 2007) while the highest serum levels in the C8 Health Study are in the 100s to 1000s of µg/L range. The median serum level in the study is about 28 µg/L. Such extensive data on the relationship between environmentally relevant exposures and effects in humans is rarely if ever available for environmental contaminants of concern.

In the draft document, the only mention of this study is on page 224 under Ongoing Studies, and even here, no background information on the design of the study is provided. Perhaps this is because the reports and publications which are now available were not available at the time when the draft document and peer review comments were written. There are currently several sources of information on this study which are essential for inclusion in the ATSDR Toxicological Profile. These include published papers on design and results of the study (Bartell et al., 2009, Frisbee et al., 2009, MacNeil et al., 2009, Steenland et al., 2009a, Steenland et al., 2009b, Steenland et al., 2009c, Stein et al., 2009), reports from the C8 Science Panel, including Fletcher et al. (2009) which reports associations with immune endpoints not yet published in a peer reviewed journal, and extensive data from the C8 Health Project which have not yet been adjusted for confounding factors (West Virginia School of Medicine, 2009).

Association of PFOA serum levels with biological endpoints, including some which may be considered to be adverse, have been observed down to the lowest exposure groups. Although causality has not been established, as is the case for most epidemiological studies for environmental contaminants, it is notable that elevated cholesterol and other lipids (Steenland et al., 2009a) and elevated uric acid (Steenland et al., 2009b), as well as changes in several indicators of inflammatory and immune response (Fletcher et al., 2009), were significantly associated with serum PFOA levels, after adjustment for age, gender, body mass index, and other factors. These associations are especially important, because the serum levels in the lower deciles in which the dose-response is seen for these endpoints coincide with the serum levels found in the general US population, as discussed by Steenland et al. (2009b).

In the cholesterol study (Steenland et al., 2009a), the median PFOA serum level was 27 µg/L, and the risk of high cholesterol increased in each quartile of exposure with a 40-50% increase in the top quartile compared to the lowest quartile.

In the uric acid study (Steenland et al., 2009b), the risk of hyperuricemia (greater than 6.0 mg/dl in women and 6.8 mg/dl in men) increased in a dose-related fashion with serum

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PFOA. The increased risk plateaued in the higher exposure groups, with an odds ratio of 1.47 and 95% confidence interval of 1.37-1.58 in the two highest quintiles.

A separate analysis of uric acid within the lower exposure group, with serum PFOA of less than or equal to 20 ug/L, revealed a dose-response by quartile within this group. . The highest quartile with serum levels of 15-20 ug/L serum PFOA had an increase in uric acid of 0.24 mg/dl above the lowest quartile with serum PFOA of less than 5 ug/L.

Additionally, data from this study which have not yet been adjusted for confounding factors (West Virginia School of Medicine, 2009) suggest associations between PFOA serum levels and multiple other clinical parameters measured in blood, including liver enzymes, hormones, and electrolytes. As for the other endpoints discussed above, the apparent exposure-response curve for many of these endpoints is steepest in the lowest deciles of exposure, and no threshold is apparent in the dose-response curves.

p.5 Laboratory Animals

Other effects besides liver should be mentioned here. At a minimum, immune system effects should be mentioned.

p. 6 Section 1.6

Effects in Children

RE: First paragraph.

The C8 Health Study includes 4915 subjects under 10 years old and 7561 subjects from 10 to 18 years old. The serum PFOA levels in these subjects spans a wide range and includes many subjects with serum levels in the range of the US general population. Preliminary data suggest associations of several parameters measured in blood with serum PFOA levels in children (West Virginia University School of Medicine, 2009).

RE: Second paragraph.

The studies referred to found associations with PFOA and/or PFOS and birth weight in the general population, not just with PFOA as stated. Apelberg et al. (2007) found associations with both PFOS and PFOA for birth weight and size, Fei et al. (2007, 2008a,b) found associations with PFOA but not PFOS for several measures of fetal growth, and Washino et al.(2009) found associations with PFOS but not PFOA for birth weight.

Also, Stein et al. (2009) identified modest associations of PFOA with preeclampsia and birth defects and of PFOS with preeclampsia, preterm births, and low birth weight in the C8 Health Study population.

Laboratory Animals

Exposure to low levels of PFOA during gestation in mice has been shown to cause metabolic effects which become apparent in adulthood, including increased weight and changes in insulin and leptin (Hines et al., 2009a). Such exposures have also been shown to cause a unique anatomical change at the junction between the cervix and the uterus in the female offspring (Hines et al, 2009b).

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p. 7 Section 1.8

Detecting Exposure

RE: Third paragraph.

In addition to Little Hocking, elevated PFOA serum levels have been found in the other five communities which are part of the C8 Health Study. These other communities had drinking water concentrations and serum levels lower than those in Little Hocking (Anderson-Mahoney, et al., 2008). Also, elevated serum levels have been found in other communities with contaminated drinking water including in Germany (Holzer et al., 2008) and Minnesota (MDH, 2009).

RE: Last paragraph.

The sentence should be revised to say, “**For example**, mean serum PFOA levels ...in Decatur, Alabama, were...” Elevated serum levels have been found in workers at sites other than Decatur, Alabama, and, as written, it implies that this was the only site where this has been found.

p. 8 First full paragraph.

It is important to mention that the USEPA Provisional Health Advisories for PFOA and PFOS are intended to protect for short term exposure, not chronic exposure.

Relevance to Public Health

p. 9, second paragraph, last sentence. Perfluoroalkyls can be formed through degradation of precursor compounds found in consumer products (D’eon and Mabury, 2007, D’eon et al., 2009, Martin et al., 2008, Washington et al., 2009)

p. 9, third paragraph. It is very important to discuss the fact that contamination of groundwater with PFOA has been found to occur via release to air from an industrial facility followed by deposition from air onto the soil and migration through the soil to the groundwater (Paustenbach et al., 2007). Unlike other groundwater contaminants, significant groundwater contamination by PFOA does not occur solely through migration of the groundwater plume. Thus, significant contamination can occur at some distance from the industrial source, beyond the groundwater plume.

Also, fluorotelomer alcohols are much more volatile than perfluoroalkyl acids, and are converted to the acids in the atmosphere by chemical reactions. Long range transport of these precursors is thought to be a major contributor to the occurrence of PFOA and related compounds in remote regions (Ellis et al., 2004)

p. 10, last paragraph.

As noted above, a major source of PFOA exposure may be exposure to the telomer alcohols and the molecules into which they are incorporated (e.g mono- and diphosphates) followed by metabolic conversion to PFOA in the body. These chemicals are present at much higher concentrations in some consumer products than PFOA itself.

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p. 11. Summary of Health Effects

Last sentence of paragraph. Studies of reproductive and developmental effects should also be mentioned here.

p. 12. Partial paragraph beginning at top of page.

Available results of the C8 Health Study and discussion of additional results that will be available from it should be included here. This information is discussed in detail above. This is a much larger study in the same community where the study of 371 subjects discussed here was done.

p. 13. Partial paragraph beginning at top of page.

Several epidemiology studies show an increase in diabetes mellitus associated with PFOA exposure (Leonard et al., 2008; Lin et al., 2009). See comments of P. Cohn for more detail. Also, regarding animal models, Hines et al. (2009a) found that exposure of mice to low levels of PFOA during gestation significantly increased body weight, and serum insulin and leptin (0.01-0.1mg/kg) in mid-life, while exposure during young adulthood did not have these effects.

p. 14. Partial paragraph beginning at top of page.

In the study described here, serum PFOA levels were not available, complicating evaluation of the results. Also, Stein et al. (2009), discussed above, should be mentioned here.

Last sentence of the paragraph: The authors of the studies themselves never concluded that the associations were causal. Why is it necessary to make the statement in the last sentence? If a statement is included, it should say that it is not known if the associations seen are causal or non-causal.

p. 15 First paragraph.

I have major concerns with the statements made in this paragraph about the implications of the toxicokinetic differences between humans and animals and of issues related to the mode of action on the relevance of animal studies to human health. This paragraph represents a summary of the discussion of these topics in the MRL section starting on p. 21. My comments on these issues are given in the MRL section, below, but also apply to the shorter discussion in this paragraph.

Second paragraph.

The discussions of the effects of PFOA that occur through activation of PPAR alpha presented here and in many other places in this document are overly simplistic, do not consider all relevant information, and may convey to the reader the unwarranted implication that all effects of PFOA that occur through PPAR alpha are not relevant to humans.

Specific to the writeup on this page, the following sentence should be revised to add the words "IN PART" as follows, as it is incorrect and contradicted by the writeup on the next page (page 16): Liver toxicity in rodents results **IN PART** from the ability of these

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compounds (with some structural restrictions) to activate the peroxisome proliferator-activated receptor- α (PPAR α), a member of the nuclear receptor superfamily.

Additionally, the information on page 20 about the EPA Science Advisory Board's reservations about attributing the hepatocarcinogenicity of PFOA totally to PPAR alpha agonism should be synthesized with the discussions on p. 15 and 16. In the current draft, the issues related to PPAR alpha and liver effects are presented separately on pages 15, 16, and 20, and the discussions on these three pages are contradictory and confusing to the reader.

It has been concluded that humans are refractory to the PPAR alpha mediated peroxisome proliferating effects in liver which are thought to lead to liver cancer in rodents (Klaunig et al., 2003). However, PPAR alpha is known to mediate many effects other than peroxisome proliferation and carcinogenesis in humans, both in liver and in other organs. Thus, the conclusions about liver cancer should not necessarily be extended to other PPAR alpha-mediated effects. It should be noted that Klaunig et al (2003) also concluded that the data are insufficient to characterize the MOA for the Leydig cell tumors and the PACT tumors of PFOA.

Effects mediated by PPAR alpha in humans include stimulation of fatty acid metabolism and suppression of inflammation (Fruchart and Duriez, 2004, Lefebvre et al. 2006), and, in fact, this is the basis for the use of PPAR alpha activators such as fibrates as hypolipidemic drugs in humans. Also, the role of PPAR alpha in human and animal development is not well characterized, but, based on their physiological roles, PPARs are expected to have important roles in reproduction and development (Abbott et al. 2008). Thus, the potential for PPAR alpha mediated effects on human development cannot be dismissed.

Most PPAR alpha activators lower cholesterol and lipids in both rodents and humans. Similarly, PFOA lowers lipid levels in experimental animals (e.g. Loveless et al. 2006). However, statistically significant elevations of cholesterol, as well as of the risk of hypercholesterolemia defined as greater than or equal to 240 mg/dl, are associated with serum PFOA and PFOS in a dose-related fashion in humans exposed through drinking water (Steenland et al., 2009a) and are also seen in occupationally exposed individuals, as summarized in Steenland et al. 2009a, 2009b.. As discussed by Steenland et al. (2009a), the findings on human serum cholesterol indicate that PFOA does not have the same effects as other PPAR alpha activators on lipid metabolism in humans.

As noted on the following page of the document (page 16), some effects of PFOA on the liver are not mediated by PPAR alpha. Effects of PFOA seen in PPAR alpha null mice include increased liver weight (Yang et al. 2002, Wolf et al., 2008) and histological changes and increased cell proliferation (Wolf et al., 2008), while the prototype PPAR alpha agonist Wyeth 14, 643 did not increase liver weight in PPAR alpha null mice in these studies. PFOA also activated genes not associated with PPAR alpha, including genes associated with other nuclear receptors such as CAR in livers of adult mice (Rosen

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et al., 2008a, 2008b) and newborn mice (Rosen et al., 2007). Additionally, PFOA caused fatty liver in mice, an effect not associated with PPAR alpha (Kudo and Kawashima, 1997).

As discussed on page 20, the USEPA SAB (2006) review of the USEPA (2005) draft PFOA risk assessment states that available data do not warrant the conclusion PPAR alpha is the sole MOA for liver tumors or that the PPAR alpha MOA for liver carcinogenesis does not occur in children.

Finally, a recent paper by Guyton et al. (2009) raises issues about the role of PPAR alpha activation in the liver carcinogenesis even in compounds which are well characterized as rodent peroxisome proliferators and the conclusion that hepatic tumors in rodents caused by PPAR alpha activators are not relevant to human risk. Guyton et al. (2009) discusses the findings of Ito et al. (2007) and David et al. (1999) on the liver carcinogenicity of di(2-ethylhexyl)phthalate (DEHP). DEHP caused liver tumors in wild type B6C3F1 mice which have PPAR alpha (David et al., 1999). However, in another strain of inbred mice, Ito et al (2007) found increased liver tumors from DEHP in PPAR alpha null mice, but not in the analogous wild type mouse strain. They also discuss the potential interindividual variability in human response to liver effects related to PPAR alpha activation due to differences in amount, structure, and function of PPAR alpha among people and the limitations of epidemiological studies on people taking PPAR alpha drugs

p. 16, first full paragraph.

Reductions in serum cholesterol and triacylglycerols are commonly seen in animals, but, as discussed above, the opposite is seen in humans. This should be mentioned.

p. 17 Second paragraph

The study of Hines et al. (2009a) showing metabolic effects in adult mice after prenatal, but not adult, exposure should be mentioned. White et al. (2009) conducted cross-fostering studies which showed that mammary gland development in mice is affected by exposure to PFOA only in utero or only during lactation. Changes in mammary gland development compared to control mice are still evident at 18 months of age. Also, anatomical changes in the uterus of mice exposed prenatally to very low doses has been reported in an abstract by Hines (2009b).

p. 18. First paragraph.

The discussion of whether developmental effects are mediated by PPAR alpha needs to be put into context by saying that the role of PPAR alpha in human development is currently unknown (Abbott et al., 2008). The discussion presented here, in the context of the PPAR alpha discussion on page 15, suggests to the reader that effects mediated through PPAR alpha are by definition not relevant to humans, which is not the case. White et al. (2007) discusses the fact that "PPAR alpha is not a critical element of mammary gland differentiation in the neonate," so that "effects of gestational PFOA exposure on neonatal mammary tissue must not be mediated through this pathway."

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The cross-fostering studies of Wolf et al (2007), as well as the more recent study of White et al. (2009) which is not cited in the document, showed that decreased body weight, increased liver to body weight ratios, and delayed mammary gland developmental changes occur in mice exposed in utero to PFOA who are nursed by unexposed animals. This finding contradicts the earlier suggestion that these effects are due to poor nutrition resulting from changes in the quantity or quality of milk produced by PFOA exposed mice.

p. 19 First full paragraph. Again, the significance of the discussions of whether or not the effects on the immune system are due to activation of PPAR alpha is not clear, particularly in this introductory section intended more for the non-scientist. As above, it has not been established that PPAR alpha mediated effects on the immune system are not relevant to humans.

p. 20 As mentioned above, this discussion of the role of PPAR alpha and the SAB's conclusion needs to be synthesized with the earlier discussions on pages 15 and 16. It is important that the fact that about three-quarters of the SAB concluded that "PFOA cancer data are consistent with the EPA guidelines descriptor 'likely to be carcinogenic to humans' " be added to this discussion.

Minimum Risk Levels

I strongly disagree that there is not enough information and too much uncertainty to develop a chronic MRL for PFOA. In general, the issues and uncertainties discussed in this section can be addressed by using 1) available information on the relationship between external dose (intake) and internal dose (serum levels) in humans, and 2) by using serum levels from animal studies, rather than administered dose, as the Point of Departure for the risk assessment. It is important to realize that this approach actually has less uncertainty than the standard approach for extrapolating from humans to animals. Detailed comments are provided below:

Human Data

A general comment is that, as is the case for the vast majority of risk assessments for environmental contaminants, the available human data are not appropriate to serve as the quantitative basis for an MRL. However, the human data do provide important information which can support a risk assessment based on animal data.

Bottom of p. 21. As discussed, a median ratio of approximately 100:1 between serum level and drinking water concentration was found in Little Hocking, Ohio, which had a high level of PFOA, about 3.5 ug/L (Emmett et al., 2006a). This approximate 100:1 ratio has been confirmed in communities with lower PFOA concentrations in their water supplies (about 0.05 ug/L or greater) by Post et al. (2009a) and is supported by the models of Harada et al. (2005). Tardiff et al. (2009) predicts similar, but slightly higher, ratios, as discussed by Post et al. (2009a, 2009b). It is also supported by the unpublished work of Hinderliter and Jepson (2001) and Gray (2005).

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Top of p. 22. Increased risk of levels of serum cholesterol (Steenland, 2009a) and uric acid (Steenland, 2009b) considered clinically elevated have been associated in a dose-related fashion with specific serum levels of PFOA. As discussed above, these findings are especially notable because dose-related increases are seen in the lower exposure groups which coincide with the exposures of the general United States population.

p. 22 Main paragraph. As discussed above, the population study of Emmett et al. (2006b) is greatly expanded upon by the C8 Health Study. Some results of this study are available and other portions of this study are ongoing.

“Furthermore, even if a wide range of end points had been examined in the studies available and points of departure could have been defined, there is currently not enough information regarding the pharmacokinetics of this group of compounds in humans to facilitate estimations of exposure levels resulting in measurable body burdens of perfluoroalkyls.”

Comment: Clewell (2006) predicts the relationship between exposure and serum level in humans, as discussed in Tardiff et al. (2009). Clewell’s model predicts factors of 0.1 and 0.127 relating intake ($\mu\text{g/kg/day}$) to serum concentration ($\mu\text{g/mL}$). Based on mean water ingestion of 17 mL/kg/day (USEPA, 2004), the 100:1 ratio between serum and drinking water levels (Post et al., 2009a) gives a factor of 0.167 $\mu\text{g/kg/day}$ intake per $\mu\text{g/mL}$ in serum (Post et al., 2009b).

Animal Data

The issues discussed here relating to differences in serum concentrations resulting from the same administered dose in humans and animals, as a result of differences in elimination rates, can be addressed by using serum levels instead of administered doses as the starting point for the risk assessment. This approach also addresses differences in elimination rates between male and female animals of the same species (e.g. rats). Measured or modeled serum levels are available for many of the key studies of PFOA in animals. This approach was used by USEPA (2005) in its draft risk assessment, as well as by Post et al. (2009a) and Tardiff et al. (2009) in their drinking water risk assessments.

The serum level at the NOAEL, LOAEL, or Benchmark Dose in animal data can be identified or predicted by modeling and used as the Point of Departure. Uncertainty factors are applied to the serum level at the Point of Departure in the same way that uncertainty factors are applied to administered doses in other risk assessments in order to develop target human serum levels.

It is important to realize that there are differences in body burden resulting from a given administered dose between species and sexes for all or most chemicals for which MRLs are developed. In most cases, this is addressed through the application of a default uncertainty factor. The approach suggested here for PFOA, which is based on internal dose and uses data specific to this chemical thus actually has less uncertainty in this regard than the approach used for most other chemicals.

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The fact that humans take longer to achieve steady state than animals should not preclude the use of animal studies as the basis for a chronic MRL, if the serum levels in animals are used as the basis for the risk assessment. Even though chronic MRLs are defined as applying to exposures of one year or longer, in practice, they are used to address chronic exposures, such as residential exposure to contaminated soil or drinking water. Humans who are exposed through environmental media (e.g. water, soil) at the level of the chronic MRL for a duration somewhat shorter than the duration required to reach steady state will have somewhat lower serum levels than they will have at steady state. Thus, application of a chronic MRL for exposures through environmental media (e.g. water, soil) for durations longer than those considered to be "Intermediate" but which are not long enough for steady state to be reached will be protective for potential health effects

Additionally, the half life of PFOA may be shorter than 1000 days, and/or four half-lives may not be required for PFOA to reach steady state in humans. Emmett et al. (2006a) found that duration of exposure to PFOA in drinking water did not impact serum levels in a group of individuals exposed for two years or longer, suggesting that the time needed to achieve steady state is much shorter than 12 years. Monkeys reached steady state in about two weeks (Butenhoff et al., 2002), much shorter than the predicted 90 days.

Recent studies relevant to human half life are Holzer et al. (2009) and Bartell et al. (2009).

In summary, based on the above considerations, kinetic extrapolations from animals to humans are likely to be less uncertain than for risk assessments of most chemicals, for which these issues are not considered quantitatively.

Maternal-fetal transfer

Information on maternal-fetal transfer and levels of the chemical under study in the fetuses of animals and humans is not available for most chemicals for which MRLs are developed. The default approach is to use the maternal dose in the animal study as the starting point and to assume that maternal-fetal transfer occurs similarly in humans and animals. For PFOA, uncertainty factors can be applied to the animal maternal serum level at the Point of Departure (NOAEL, LOAEL, or Benchmark Dose) to develop the target human maternal serum level which is the basis for the MRL. Fenton et al. (2009) showed that mouse pups exposed to a single dose of PFOA on gestation day 17 have significantly higher PFOA concentrations than their dams, and that their body burden increases after birth until at least day 8. Monroy et al. (2008) provides data on the concentrations of PFOA, PFOS, and other perfluorinated chemicals in maternal serum and umbilical cord serum in humans at delivery.

PBPK Models

A human PBPK model developed by Clewell (2006) is discussed by Tardiff et al. (2009). Harada et al. (2005) also developed a kinetic model for PFOA in humans.

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p. 28 PFOA – Oral Exposure

Throughout this section, there are discussions of whether or not the effects being mentioned have been found to occur through PPAR alpha. The significance of this information as presented in the draft document is likely to be unclear to the reader. If this information is included, it should also be stated that PPAR alpha mediated effects may also occur in humans, with the possible exception of peroxisome proliferation and tumors resulting from peroxisome proliferation in the liver.

Several additional studies which provide NOAELs or LOAELs more sensitive than the studies mentioned in the draft document should be included. PFOA serum levels are available or could be modeled for these studies:

Significantly increased body weight, leptin, and insulin in mid-life were found in mice exposed to doses of PFOA as low as 0.01 mg/kg/day for 17 days of gestation, but not in mice exposed as young adults (Hines et al., 2009a).

In an abstract, Hines et al. (2009b) also reported that mouse pups exposed to doses as low as 0.01 mg/kg/day during gestation had increased uterine weight and a unique anatomical change at the utero-cervical junction.

White et al. (2009) reported changes in mammary gland development and differentiation in cross-fostering studies in which mouse pups were exposed during gestation, lactation, or both. Delayed development was seen for exposure periods as short as one day or less in mice exposed only through lactation. Effects were seen at serum levels as low as about 2000 ug/L.

The NOAEL for reduced mouse pup survival of 0.3 mg/kg/day for 17 days of gestation (Abbott et al., 2007) is mentioned in the draft document. However, a LOAEL of 0.1 mg/kg/day (the lowest dose tested) for increased pup liver/body weight ratio was also seen in this study, and data on serum levels are presented.

Loveless et al. (2006) reported a LOAEL of 0.3 mg/kg/day (the lowest dose tested) for increased liver to body weight ratio in mice given PFOA for 14 days. Serum levels are reported.

It should be noted that mortality occurred in 1 of 4 monkeys (25%) in the lowest dose group (3 mg/kg/day) in the study of Butenhoff et al. (2002).

Health Effects

Inhalation Exposures

Detailed comments on occupational epidemiology studies are being submitted by Dr. Perry Cohn of New Jersey Dept. of Health and Senior Services. Concise and relevant summaries of some of the findings of the occupational studies are provided in Steenland et al. (2009a, 2009b). They discuss associations of elevated uric acid in two occupational studies, increased cholesterol in six occupational studies, increased liver enzymes in three occupational studies, and diabetes mortality in one occupational study.

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Oral Exposures

p. 56. In the cynomolgus monkey study of Butenhoff (2002), 1 of 4 monkeys in the 3 mg/kg/day group and 1 of 6 monkeys in the high dose group (30 mg/kg/day lowered to 20 mg/kg/day) were sacrificed *in extremis* during the study. Thus, mortality should be considered an effect in this study.

p. 116 Hepatic Effects

The C8 Health Study will provide additional data on liver effects in humans exposed to PFOA through drinking water. Preliminary data associations of increased serum liver enzymes with serum PFOA levels (West Virginia School of Medicine, 2009). No threshold for increase in some liver enzymes is apparent in these preliminary data. These associations have also been observed in occupational studies, as discussed by Steenland et al. (2009a).

Second paragraph. The hepatic response of rodents to PFOA is partially independent of PPAR alpha, as shown by studies in PPAR alpha null mice by Yang et al. (2001), which is cited in the document, and Wolf et al. (2008) which is not cited in the document. Wolf et al. (2008) showed increased liver weight and increased labeling index caused by PFOA in PPAR alpha null mice. Additionally, Kudo and Kawashima (1997) showed that PFOA caused fatty liver in mice, an effect not seen with typical PPAR alpha activators such as fibrates.

p. 117 As mentioned above, Loveless et al. (2006) reported a LOAEL of 0.3 mg/kg/day (the lowest dose tested) for increased liver to body weight ratio in mice given PFOA for 14 days.

As above, the studies in PPAR alpha null mice of Wolf et al. (2008) should be cited along with Yang et al. (2001).

p. 118. Full paragraph beginning with "Treatment..." Abbott et al. (2007) is a mouse study, not a rat study as stated here.

Also, in this study, liver weight was increased in wild type pups at 0.1 mg/kg/day and higher.

p. 119 First paragraph. Regarding the Butenhoff et al. (2002) study, it should be mentioned in this section or elsewhere that 1 of 4 monkeys in the 3 mg/kg/day group and 1 of 6 monkeys in the high dose (30/20 mg/kg/day) group were sacrificed in moribund condition during the study. Three additional monkeys in the high dose group were removed from the study because they could not tolerate the dosing.

p. 124 and 125. Renal Effects, Endocrine Effects

Steenland et al. (2009b) reported no interactions between PFOA and creatinine, an indicator of kidney disease in ~55,000 adults who were part of the C8 Health Study. The

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C8 Health Study will provide additional data on whether there is an association between serum PFOA and these effects.

Immune

Fletcher et al. (2009) reported that changes in several indicators of inflammatory and immune response were significantly associated with serum PFOA levels, after adjustment for age, gender, body mass index, and other factors. These include IgA, IgE, antinuclear antibodies, and C-reactive protein.

p. 132 DeWitt et al. (2009) showed that the suppression of humoral immunity by PFOA in mice is independent of increased corticosterone levels and thus is not secondary to liver toxicity or stress.

Son et al. (2008) showed effects of PFOA on T lymphocyte phenotypes and cytokine expression in mice.

Loveless et al. (2008) studied immune effects of PFOA in rats and mice.

p. 133 Neurobehavioral Effects

Johansson et al. (2008) which showed permanent behavioral changes in mice after a single dose of PFOA or PFOS at age 10 days should be mentioned here.

Also, Johansson et al. (2009) showed that a single dose of PFOA or PFOS given to neonatal mice altered the levels of proteins important for brain development.

p. 135 Reproductive Effects

Two recent studies in the general population should be mentioned in this section. Joensen et al. (2009) studied associations between semen quality and reproductive hormone levels with serum levels of perfluoroalkyl acids in young Danish men. They reported a significant association of high levels of PFOS and PFOA with fewer normal sperm, and non-significant associations with other related parameters.

Fei et al. (2009) found that increased time to pregnancy, which is considered to be a measure of infertility, was significantly associated with maternal serum PFOA and PFOS in the Danish general population.

p. 136 Butenhoff et al. (2002) reported that estradiol levels in the high dose monkeys appeared to be decreased.

p. 136 Last paragraph. White et al. (2009) is not mentioned in the document. It is a followup study to White et al. (2007). This study had a cross-fostering design, so that pups were exposed in utero, through lactation, or both. Exposure only in utero only during the final days of pregnancy or only through lactation caused adverse mammary development as early as post-natal day 1 that persisted beyond post-natal day 63. The findings that these effects occurred in pups exposed only late in gestation, with no exposure through lactation because they were nursed by unexposed mice, contradicts the

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earlier suggestion that the effects on mammary gland development are due to alterations in the quality of the milk which the pups consumed.

p. 141 The studies of developmental endpoints in human populations of Monroy (2008) and Stein et al. (2009) should be discussed.

p. 142 The rat multigeneration study of Butenhoff et al. (2004) which is mentioned on page 136 should be discussed here. The fact that female rats excrete PFOA very quickly so that exposure to pups is lower than in other species given the same dose should be mentioned. Effects seen included reduced body weight during lactation in the F1 generation given 30 mg/kg/day, increased deaths of F1 males given 30 mg/kg/day at 2-4 days post-weaning, delays in sexual maturation in F1 males and females,

p. 143 It should be mentioned that lactational exposure alone caused decreased body weight and increased relative liver weight in the cross fostering studies of Wolf et al. (2007).

p. 144 The findings of the following recent mouse developmental studies should be added: White et al. (2009), Yang et al. (2009), Hines et al. (2009a), Hines et al. (2009b). These studies show developmental effects at lower doses and/or shorter exposures than previous studies. Furthermore, White et al. (2009) showed that mammary gland changes caused by short exposures during development persist into adulthood, Hines et al. (2009a) showed metabolic changes not evident in adulthood as a result of developmental exposures, and Hines et al. (2009b) showed a unique anatomical change in the uterus after exposure to a very low dose for only 3 days of gestation. These effects may be more significant than the developmental delays reported in earlier studies.

p. 148 Cancer

I suggest removing the following sentence regarding 3M (1983): "The investigators did not consider PFOA carcinogenic in the rat under the conditions of the study." If it is not removed, it should also be stated that the USEPA SAB (2006) judged PFOA to be a "likely carcinogen" based on data from this study and the study of Beigel et al. (2001).

Toxicokinetics

p. 162 Oral Exposure

Post et al. (2009a) discussed exposures through drinking water with PFOA at lower concentrations than those in Little Hocking studied by Emmett et al. (2006a). The recent Minnesota Dept of Health Biomonitoring Project (2009, <http://www.health.state.mn.us/divs/eh/tracking/finalpfcrrpt.pdf>) studied exposure to 7 PFCs from drinking water. Data currently being analyzed from this study will provide further information on the relationship between drinking water concentrations and serum levels in residents with contaminated private wells.

p. 172 Metabolism

It should be stated that PFOA is a stable compound that does not undergo chemical reactions in the body (or in the environment, under normal circumstances). This is one of

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the most notable features of PFOA as compared to most other organic chemicals which are found in the environment (Lau et al., 2007).

p. 190 Risk Assessment

As discussed above, I do not agree that the pharmacokinetic differences between humans and animal species preclude development of MRLs, since extrapolations can be done on the basis of serum levels. A pharmacokinetic model developed for monkeys has been adapted to humans and used in risk assessment, as discussed in Tardiff et al. (2009).

p. 195. 3.5.2 Mechanisms of Toxicity

The same general comments provided on page 6 above about discussions of PPAR alpha mediated effects apply to this section.

This sentence should be changed as follows: Liver toxicity in rodents results IN PART from the ability of these compounds (with some structural restrictions) to activate the peroxisome proliferator activated receptor- α (PPAR α),....” As discussed above, PFOA caused increased liver weight, fatty liver, and histological changes in PPAR alpha null mice, and has been shown to activate genes associated with pathways other than PPAR alpha in liver.

“Although humans are refractory to the many effects induced by peroxisome proliferators in rodents, humans have a functional PPAR α as suggested by the pharmacological reductions in serum triglycerides and cholesterol in patients treated with the peroxisome proliferator clofibrate, a response known to be mediated by the PPAR α in mice.” As discussed above, PPAR alpha is known to mediate many effects in humans in liver and in other organs, and its role in human development and in young children has not been characterized. Furthermore, PFOA has been shown to be associated with increased cholesterol in humans both in occupational studies and in a very large population exposed through drinking water with much lower serum PFOA levels (Steenland et al., 2009a). In this way, it differs from the fibrate drugs which lower cholesterol in humans.

p. 197 In discussing Tilton et al. (2008), it should be mentioned that PFOA acted as a promoter for liver tumors in rainbow trout exposed to an initiator. Rainbow trout have been used for many years as a model for human liver cancer, since they are also insensitive to peroxisome proliferation in the liver. The authors concluded that the liver tumors in trout occurred through an estrogenic mechanism that may be relevant to humans.

p. 197, Second paragraph

Discussion of non-PPAR alpha mechanisms needs to be mentioned at the beginning of this section on page 195, not just at the end where it is not connected with the earlier discussion.

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Section 3.5.3 Animal-to-Human Extrapolations

I strongly disagree with the statements made in the first paragraph of this section. Details are given below.

Toxicokinetic Differences

This issue is also discussed in detail under Animal Studies in the MRL Development section above. As stated above, the issues discussed here relating to differences in serum concentrations resulting from the same administered dose in humans and animals, as a result in differences in elimination rates, can be addressed by using serum levels instead of administered doses as the starting point for the risk assessment. This approach also addresses differences in elimination rates between male and female animals of the same species (e.g. rats). Measured or modeled serum levels are available for many of the key studies of PFOA in animals. This approach was used by USEPA (2005) in its draft risk assessment, as well as by Post et al. (2009a) and Tardiff et al. (2009) in their drinking water risk assessments.

As discussed above. The serum level at the NOAEL, LOAEL, or Benchmark Dose can be identified and used as the Point of Departure/ Uncertainty factors are applied, in the same way that uncertainty factors are applied to administered dose in other risk assessments, to develop target human serum levels. It is important to realize that there are differences in body burden resulting from a given administered dose between species and sexes for all or most chemicals for which MRLs are developed. In most cases, this is addressed through the application of a default uncertainty factor. The approach suggested here for PFOA, which uses data specific to this chemical thus actually has less uncertainty in this regard than the approach used for most other chemicals.

The fact that humans take longer to achieve steady state than animals does not preclude the use of animal studies if serum levels are used as the basis for the risk assessment. The half-life of PFOA in humans exposed through drinking water has recently been estimated to be 2.3 years (Bartell et al, 2009). Additionally, PFOA may not take four half lives to reach steady state in humans. Emmett et al. (2006a) found that duration of exposure to PFOA in drinking water did not impact serum levels in a group of individuals exposed for two years or longer, suggesting that the time needed to achieve steady state is much shorter than 12 years. Monkeys reached steady state in about two weeks (Butenhoff et al., 2002), much shorter than the predicted 90 days.

p. 198 "As a result of these large differences in kinetics, internal doses (i.e., serum concentrations of PFOA) achieved during intermediate-duration exposures in rats or monkeys would not represent steady-state internal doses that might be achieved in humans over longer exposure durations." The logic and intent of this sentence is unclear. Animals reach steady-state more quickly than humans, so any comparison based on serum levels in which humans have not yet reached steady state might be slightly overprotective, rather than underprotective, and thus the use of animal serum levels as the basis for human risk assessment should not be precluded. Also, as discussed above, humans may reach steady state more quickly than the 12 years mentioned in the draft document. As above, because of the availability of data on the relationship between

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administered dose and serum levels in both humans and animals, the uncertainties in this area are less than for the risk assessments for most other chemicals for which a default uncertainty factor is used for interspecies extrapolation.

Lack of Reported Effects in Humans

This paragraph should be rewritten to better convey a balanced summary of the data on associations seen in occupational and general population studies. Concise summaries of some of these data are provided in the introductory sections of Steenland et al. (2009a) and Steenland et al. (2009b),

As mentioned above, Steenland et al. (2009a) report a dose-related increased risk of hypercholesteremia in a large population exposed through drinking water, with an odds ratio of 1.51 in the highest quartile compared to the lowest quartile. The data of Steenland et al. (2009a) are especially significant because the associations exhibited no threshold down to the lowest deciles of exposure, and the serum levels in the lower deciles in the C8 study population are within the range of exposures of the general US population (Calafat et al., 2007).

In the uric acid study (Steenland et al., 2009b), the risk of hyperuricemia (greater than 6.0 mg/dl in women and 6.8 mg/dl in men) increased in a dose-related fashion with serum PFOA. The increased risk plateaued in the higher exposure groups, with an odds ratio of 1.47 and 95% confidence interval of 1.37-1.58 in the two highest quintiles.

A separate analysis of uric acid within the lower exposure group (within the range of the US general population), with serum PFOA of less than or equal to 20 ug/L, revealed a dose-response by quartile within this group. . The highest quartile with serum levels of 15-20 ug/L serum PFOA had an increase in uric acid of 0.24 mg/dl above the lowest quartile with serum PFOA of less than 5 ug/L.

Steenland et al. (2009a) summarize some of the literature on associations in humans as follows: "It (PFOA) 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."

Steenland et al. (2009b) summarizes as follows: "PFOA has been found to be significantly associated with elevated uric acid in two cross-sectional studies of workers (n=160 and n=1024) (Sakr et al. 2007a; Costa et al. 2009). There is also evidence in the literature for an association of PFOA with cholesterol and diabetes in humans. A positive correlation of PFOA with cholesterol was observed in six occupational studies (Sakr et al. 2007a; Costa et al. 2009; Sakr et al. 2007b; Olsen et al. 2000; Olsen and Zobel 2007b; Olsen et al. 2003), and two community studies (Emmett et al. 2006; Steenland et al. 2009), although in one community study and two occupational studies, the relationship was not statistically significant. PFOA exposure was observed to be associated with a

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two-fold increase in diabetes mortality in one cohort study of highly-exposed workers when the exposed workers were compared to non-exposed workers, although no association was seen in another cross-sectional study of diabetes prevalence (Leonard et al. 2008; McNeil et al. 2009)."

Additionally, among other studies showing associations of PFOA exposure with health endpoints, Lundin et al. (2009) recently reported associations of occupational exposure with prostate cancer, cerebrovascular disease, and diabetes. Costa et al. (2009) reported associations with increased uric acid, as well as cholesterol.

As mentioned above, Dr. P. Cohn of the NJ Dept. of Health and Senior Services will provide extensive comments on human studies.

Mode(s) of Action

As discussed in detail above, the following sentence is an oversimplification and should be modified to add the words in capitals as follows: "As previously mentioned, many PFOA-or PFOS-induced effects in rats and mice are mediated through the PPAR α and it is generally agreed that humans and nonhuman primates are refractory, or at least less responsive than rodents, to PPAR α -mediated effects IN THE LIVER THAT LEAD TO TUMOR FORMATION."

"Therefore, further studies in PPAR α -null mice are needed to expand the knowledge regarding PPAR α -dependent and independent effects that would allow selection of an appropriate animal model for perfluoroalkyls toxicity." Comment: This sentence should be rewritten to emphasize that PPAR alpha does mediate effects in humans other than liver cancer. As written, it implies that only effects seen in PPAR alpha null animals are relevant to humans, which is not the case.

p. 198 Section 3.6 Toxicities Mediated Through the Neuroendocrine Axis

The following studies which have been discussed above relate to endocrine effects and should be considered for inclusion in this section:

Joensen et al. (2009) studied associations between semen quality and reproductive hormone levels with serum levels of perfluoroalkyl acids in young Danish men. They reported a significant association of high levels of PFOS and PFOA with fewer normal sperm, and non-significant associations with other related parameters.

Fei et al. (2009) found that increased time to pregnancy, which is considered to be a measure of infertility, was significantly associated with maternal serum PFOA and PFOS in the Danish general population.

White et al. (2009) conducted cross-fostering studies which showed that mammary gland development in mice is affected by exposure to PFOA only in utero or only during lactation. Changes in mammary gland development compared to control mice are still evident at 18 months of age.

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Exposure to low levels of PFOA during gestation in mice has been shown to cause metabolic effects which become apparent in adulthood, including increased weight and changes in insulin and leptin (Hines et al., 2009a). Such exposures have also been shown to cause a unique anatomical change at the junction between the cervix and the uterus in the female offspring (Hines et al., 2009b).

p. 203 Children's Susceptibility

The ongoing C8 Health Project will provide information on associations of many endpoints with PFOA exposure in children as well as in adults.

Hoffman et al. (2009) recently reported an association with serum levels of PFOA and several other perfluorinated chemicals and attention deficit hyperactivity disorder in U.S. children age 12-15.

It should be mentioned that children exposed to PFOA in drinking water have higher serum PFOA levels than adults (Emmett et al., 2006a, Steenland et al., 2009c). This could be due to a greater volume of water consumed per kilogram body and/or differences in the toxicokinetics of PFOA in children and adults.

p. 204 Last paragraph

Hines et al. (2009a, 2009b) which showed metabolic effects in adulthood and anatomical changes in the uterus after fetal exposure should be mentioned here.

p. 205 Partial paragraph at top of page

In discussing the developmental effects of PFOA in wild type and PPAR alpha null mice (Abbott et al., 2007), it should be mentioned that full litter resorptions were independent of PPAR alpha. Also, if this topic is discussed, it should be mentioned that the role of PPAR alpha in human development is uncharacterized, and that it cannot be concluded that developmental effects mediated through PPAR alpha are not relevant to humans.

p. 207 Biomarkers used to characterize effects by perfluoroalkyls

It is agreed that there are no biomarkers of effects specific to perfluoroalkyls. However, the following sentence is misleading and is also contradicted by the recent publications of Steenland et al. (2009a, 2009b) mentioned above. It is not necessary to include this statement in order to make the point that there are no biomarkers SPECIFIC to perfluoroalkyls, and I suggest that it be deleted.

"Health evaluations of workers exposed to perfluoroalkyl compounds or of subjects environmentally exposed via their drinking water have not provided evidence of adverse health effects in the groups studied (Emmett et al. 2006a; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1999, 2003a; Sakr et al. 2007a, 2007b)."

p. 207 3.10 Populations that are unusually susceptible

Steenland et al. (2009a) as well as the occupational studies cited by Steenland et al. (2009a, 2009b) show that PFOA has effects opposite to the hypolipidemic drugs on serum lipid levels. As mentioned in Steenland et al. (2009a), several studies have shown associations with increased liver enzymes, so it is agreed that people with compromised

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liver function may be particularly susceptible. Similarly, Steenland et al. (2009b) has found associations of PFOA exposure with clinically elevated uric acid and Fletcher et al. (2009) has reported changes in immune function, so that people who already have elevated uric acid or immune system abnormalities may be particularly susceptible. There are also two occupational studies showing increased uric acid, as discussed in Steenland et al. (2009b)

p. 208 3.11.12 Reducing Body Burden

Bartell et al. (2009) recently reported on the rate of decline in serum PFOA concentrations after granular activated carbon filtration in the C8 Health Study population in Ohio and West Virginia.

p. 209 3.11.3 Interfering with the Mechanism of Action for Toxic Effects

It is agreed that there is no known method for interfering with the mechanism of toxicity of PFOA. However, the statements about no associations being found with adverse health effects should be removed, as they are not needed to make this point. If the statements are not removed, they should be modified as discussed under Section 3.10 above.

p. 212 First full paragraph

The data from the C8 Health Study on general population exposure, should be mentioned here. These include published papers on design and results of the study (Bartell et al., 2009, Frisbee et al., 2009, MacNeil et al., 2009, Steenland et al., 2009a, Steenland et al., 2009b, Steenland et al., 2009c, Stein et al., 2009), reports from the C8 Science Panel, including Fletcher et al. (2009) which reports associations with immune endpoints not yet published in a peer reviewed journal, and extensive data from the C8 Health Project which have not yet been adjusted for confounding factors (West Virginia School of Medicine, 2009). These data are quite extensive, so it should be stated that data from both occupational and general population (environmental) exposures are available, without saying that the environmental data is limited.

p. 213 3.12.2 Identification of Data Needs

As discussed in detail above, I do not agree that there is insufficient information or too much uncertainty to develop a chronic oral MRL for PFOA.

p. 214. Chronic Duration and Cancer

I disagree with the statement that “for the most part, no significant adverse effects have been identified”,

The DuPont incidence study (Leonard, 2003) and the more recent occupational studies of Lundin et al., (2009), Costa et al. (2009), and others should be discussed.

p. 215-216.

“In a 2-year bioassay, PFOA induced a “tumor triad” in rats, that is, liver tumors, Leydig cell tumors, and tumors in pancreatic acinar cells, characteristic of PPAR α -agonist activation in rats (3M 1983; Biegel et al. 2001). The relevance of these findings to

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humans has been questioned by some since humans are considered refractory to most, but not all PPAR α -activation effects (Klaunig et al. 2003).” Comment: The focus of Klaunig et al. (2003) was on rodent tumors, not “all PPAR alpha activation effects”, which include effects on lipid metabolism and many other biological endpoints in the liver and other organs, as well as on development. The statement as written is misleading.

“PFOA also increased the incidence of mammary gland fibroadenomas (3M 1983) and of mammary gland adenocarcinomas (mid-dose only).” Since PPAR alpha is discussed so extensively in this draft document, it should be mentioned that PPAR alpha is not known to be involved with mammary gland tumor formation.

p. 216. Reproductive Toxicity

As above, it should be mentioned that Joensen et al. (2009) found a significant association of high levels of serum PFOS and PFOA with fewer normal sperm, and non-significant associations with other related parameters, in young Danish men.

Also, it should be mentioned that Fei et al. (2009) found that increased time to pregnancy, which is considered to be a measure of infertility, was significantly associated with maternal serum PFOA and PFOS in the Danish general population.

p. 218 Developmental Toxicity

As above, the study of Hines et al. (2009a) showing metabolic effects in adult mice after prenatal, but not adult, exposure should be mentioned. White et al. (2009) conducted cross-fostering studies which showed that mammary gland development in mice is affected by exposure to PFOA only in utero or only during lactation. Changes in mammary gland development compared to control mice are still evident at 18 months of age. Also, anatomical changes in the uterus of mice exposed prenatally to very low doses has been reported in an abstract by Hines (2009b).

p. 219. Immunotoxicity

The findings of associations with changes in immune parameters in the C8 Health Study population (Fletcher et al., 2009) should be mentioned here.

p. 220 Epidemiological and Human Dosimetry Studies

The findings of the C8 Health Study should be mentioned here, including the publications of the C8 Science Panel (Bartell et al., 2009, Frisbee et al., 2009, MacNeil et al., 2009, Steenland et al., 2009a, Steenland et al., 2009b, Steenland et al., 2009c, Stein et al., 2009) as well as the data of Fletcher et al., 2009 and the West Virginia University School of Medicine (2009). Since the focus of this document is health effects from environmental exposures, these data are even more relevant than the occupational studies.

p. 222 Second full paragraph

It should be mentioned that mice do not show the marked sex difference in elimination rate seen in rats. It is important to mention this because of the many studies showing developmental effects in mice which were not seen in rat developmental studies.

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Bartell et al. (2009) recently reported that there is not a gender difference in elimination of PFOA in humans exposed through drinking water.

The relevance of the discussion of possible gender differences in humans with dose or plasma concentration is not clear, as the data from humans involve serum levels relevant to human exposure.

p. 223 Children's Susceptibility

As discussed above, the ongoing C8 Health Project will provide information on associations of many endpoints with PFOA exposure in children as well as in adults. It should be mentioned that children exposed to PFOA in drinking water have higher serum PFOA levels than adults (Emmett et al., 2006a, Steenland et al., 2009c). This could be due to a greater volume of water consumer per kilogram body and/or differences in the toxicokinetics of PFOA in children and adults.

p. 224 3.12.3 Ongoing Studies

As mentioned above, the C8 Health Study should be discussed in much more detail than in the draft document. In the draft document, the ongoing studies by the C8 Science Panel are simply mentioned with no context provided.

This ongoing study is unprecedented in size and scope among studies of exposure and effects of humans exposed to an environmental contaminant. It will provide extensive data on the relationships between human exposure, internal dose, and health effects. The design, scope, and currently available data from this study should be discussed. The design of the study is discussed in Frisbee et al. (2009). Information on predictors of serum levels is discussed in Steenland et al. (2009b) and on half-life in Bartell et al. (2009). Data on associations with health endpoints are found at (WVU School of Medicine C8 Health Project website and C8 Science Panel website), as well as in the following peer-reviewed publications: Stein et al. (2009), MacNeil et al. (2009), and Steenland et al. (2009a, 2009b).

Potential for Human Exposure

The following studies should be discussed under this section:

Fromme et al. (2009) summarizes perfluorinated chemical concentrations in indoor and ambient air, house dust, drinking water and food, as well as biomonitoring data in blood, breast milk, and human tissues. These data are used to estimate overall human exposures.

Vestergren and Cousins (2009) conclude that dietary exposure is a major pathway of PFOA exposure in the general population.

Post et al. (2009a) show the exposure contribution of low concentrations of PFOA in drinking water (e.g. 0.01 ug/L) can be substantial relative to the total exposure of the general population.

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Washburn et al. (2005) evaluate exposure from trace levels of PFOA in consumer products.

Tittemier et al. (2007) report on dietary exposure of Canadians to perfluorocarboxylates and PFOS.

Tao et al. (2008) report on perfluorinated compounds in human breast milk in Asia, and in infant formula and dairy milk in the U.S.

Jogsten et al. (2009) report on dietary exposures to perfluorinated compounds in Spain.

Fromme et al. (2007) report on dietary exposures in Germany.

Guo et al. (2009) report perfluorocarboxylic acid content in 116 articles of commerce.

p. 249 Second full paragraph beginning with "Mean PFOA, PFOS,..."

It should be mentioned that telomer alcohols from food packaging can be metabolized in the body to PFOA and that this is may to be a greater source of exposure to PFOA from food packaging than residual PFOA in these products (D'eon and Mabury, 2007, D'eon et al., 2009). Vestergren et al. (2008) evaluated the contribution of precursor compounds in consumer exposure to PFOS and PFOA.

6.2 Releases to the Environment

6.21 Air

Gewurtz et al. (2009) recently reported on studies of perfluoroalkyl compounds on indoor and outdoor window films. These data were used to evaluate potential sources by sampling window films before and after new carpet installation and floor wax application, as well as in carpet stores. The results suggested that carpets may be a source of exposure indoors.

6.22 Water

The following studies are relevant to wastewater discharges of perfluorinated chemicals:

Kelly and Solem (2008) identified discharge from a chrome plating operation as the major source of PFOA at a wastewater treatment plant in Brainerd, Minnesota.

In Alabama, perfluoroalkyls from the land-applied sludge from a wastewater treatment plant were found to contaminate groundwater and soil. These chemicals may potentially enter the food chain (milk, meat) through grazing of cattle or other animals (Renner, 2009, USEPA Region 4, 2009).

Sinclair and Kannan (2006) studied perfluorinated chemicals in sewage treatment plant influent and effluent. Increased concentrations of some chemicals in effluent was attributed to biodegradation of precursors present in the influent.

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A similar study was reported by Loganathan et al. (2007).

Clara et al. (2008) studied perfluorinated chemicals in industrial wastewaters and wastewater treatment plant effluents.

Yu et al. (2009) reported on perfluorinated chemicals in sewage treatment plants.

D'eon et al. (2009) Reported on the occurrence of di-PAPS, the compound containing fluorotelomer alcohols in paper products, in wastewater and sludge. This compound can biodegrade to fluorotelomer alcohol which can further biodegrade to PFOA.

6.3 Environmental Fate

6.3.1 Transport and Partitioning

In addition to long range atmospheric transport, it is very important to discuss that contamination of groundwater near industrial facilities occurs through air emissions followed by deposition on the soil and migration to groundwater, as well as through migration in a groundwater plume from the facility (Paustenbach et al., 2007).

Issues related to environmental fate and transport and pathways of human exposure to PFOA released from an industrial facility are evaluated in Small et al. (2009).

6.4.2 Water

The following studies are relevant to occurrence of perfluorinated chemicals in surface water and ground water:

Murakami et al. (2009) reports on groundwater pollution by perfluorinated chemicals in Tokyo.

Loos et al. (2008) reports on PFOS and PFOA in European river waters.

Konwick et al. (2008) reports on concentrations and patterns of perfluoroalkyl acids in surface waters in Georgia near and distant to a major use source.

Orata et al. (2008) reported on PFOA and PFOS in Lake Victoria Gulf in East Africa.

Murakami et al. (2008a) reported on perfluorinated chemicals in rivers in Japan.

Murakami et al. (2008b) reported on wastewater and street runoff as sources of perfluorinated chemicals in water.

p. 281. Several studies have reported on occurrence of PFOA and other perfluorinated chemicals in drinking water supplies not located near an industrial facility known to discharge these chemicals.

Post et al. (2009a) reported on occurrence of PFOA in New Jersey public drinking water supplies. Data on PFOS from this study is found in NJDEP (200?). NJDEP is currently conducting an occurrence study of 30 additional public water supplies for 10

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perfluorinated chemicals, and we will submit these data when available (anticipated to be within the next few months).

Ericson et al. (2009) reported on levels of perfluorinated chemicals in municipal drinking water from Catalonia, Spain.

Jin et al. (2009) reported on drinking water levels of PFOA and PFOS in China.

Loos et al. (2007) reported on PFOA and PFOS in surface and tap waters around Lake Maggiore in Northern Italy.

Rumsby et al. (2009) reviews PFOA and PFOS in drinking and environmental waters worldwide.

Mak et al. (2009) presents data on perfluorinated compounds in tap water in China, Japan, India, the U.S., and Canada.

Takagi et al. (2008) reported on PFOA and PFOS in raw and treated tap water in Osaka, Japan.

6.4.3 Sediment and Soils

As mentioned above, perfluorinated chemicals in land applied sludge from a local wastewater treatment plant has contaminated grazing land in Alabama. This could potentially be a route of contamination of the food supply. Currently, tissue levels of perfluorinated chemicals in cattle that grazed on this land are being studied.

p. 284 Paragraph beginning with "Limited monitoring data..."

As mentioned above, Paustenbach (2007) discussed soil deposition of PFOA emitted into the air from the Washington Works facility. This is a pathway for groundwater contamination in this vicinity.

House Dust

Kato et al. (2009) measured perfluoroalkyl chemicals in house dust.

Bjorklund et al. (2009) measured PFOA and PFOS in indoor dust in houses, apartments, day care centers, offices, and cars.

Section 6.5 General Population and Occupational Exposure

The studies listed under Potential for Human Exposure above are relevant to this section (e.g the discussions on p. 291-292).

p. 295. Emmett et al. (2006a) and Steenland et al. (2009c) reported higher serum levels for children than for young adults in a population exposed to PFOA in drinking water.

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Section 6.7 Populations with Potentially High Exposure

Minnesota Department of Health (2009) reported on biomonitoring of populations exposed to perfluorinated chemicals through private wells or public water supplies.

Data from the C8 Science Panel about exposure in their study area should be discussed here: Steenland et al. (2009c), Bartell et al. (2009), West Virginia University School of Medicine (2009).

Section 6.8.1

Small et al. (2009) discusses data needs related to environmental fate and transport.

p. 315. 8. Regulations, Guidelines, and Advisories

PFOA and PFOS are included in USEPA's Contaminant Candidate List 3 for consideration for MCL development (USEPA, 2009).

<http://www.epa.gov/ogwdw000/ccl/ccl3.html>) and USEPA is currently developing Lifetime Health Advisories for drinking water for PFOA and PFOS.

p. 316. Table 8.1. It is important to note that the provisional USEPA Health Advisories for PFOA and PFOS in drinking water are intended to protect for short term exposure and are not intended to protect for chronic exposure.

Citations

The citations listed below are not included in the draft document. Additionally, some citations mentioned in the comments above are listed in the citation list of the draft document, but are not currently cited in the text. It is recommended that those citations should be discussed in the text.

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Office of Science
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Mark N. Mauriello
Acting Commissioner

November 2, 2009

Ms. Nickolette Roney
Division of Toxicology and Environmental Medicine, ATSDR
Mailstop F-62, 1600 Clifton Road, NE
Atlanta, Georgia 30333

RE: Addendum to Comments on Draft Toxicological Profile for Perfluoroalkyls, Docket
Control Number ATSDR-253

Dear Ms. Roney,

I would like to bring to your attention two additional studies that have just become available which are relevant to evaluation of effects of perfluorinated chemicals in the general population.

Steenland et al. (2009) found a statistically significant increased risk of high cholesterol in children associated with increasing PFOA and PFOS in the C8 Health Study population in Ohio and West Virginia.

Nelson et al. (2009) report positive associations between PFOA, PFOS, and PFNA and total and non-HDL-cholesterol in participants of the 2003-2004 NHANES study, representative of the general U.S. population.

Thank you for the opportunity to comment on the draft Toxicological Profile, and please feel free to contact me at gloria.post@dep.state.nj.us if you need further information.

Citations:

Nelson, J.W., Hatch, E.E., and Webster, T.F.. Exposure to Polyfluoroalkyl Chemicals and Cholesterol, Body Weight, and Insulin Resistance in the General U.S. Population. *Env. Health Perspect.* doi: 10.1289/ehp.0901165. Online 2 November 2009.

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http://www.c8sciencepanel.org/pdfs/Status_Report_C8_and_lipids_in_children_28Oct2009.pdf

Sincerely,

Gloria B. Post, Ph.D., DABT
Research Scientist

cc: Judy Louis, NJDEP
Perry Cohn, NJ DHSS



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October 30, 2009

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Mailstop F-62
1600 Clifton Road, NE
Atlanta, Georgia 30333

Subject: Comments on draft Perfluoroalkyls Toxicological Profile, docket control number ATSDR-253

Dear Ms Roney:

As requested in the Federal Register notice of July 23, 2009, I would like to submit comments on the ATSDR Draft Toxicological Profile for Perfluoroalkyls.

The attached comments on the epidemiological studies reviewed in the draft Toxicological Profile for Perfluoroalkyls represent my analysis of human health effects, primarily focused on perfluorooctanoic acid (PFOA). They accompany comments focused primarily on laboratory animal studies, submitted separately by Dr. Gloria Post of the New Jersey Department of Environmental Protection

Dr. Post and I serve on the New Jersey Drinking Water Quality Institute and its Health Effects Committee and develop risk assessments on drinking water contaminants. (The Institute is a legislatively mandated advisory body that recommends drinking water standards to the New Jersey Department of Environmental Protection.) Currently, we are updating our current drinking water guidance on PFOA and developing a New Jersey Health-based Maximum Contaminant Level for New Jersey.

We have recently been informed about the imminent publication of another epidemiological study shortly after the due date for these comments and we plan to send a separate letter briefly discussing this study after its release.

If there is any question on the material discussed here, I can be reached by email at Perry.cohn@doh.state.nj.us or by phone at 609-588-3128. However, the phone number will be changing shortly because the office is being moved to another location.

Sincerely,

Perry Cohn, PhD MPH
Research Scientist
New Jersey Department of Health and Senior Services
Consumer Environmental and Occupational Health Services
P.O. Box 369
Trenton, NJ 08625-0369

C: Jerald Fagliano, NJDHSS
Gloria Post, NJDEP

**Comments on the Draft ATSDR Toxicologic Profile on Perfluoroalkyls:
Assessment of Epidemiological Studies**

**Perry Cohn, PhD MPH
New Jersey Department of Health and Senior Services
Consumer Environmental and Occupational Health Service**

October 30, 2009

Introductory Comments

These comments on the draft Toxicological Profile on Perfluoroalkyls are directed at the descriptions and conclusions about the epidemiological studies involving exposures to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), as requested in the Federal Register notice of July 23, 2009. These include separate sections on occupational and population-based studies. General comments in each section include relevant studies available by August, 2009. Specific comments on studies that were included in the draft ATSDR Toxicological Profile are noted in the page-by-page analysis following the general comments. Citation of new studies, including a synopsis and critique, are listed at the end in each section.

An important concern is that the epidemiological studies reviewed in this Toxicological Profile do not seem to have been critically analyzed beyond what each of the cited authors noted in their text. In addition, there was a general absence of reporting on marginally statistically significant findings and trends that tended to show concordance among the studies. Subdividing categories of mortality or morbidity often results in too few cases to achieve statistical significance and can obscure more generalized effects, such as the combination of metabolic disease, hypertension and atherosclerosis that can affect the overall system.

I also think that it important that the final draft include findings from both the C8 Health Project and the C8 Science Panel on the populations served by the perfluoroalkyl (largely PFOA) contaminated water systems around DuPont Washington Works in Parkersburg, West Virginia, even though it is a cross-sectional study. Since the focus of this document is health effects from environmental exposures, these data are even more relevant than the occupational studies.

The available epidemiological studies have numerous limitations, as discussed in this document, but the health effects reported in the epidemiological literature are more concordant, given those limitations, than reflected in the summary opinions expressed in the Toxicological Profile. In particular, there is insufficient rationale to the statement, "Thus, the lack of reported health effects at the reported body burdens precludes identifying the animal model that would be most appropriate for human risk assessment based on similar toxic effects." (Animal-to-Human Extrapolation. Lack of Reported Effects in Humans, p. 198). ATSDR should not use that rationale to avoid development of Maximum Risk Levels (MRLs). Especially for PFOA there is more than adequate data from experiments with laboratory animals to develop a quantitative risk assessment that can be used to develop a chronic oral MRL (further addressed in the comments on the Minimal Risk Levels portion of the Relevance to Public Health section), and there is sufficient evidence from the epidemiological literature, even with the limitations discussed in the draft document and below, to support the development of health-based guidelines and standards for the perfluoroalkyls.

General Comments

Inhalational Exposure: Occupational Studies

Occupational exposures included primarily inhalation, but probably also dermal and oral routes. Occupational studies were conducted at the 3M Cottage Grove, MN, Decatur, AL, and Antwerp, Belgium facilities, the DuPont Washington Works plant in Parkersburg, WV, and the Miteni plant in Italy. These facilities included buildings where PFOA and/or PFOS were manufactured, as well as buildings using these chemicals in the manufacture of other chemicals and films. Workers at the 3M Decatur plant, which manufactured POSF, had elevated serum PFOA and PFOS (Olsen et al., 2003b).

Chronic Diseases

Several mortality studies, one incidence study and one health claims study of workers at the two companies, 3M and DuPont, with facilities in the U.S. constitute the literature on health effects from occupational exposures. (The incidence study and the health claims study were not included in the draft Toxicological Profile, but are highly relevant.) Unfortunately, in the DuPont studies did not include any analysis by exposure, except for ischemic heart disease. Some commonalities have been observed among the results of those studies, in contrast to the statements made in the Draft Toxicological Profile.

Bladder cancer incidence appeared to be elevated among the entire workforce (no exposure assessment) (Leonard, 2003), but not with mortality data at the DuPont Washington Works. It was also found to be elevated by job exposure assessment using mortality and health claims data at the 3M Decatur plant (Alexander et al., 2003; Alexander and Olsen, 2007).

Kidney cancer mortality was elevated among the exposed workforce at the 3M Decatur plant (Alexander et al., 2003), and kidney cancer incidence among the entire workforce (no exposure assessment) using incidence (Leonard, 2003).

Prostate cancer mortality was increased with exposure at the 3M Cottage Grove plant (Lundin and Alexander, 2007) and prostate cancer health claims were marginally elevated at the 3M Decatur plant (Olsen et al., 2004). (Prostate cancer incidence was elevated with marginal significance versus serum PFOS level in the Danish population-based study (Eriksen et al., 2009).) DuPont did not find an increase in prostate cancer mortality or incidence, but the DuPont studies were not based on exposure (Leonard, 2003; Leonard et al., 2008).

Multiple myeloma incidence and mortality were elevated with marginal statistical significance at the DuPont Washington Works (Leonard, 2003; Leonard et al., 2008), though at the 3M Cottage Grove plant there were fewer deaths. There was no analysis of leukemia and lymphoma health claims at the 3M Decatur plant.

Deaths from diabetes, ischemic heart disease (IHD), acute myocardial infarction, and the category, atherosclerosis and aneurysm, were elevated among workers at the Washington Works plant (Leonard et al., 2008). Death attributed to IHD was elevated among exposed workers in the top two quartiles of serum PFOA (Sakr et al., 2009). These findings are consistent with elevated total cholesterol and LDL (Sakr et al., 2007a,b). Diabetes and cerebrovascular disease (CVD) mortality was elevated among exposed workers at the 3M Cottage Grove plant (Lundin and Alexander, 2009), which parallels the association (though not in all analyses) of PFOA levels with elevated total cholesterol and TG and decreased HDL (Olsen et al., 2000; Olsen et al., 2007). Death from hypertension with and without heart disease was marginally elevated among those with known or probable exposures (Lundin and Alexander, 2007). In addition, there were increased health claims at the 3M Decatur plant for diabetes, as well as biliary tract disorders and combined acute and chronic cholecystitis (Olsen et al., 2004). It appears that the combination of all heart disease with the related category, cerebrovascular disease, suggests an overall connection between PFOA exposure and atherosclerosis across the various studies, which is also consistent with effects on serum lipid chemistry.

There were also notable increases of white cell neoplasms (Leonard, 2003; Leonard et al., 2008) and carcinoid (Morel-Symons et al., 2007) at the Washington Works.

There are general limitations among the available studies assessed in the draft Toxicologic Profile. These were only partially acknowledged for some studies. In addition, some associations that were reported in the literature were not acknowledged.

Many of the studies reported on mortality rates. Death certificates provide information that is frequently inaccurate because there can be multiple contributing causes. For example, prostate cancer is usually not the primary of death in men with prostate cancer. Another example is diabetes. In a study of known diabetic patients (N = 2766), only 10% had diabetes listed as the cause of death (Bild and Stevenson, 1992). In addition, incorrect diagnoses increase with age of the patient (Bain et al., 1998).

The issue of the "healthy worker effect" is partly addressed by internal workplace rate comparisons, but the general failure of available studies to include short-term workers who may have had very high exposures (e.g., those cleaning batch-processing equipment) could have missed important associations. There is a history of many chemical companies using short-term workers to clean the most contaminated equipment. The rationale is that the longer the duration of exposure, the better the chances of detecting an effect if it is true, but that is not necessarily the reality. One interesting observation (Olsen et al., 2003b) is that the highest serum PFOA levels among 3M Cottage Grove plant employees who worked 5 years or less. Of the 11 male employees with serum PFOA above 10 ppm, 5 worked 5 years or less, and, likewise, above 20 ppm 4 of the 7 worked 5 years or less. It appears that longer-term employees (up to 40 years) had job duties with much less exposure. Therefore, exclusion of short-term workers with < 1 yr employment, as done in the 3M studies reported above, may undercount exposed cases.

Another issue is that the small proportion of female employees limits the ability of the occupational epidemiology to adequately address specific effects among women.

A final issue is that differences in the exposure to other chemicals between the different manufacturing facilities may also influence outcomes by effect modification.

Blood Chemistry (Hepatic Effects and Endocrine Effects)

Regarding serum liver chemistry observations, both the studies at 3M (Olsen and Zobel, 2007), at DuPont (Sakr et al., 2007a,b) and at Miteni (Costa et al., 2009) showed elevated levels of either aspartate aminotransferase (AST), alanine aminotransferase (ALT) or gamma glutamyl transpeptidase (GGT).

One of the potential problems with the blood chemistry studies is the failure to account for sample times relative to biorhythms, i.e., shift, time within shift, and time relative to meals, which can affect the parameters studied

Not mentioned in the Toxicological Profile is the finding by Sakr et al. (2007a) that serum calcium, iron, potassium, and the enzyme lactate dehydrogenase were significantly associated with serum PFOA, though the direction of those associations was not given. No mention was made of those parameters in any other occupational study, but the C8 Health Project descriptive statistics revealed similar phenomena with calcium iron, magnesium, and, among women, potassium. The point is that there are data in the literature that were not addressed, and that there may be a significant number of parameters that had also been measured to which study author paid inadequate attention.

A more subtle issue is that dose-response may be stronger at lower, environmentally relevant, levels (see Oral Exposure section, below). Therefore, a comparison of blood chemistry results in the occupational setting, where even the least exposed had levels that were high compared to the highest levels seen in environmental studies, might not always show associations with exposures that are observed within the lower range of exposures in the general population.

Oral Exposure: Community and Population-Based Health Studies

Community health studies include those conducted and in progress in the area around the DuPont Washington Works facility located in Parkersburg, WV (C8 Health Project and C8 Science Panel). These were largely due to a court settlement. In particular, the Little Hocking, OH, water system had the highest water contamination (≥ 3 ug/L) and its residents had the highest serum PFOA level. Five other communities around Little Hocking had lower levels (≥ 0.05 ug/L) of PFOA in the drinking water. People with at least one year of residence, work or school in one of those communities were eligible for inclusion in the studies. There are various studies in progress and completed. Serum PFC and clinical data were collected for most of the 67,000 subjects. Participation was estimated to be approximately 80% (MacNeil et al., 2009). The richness and size of the

collected data is unusual for situations of environmental contamination, but was relegated to brief mention in the Ongoing Studies section in the draft Toxicological Profile.

The median serum levels in the first and second deciles, 6 and 9.8 µg/L are within the range prevalent in the U.S. general population, as shown in the 2003-2004 National Health and Nutrition Evaluation Survey (NHANES), where the 75th and 95th percentile levels were 5.8 and 9.8 µg/L (Calafat et al., 2007). The highest serum levels in the Little Hocking area were in the 100s to 1000s of ug/L range. The median serum level was approximately 29 ug/L.

Serum levels of total cholesterol, LDL cholesterol and uric were significantly elevated with increased PFOA among adults and appeared to plateau at higher levels (Steenland et al., 2009a; Steenland et al., 2009b). Similar results were seen for the relationships between PFOA and lipids (C8 Science Panel, 2009b). The liver enzymes, ALT and AST, also showed a strong dose-response with serum levels of PFOA using with univariate analysis (C8 Health Project, 2009), but the dose-response curve appears to plateau within the concentration bounds of the study. Anti-nuclear antibody and the self-reported incidence of Sjögren's disease and scleroderma, which both primarily affect women, were associated with serum PFOA levels in 30-50 year old females (C8 Health Project, 2009a).

(The Emmett et al. (2006) study of the C8 exposed population, which was the first analysis of health effects in these communities to be published, was small and suffered from low participation.)

In addition, there have been a series of population-based reproductive outcome studies in a variety of locations around the world. A general comment about those studies is that analysis with more data on potential confounders, such as the Apelberg et al. (2007) study in Baltimore, the Danish (Fei et al. (2007, 2008a,b) study, and a Japanese (Washino et al., 2009) study found associations between reproductive effects and perfluoroalkyls, while those with the less data on confounders (Grice et al., 2007; Monroy et al., 2007) did not find associations. This trend of being able to detect associations when there is better adjustment for confounding was also noted by Olsen et al. (2009). Stein et al. (2009) did not find associations between low birth weight or preterm birth with PFOA in the Little Hocking area, but the incidence of preeclampsia was moderately associated. They did find that PFOS was associated with preterm births and low birth weight, as well as preeclampsia. However, 60% of the women included in the PFOS analysis were excluded from the PFOA analysis due to missing data on residency in a water system of interest, even though the analysis method used only serum PFOA or PFOS levels.

Two population-based studies on adult-onset diabetes (i.e., Type 2) are also available, including one by the C8 Science Panel (MacNeil et al., 2009), which was negative. In that study ≥20 years of residence in the contaminated water systems was required for eligibility, which excluded many cases. Furthermore, ascertainment depended initially on self-reporting, which probably excluded a large number of adults who were unaware that they were insulin-resistant. However, the Lin et al. (2009) study of 2003-2004 data

from the CDC National Health and Nutrition Evaluation Survey (NHANES) found an association with PFOA and PFOS and was analyzed with much more biochemical detail relevant to the insulin-resistant form of adult onset diabetes.

A matter is that is not addressed by any study at this point is whether there are effects in adulthood resulting from exposures during development (prenatal or infancy), such as the effects seen in the study by Hines et al. (2009) on metabolic endpoints and White et al. (2008) on mammary gland development in mice.

Specific Comments

Page 4. Public Health Statement, HOW CAN PERFLUOROALKYLS AFFECT MY HEALTH?

Workers	Inhalation/dermal—Long-term exposure to perfluoroalkyls at work has not been associated with significant adverse health effects, but two studies in workers found changes in sex hormones and cholesterol associated with the levels of PFOA in blood.
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This statement falls short of describing the published observations and those from the unpublished reports available through the USEPA docket AR-226 which contains a tremendous amount of published and unpublished information on these chemicals. There is reasonable evidence (see above and below), given that most of the investigations are based on death certificates, that exposed workers are indeed affected.

General population	Little research has been done on the general population to answer the question of whether perfluoroalkyls may be associated with adverse health effects. Ingestion—A single study of people whose drinking water contained perfluoroalkyls did not find problems in a number of clinical measures tested. The study did not, however, examine developmental risks for children or cancer. The 326-person study was too small to address these issues.
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At this time there are unpublished data as well as peer-reviewed studies stemming from the C8 Health Study of 67,000 subject in Ohio and West Virginia exposed to drinking water contaminated with ≥ 0.05 ug/L to over 3 ug/L of PFOA. These studies are using data collected on serum perfluoroalkyls, liver enzymes, lipoproteins, hormones, and other blood constituents, as well as self-reported diseases. The lowest decile of serum PFOA, which has a median of 6 ug/L of serum, approximates the 75th percentile level, 5.8 $\mu\text{g/L}$, found in the 2003-2004 National Health and Nutrition Evaluation Survey (Calafat et al., 2007). The highest levels are in the 100s – 1000s ug/L range. More studies are underway. The size of this effort dwarfs the small studies by Emmett et al. (2006a,b) that were cited in the draft Toxicological Profile.

Two of these studies (Steenland et al., 2009a,b) show an increased percentage of subjects with clinically elevated cholesterol and uric acid, starting with PFOA concentrations just above the lowest category.

Preliminary descriptive statistics from the C8 Health Project suggest that there are other clinical parameters, including serum levels of liver enzymes, hormones and electrolytes that are associated with serum PFOA. The slope of some of these appears to be steepest at the lowest deciles of exposure.

Page 6. Public Health Statement, HOW CAN PERFLUOROALKYLS AFFECT CHILDREN?

The C8 Health Study includes almost 5000 children under 10 years old and approximately 7500 children from 10-18 years old. Preliminary evidence suggests associations of several parameters and serum PFOA levels.

The developmental studies noted in the Statement also found associations with PFOS. For example, Apelberg et al. (2007) found associations with both PFOS and PFOA for birth weight and size, Fei et al. (2007, 2008a,b) found associations with PFOA but not PFOS for several measures of fetal growth, and Washino et al. (2009) found associations with PFOS but not PFOA for birth weight. Stein et al. (2009) identified modest associations of PFOA with preeclampsia and birth defects and of PFOS with preeclampsia, preterm births and low birth weight in the C8 Health Study population.

Page 7 Public Health Statement. IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PERFLUOROALKYLS?

In the Detecting Exposure section, elevated perfluoroalkyl serum levels in residents exposed to contaminated drinking water have also been found in Germany (Holzer et al., 2009) and in Minnesota (Minnesota Department of Health, 2009). Also, elevated serum PFOA among workers has also been found at other facilities, so the last sentence in this section should start with, "For example,".

Pages 7-8 Public Health Statement. WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

It should be noted that the USEPA Provisional Health Advisories for PFOA and PFOS are intended to protect for short-term exposure, not chronic exposure.

Pages 11-14 Relevance to Public Health. Summary of Health Effects

This section is densely packed with summary statements. The General Comments (above) and the Specific Comments (below) show some disagreements with those statements. Certainly, the occupational studies, which are the primary source of the statements, have numerous limitations, e.g., use of death certificates, inclusion of few females, and insufficient person-years for less frequent diseases. The DuPont study that was summarized on Page 14 was based on the whole plant and did not include an analysis by exposure, with the exception of one disease category.

Nevertheless, there are concordant findings across a larger body of studies, including new studies and older studies not included in the draft document. The concordant morbidity and/or mortality findings, as noted in General Comments, include diabetes, a combination of cardio- and cerebrovascular end points, bladder cancer and prostate cancer. Blood chemistry results from cross-sectional studies indicate that liver enzymes and lipid chemistry results can be seen as concordant across studies at 3M, DuPont, and Miteni (Italy).

The developmental studies are not concordant, but the ones that had better adjustment for confounding found significant outcome associations with serum PFOA levels.

Pages 21-22 Relevance to Public Health. Minimal Risk Levels. Human Data.

As noted in my General Comments, the draft Toxicological Profile does not present sufficient justification for the decision not to develop a chronic oral MRL based on the animal studies supported by the results of the epidemiology. This was more or less acknowledged in the statement, summarized on Page 25 of the draft,

“Although MRL derivation is not recommended for perfluoroalkyls at this time based on the information [on humans] summarized above, relevant information from animal studies that could have been considered for MRL derivation (i.e., studies with the LOAELs) for perfluoroalkyls with at least a minimal size database is summarized below.”

There are similar epidemiological issues for most chemicals for which MRLs have been developed.

By comparing across species by using internal dose and using the relationship between external dose in ug/kg./day and serum concentration (ug/L) discussed by Post et al. (2009a,b) and Tardiff et al. (2009), one can develop a chronic MRL in mg/kg/day from the extensive scientific literature on health effects of PFOA in laboratory animals. Clewell (2006) predicts the relationship between exposure and serum level in humans, as discussed in Tardiff et al. (2009). Clewell's model predicts factors of 0.1 and 0.127 relating intake ($\mu\text{g/kg/day}$) to serum concentration ($\mu\text{g/mL}$). Based on mean water ingestion of 17 mL/kg/day (USEPA, 2004), the 100:1 ratio between serum and drinking water levels (Post et al., 2009a) gives a factor of 0.167 $\mu\text{g/kg/day}$ intake per $\mu\text{g/ml}$ in serum (Post et al., 2009b). The USEPA (2005) draft risk assessment also made comparisons between species (e.g. experimental animals and humans) by serum PFOA level. Through the use of uncertainty factors established by ATSDR, USEPA, and other regulatory agencies, one can address the interests of public health before fully resolving the issues in the epidemiology. However, as noted in these comments, there is sufficient support from the results of epidemiological studies, as discussed in these comments to warrant moving ahead with an MRL.

The comments provided by Dr. Gloria Post elaborate further on this subject.

“The fact that humans take longer to achieve steady state than animals should not preclude the use of animal studies as the basis for a chronic MRL, if the serum levels in animals are used as the basis for the risk assessment. Even though chronic MRLs are defined as applying to exposures of one year or longer, in practice, they are used to address chronic exposures, such as residential exposure to contaminated soil or drinking water. Humans who are exposed through environmental media (e.g. water, soil) at the level of the chronic MRL for a duration somewhat shorter than the duration required to reach steady state will have somewhat lower serum levels than they will have at steady state. Thus, application of a chronic MRL for exposures through environmental media (e.g. water, soil) for durations longer than those considered to be

"Intermediate" but which are not long enough for steady state to be reached will be protective for potential health effects."

Page 35. Inhalation: Death.

Subjects in the Gilliland and Mandel (1993) at the 3-M Cottage Grove APFO plant were assembled from workers with >6 months of employment, which may have excluded short-term highly exposed workers.

3M also conducted a major mortality study of workers at the Cottage Grove plant (Lundin and Alexander, 2007; now published as Lundin et al., 2009). This was in the USEPA docket but was missed.

The cohort was assembled from workers who spent one year or more employed between January, 1943 and December, 1997. Follow-up continued until December, 2002. Jobs were categorized by a panel of "veteran" workers and industrial hygienists (Alexander, 2001) as having had jobs with definite exposure, probable exposure and no exposure to PFOA (in the absence of air data or serum levels). There were 68, 368 and 371 death certificates available for workers with definite exposure, probable exposure and no exposure to PFOA. Only 25 deaths were ascertained for those with > 1 year of working in a job with definite exposure. Exposure-stratified SMRs were calculated by life table analysis using data for Minnesota, and internally compared hazard ratios (HR) were calculated using Cox time-dependent modeling. HRs were adjusted for gender, age at entry to the study, birth year, and wage type (hourly versus salary). In addition, HRs were generated using actual and imputed smoking data, though there was a problem with the degree of missing data.

The SMR for **diabetes** mortality (N = 18) was elevated among workers with probable (2.0, 95% CI 1.2, 3.2) PFOA exposure. In contrast, those never exposed had an SMR of 0.5. The known exposed group had zero deaths from diabetes, but that group was too small and had too little follow-up time to have meaningful numbers. The adjusted HR comparing those with probable exposure to those with no exposure was 3.7 (95% CI 1.4, 10).

Death from hypertension with and without heart disease was somewhat elevated among those with known or probable exposures, SMR = 1.7 (95% CI 0.3, 5) and 1.8 (95% CI 0.4, 5), respectively, stemming from 3 cases in each disease category. The weighted SMR for death from hypertension overall would be 1.75 with an approximate 95% CI of 0.6 to 4 (using tabulated 95% CI factors for estimating a Poisson-distributed variable; Breslow and Day, 1987). Data on all hourly workers includes 5 deaths from heart disease with hypertension and 4 from hypertension only. The respective SMRs are 2.1 and 1.8 and the combined weighted SMR would be 1.95 with an estimated 95% CI of 0.9 – 3.7. This is marginally significant and is consistent with elevated deaths from diabetes and an increase in total cholesterol in most occupational- and community-based studies of PFOA. No internal HR comparisons were reported for these categories.

Cerebrovascular disease (CVD) exhibited statistically significant adjusted HRs in the range of 5 to 7, based on 3 deaths among those definitely exposed for ≥ 6 months, and HRs of approximately 2 among those moderately exposed, based on 19 deaths, depending on whether and which smoking data was included (Lundin and Alexander, 2007). (Adjustment included gender, age at study eligibility, birth year and wage type.) In Lundin and Alexander (2009) the HRs for CVD among workers with high or moderate exposure jobs were 4.6 (95% CI 1.3, 17) adjusted for gender and birth year. The HR of workers with ≥ 5 years of cumulative time in a job with definite exposure was 2.1 (95% CI 1.0, 4.6) compared with those with < 1 year. Stratifying on latency period reduced the HR to 4.4 in the analysis with a 10-year exposure lag. (It is notable that the risk dropped with extended follow-up: the SMR was 1.6 (95% CI 0.5, 3.7) based on 5 deaths among workers with definite exposures, but in an earlier analysis (Alexander, 2001) the SMR was notably higher, 2.6 (95% CI 0.84, 6.0), based on the same 5 deaths, and 3.1 (95% CI 0.89, 8.5) when analyzed by cumulative exposure. In that study workers with ≥ 5 years of exposure to PFOA had 3 observed deaths from CVD while 0.42 deaths were expected, yielding an SMR of 7.1 with an estimated 95% CI of 1.5 to 21.) This observation would be consistent with decreasing risk after exposure was diminished, e.g., by changing jobs or retirement, but that analysis was not presented.

The SMR for death from prostate cancer among workers with known exposure for any amount of time was 2.1 (95% CI 0.4, 6.1), based on 3 cases, while workers with probable exposure had an SMR of 0.9 and office-based employees had an SMR of 0.5. Workers with at least one year of known exposure had an SMR of 2.7 (95% CI 0.3 – 10), based on 2 cases. The HR for the high exposure group was statistically significant 6.6 (95% CI 1.1, 38), based on 2 deaths, while those in the moderately exposed group exhibited an HR of 3.0 (95% CI 0.9, 9.7), based on 10 deaths. The HR in the combined moderate and high exposure category was 3.2 (95% CI 1.0, 10). The HR of workers with ≥ 5 years of cumulative time in a job with definite exposure was 3.7 compared with those with < 1 year. Adding a 10-year latency period (Lundin and Alexander, 2007) increased the respective adjusted HRs to 8 (95% CI 1.5, 45) and 3.4 (95% CI 1.1, 11), based on 2 and 8 deaths, respectively. Inclusion of data on smoking had only a small effect on the observed HRs. Since most prostate cancer is a disease from which men usually die of other causes before it becomes fatal, these numbers may represent death from more aggressive forms of the cancer.

Limitations of this study included the reliance on mortality data, the relatively small number of definitely exposed workers and their ascertained deaths, and the exclusion of workers with less than one year of employment. This latter approach may miss very high exposures among short-term workers who have been found in other occupational studies to be used to conduct cleanings of highly contaminated equipment, such as batch reactors. In addition, for the HR analysis those employed for less than 6 months in high exposure job were added to the probable exposure group, which may have removed some employees who should have remained a purely high exposure group analysis. Another limitation was that smoking data, an important risk factor for bladder cancer, was available for only 36% of the cohort, though there was a much greater percentage (65%) from those with definite exposures compared with the unexposed (20%). Among those

with data, workers definitely exposed to PFOA had a higher prevalence of those who ever smoked, 65%, compared to unexposed workers, 47%, but there may be substantial bias due to the minimal data available. Lung cancer was not increased among any exposure group.

Page 36. Inhalation: Death.

The Alexander et al. (2003) study at the 3-M Decatur plant required at least one year of employment to be included in this analysis, which similarly may have excluded short-term highly exposed workers.

Notably, the 1998 biomonitoring at the Decatur POSF plant conducted by Olsen et al. (2003b) showed serum PFOA levels as high as PFOS levels, which indicates that PFOA levels were elevated even before initiation of PFOA manufacture in 1999, and that the epidemiology conducted at that plant is relevant to the discussion. There was little relationship between individual PFOS and PFOA levels.

Deaths from cerebrovascular disease and heart disease were not elevated, but there were too few cases of the former to support any conclusion. Diabetes mortality was not reported.

Page 36 Inhalation: Death.

As noted in the Toxicological Profile, follow-up of bladder cancer occurrence (incidence and mortality) among the 2083 3-M Decatur workers through 2002 was more thorough, using a series of outreach efforts with questionnaires to obtain information (Alexander and Olsen, 2007). A total of 11 bladder cancer cases were ascertained, compared with 3 cases in the earlier effort (see above), though 4 more self-reported cases were not included since they did not consent to validation. Thus, the exposures of those 4 cases were not characterized and the effect of their exclusion was not tested in a sensitivity analysis.

Bladder cancer was elevated for the whole group of participants, 11 observed versus 8.6 expected, SIR = 1.3 (95% CI 0.64, 2.3), though if the 4 excluded cases were also counted, the SIR would be 1.7 (0.98, 2.9; using tabulated 95% CI factors for estimating a Poisson-distributed variable; Breslow and Day, 1987).

Although there are various study limitations, these findings are consistent with the observation of elevated bladder cancer incidence among DuPont workers (Leonard, 2003; see below).

A minor note is that the text in the Toxicological Profile states that this follow-up of bladder cancer at the Decatur plant included "all current, retired, and former employees", as well as information about 188 deceased workers. The writers probably did not intend to confuse the reader by implying that even short-term employees were included in this

analysis. In fact, this is exactly the same cohort as in Alexander et al. (2003), but with more thorough follow-up that also added 5 additional years.

Epidemiological investigations at the Decatur plant also included a health claims study (Olsen et al., 2004), which is discussed in more detail below (Inhalation: Cancer and Inhalation: Endocrine Effects).

Pages 37-38 Inhalation: Death.

The Leonard (2006) study of mortality at the DuPont Washington Works from 1948 through 2002 has been published (Leonard et al., 2008 and Sakr et al., 2009).

The text in the Toxicological Profile should make clear that all SMRs were based on the entire plant, without additional analyses by exposure or job category. Only the Cox proportional hazards modeling of IHD (Sakr et al., 2009) employed exposure categories and cumulative exposure.

Regarding diabetes, the Toxicological Profile states that the “investigator noted that the lack of agreement with other studies of PFOA workers”. This is in sharp contrast to results at the 3-M Cottage Grove plant (Lundin and Alexander, 2007) where the SMR for diabetes mortality (N = 18) was elevated among workers with probable (2.0, 95% CI 1.2, 3.2) PFOA exposure. In contrast, those never exposed had an SMR of 0.5. At the 3-M Decatur plant health claims for diabetes among those with 10+ years of employment in the chemical plant was 30% elevated above expected with marginal significance. Of course, as note above, death certificate ascertainment of and treatment for adult-onset diabetes are likely incomplete.

In addition to the elevated internal SMRs for kidney cancer and diabetes mentioned in the Toxicological Profile, death from hypertension without heart disease was elevated compared to other DuPont workers in the region, though not to statistical significance (SMR = 2.0; 95% CI 0.7, 4.8; based on 5 deaths). The impact on deaths attributed to hypertension and diabetes is consistent with observations at 3-M plants.

Page 46 Inhalation: Cardiovascular Effects. : DuPont Washington Works

In contrast to the statement made in the Toxicological Profile that there is “no convincing evidence of increased mortality due to heart disease in general or IHD specifically” in Leonard et al. (2006, now published as Leonard et al. (2008) and Sakr et al. (2009)), death from all heart disease (N = 314) was elevated with marginal statistical significance: the internally-based SMR for all heart disease was 1.10 (95% CI 0.98, 1.23) and the internally-based SMR for IHD (N = 239) was (1.09, 95% CI 0.96, 1.24). In heart disease studies even small elevations are regarded as important because of the frequency of occurrence. The SMRs for females were higher, but based only upon a handful of deaths. In addition, death from hypertension without heart disease was elevated compared to other DuPont workers in the region, though not to statistical significance (SMR = 2.0; 95% CI 0.7, 4.8; based on 5 deaths).

Only IHD was examined by exposure category and was found to be 40-60% elevated with marginal statistical significance among those in the third and fourth quartiles of serum PFOA. Sakr et al. (2009) concluded that there was “no convincing evidence” to link PFOA exposure to IHD mortality, but there was a general trend and the inability to adjust for known confounders could easily obscure an actual association.

The Toxicological Profile did not include Lundin and Alexander (2007, published in 2009), which is described below. Discussion of this study should be added. It provided strong evidence of an association between job exposure to PFOA and cerebrovascular disease as well as the suggestion that deaths attributable to hypertension were also associated with job exposure.

In addition, in Leonard (2003, see “new” studies, below) the SMR for acute myocardial infarction was 1.4 (95% CI 1.2, 1.6), based on 126 cases and the SMR for atherosclerosis and aneurysm was 2.0 (95% CI 1.2, 3.1), based on 18 cases, respectively from the 1957-2000 period. There was no analysis by exposure measures (job, serum PFOA, or duration) or personal lifestyle, BMI or SES.

Page 47 Inhalation: Hepatic Effects.

The study at the 3M Cottage Grove conducted by Gilliland and Mandel (1996) was small, as noted, composed of all directly exposed workers employed between 1985 and 1989 (N=50) and 65 randomly picked “low” exposure workers (without direct exposure for at least 5 years) workers. Total serum organic fluorine, representing all polyfluorinated chemicals, was used as a surrogate for PFOA exposure. Having “low” exposure workers was meant to provide a range of exposures, but this group had high total serum fluorine levels as well.

Page 48 Inhalation: Hepatic Effects.

This longitudinal study (Olsen et al., 1999) of blood sampling at the 3-M plants in Decatur and Antwerp in 1995 and 1997 was small and depended on volunteers. Missing from the description of the study in the draft Toxicological Profile are observations that are consistent with those in other studies. Total cholesterol exhibited a marginal statistically significant increase with serum PFOS in the 1997 sampling at each locations. Alkaline phosphatase displayed a non-significant trend of increase with serum PFOS in both 1995 and 1997 with combined data from both plants, while GGT showed a similar trend of increase in the 1997 data. Those with the highest serum PFOS exhibited a notably higher mean and median AST (33 IU/L) than the lowest category (25 IU/L) in the 1995 testing, while median ALT was notably elevated in the highest serum PFOS category (49 and 45 IU/L) versus the lowest PFOS category (43 and 30 IU/L) during both years. Unfortunately, there were no statistical tests to compare PFOS categories with the lowest category. As noted in the draft, there were only a handful of volunteers in the highest category.

Page 48 Inhalation: Hepatic Effects.

In addition to what is noted in the draft Toxicological Profile, multivariate analysis of combined data from all 3M plants showed statistically significant associations between PFOA and increased ALT and GGT (Olsen and Zobel, 2007). Analysis of the separate plants found a significant association of PFOA with increased AP, ALT, GGT, and marginally significantly increased cholesterol and TG among the workers at the Decatur plant. Serum AST was associated with PFOA among workers at the Cottage Grove plant. Exceedances of clinical reference range at the combined group of workers were greater in the 7th, 8th and 9th PFOA deciles for ALT and TG and the 9th and 10th PFOA deciles for GGT.

Page 49 Inhalation: Hepatic Effects.

In addition to what is noted in the draft Toxicological Profile about the Sakr et al. (2007a) study at the DuPont Washington Works, slopes for TG, LDL and ALT were positive. Statistical significance may have been difficult to achieve for ALT and GGT since there were only 233 tests available for analysis. Because of differences in longitudinal participation and because there were more than one test per individual, some individuals carried greater weight in the analyses.

Page 49 Inhalation: Hepatic Effects.

In the subset of the Sakr et al. (2007b) study in which persons using lipid/cholesterol control agents were excluded, serum PFOA was statistically significantly associated with elevated serum AST and ALT, in addition to elevated GGT noted by the draft Toxicological Profile. Age and family history were not statistically significant covariates for any measured serum liver enzyme or bilirubin and alcohol use was not significant for bilirubin. The models where PFOA was statistically significant explained 14 - 29% of the variance. This is important because it demonstrates that there was a greater association of liver chemistry endpoints with PFOA after obvious confounding was removed without over-adjusting.

Page 49 Inhalation: Hepatic Effects.

The Costa et al. (2004) study of the Miteni plant (Italy) has been published with updates (Costa et al., 2009). Testing in the 2000-2007 timeframe showed an association between PFOA and AST, ALT and GGT.

Pages 51 and 54 Inhalation: Endocrine Effects and Reproductive Effects.

The Toxicological Profile correctly notes that among male workers, estradiol and testosterone were elevated with higher serum PFOA in both the 3M (Olsen et al., 1998) and the DuPont (Sakr et al., 2007b) cross-sectional studies. (Unfortunately, the DuPont study did not give the units or further elaborate, so it is difficult to further interpret those findings.) However, the statement, "Taken together, the results showed no significant hormonal changes at the levels of PFOA measured [in the 3M study].", does not fit with

the acknowledgement of similar findings at DuPont. The statement refers to the small number of workers in the high exposure groups and confounding by BMI, but the commonality of findings should be the focus of attention.

Unfortunately, hourly changes in the release of many hormones and the pulsatile nature of that release means that multiple samples should be taken and that time of day and, for occupational studies, shift, should be included in the analyses. In these studies there was only one sample.

Page 51 Inhalation: Renal Effects.

While it is not clear whether renal function was affected, certain serum metals, calcium, iron, magnesium, potassium, and sodium had higher serum levels with increasing serum PFOA among workers at the DuPont Washington Works (Sakr et al., 2007a). This is consistent with univariate results from the C8 Health Project.

Page 52 Inhalation: Endocrine Effects.

It should be noted that there is only one occupational study of thyroid hormones. In addition, iodine sufficiency (urinary iodide) should also be measured in any study of potential thyroidal impact.

The health claims study at the 3M Decatur plant (Olsen et al., 2004) found that claims for diabetes was marginally elevated (RR = 1.3, 95% CI 0.9, 2.0), based on 42 cases among those who worked ≥ 10 years in the chemical plant.

Page 54 Inhalation: Developmental Effects.

The Grice et al. (2007) study of the 3M Decatur plant should be dropped from consideration for developmental effects because gestational age, the single most important determinant of birth weight, was not available for inclusion in the analysis.

Page 55 Inhalation: Cancer.

Again, the study at the DuPont Washington Works (Leonard, 2006, Leonard et al., 2008) had no analyses based on exposure, except for the analysis of IHD (Sakr et al., 2009).

The DuPont Cancer Registry surveillance report from Leonard (2003) indicated that bladder and kidney cancer incidence among male employees was elevated during the 1959-2001 period. The Registry relies on data from active employees and SIRs were calculated based on internal comparison (5-year time and age categories) with company-wide incidence rates. The respective SIRs for bladder and kidney cancer were 1.9 (95% CI 1.2, 3.1) and 2.3 (95% CI 1.4, 3.6), based on 18 cases each. They point out that the incidence of both types of cancer was higher in West Virginia than in the U.S. or in neighboring Ohio. However, elevated bladder cancer is consistent with the analysis of mortality among workers at the 3M Decatur facility (Alexander et al., 2003; see above).

In addition, myeloid leukemia incidence was marginally significantly elevated, SIR = 2.0 (95% CI 0.86, 4.0), based on 6 cases, and multiple myeloma incidence had an SIR of 1.7 (95% CI 0.69, 3.6), based on 7 cases. Including 2 cases (0.14 expected) among females attributed to combined multiple myeloma and immunoproliferative neoplasms, resulted in an SIR of 2.1 for the entire group with an estimated 95% CI of 1.0 – 4.1 (using tabulated 95% CI factors for estimating a Poisson-distributed variable; Breslow and Day, 1987). There was no analysis by exposure, duration or personal lifestyle (e.g., tobacco and alcohol use), BMI or SES.

Leonard (2003) also reported on internally-based SMRs among males from the DuPont Mortality Registry from 1959 through 2000. In general there were too few female employees and too few deaths, with one exception, noted below. Death from bladder (N = 7) and kidney (N = 8) cancer had SMRs of 1.6 (95% CI 0.64, 3.3) and 1.5 (95% CI 0.68, 3.0), respectively, which is consistent with the incidence results. Similarly, death from myeloid leukemia (N = 6) and combined multiple myeloma and immunoproliferative neoplasms (N = 5) had SMRs of 1.7 (95% CI 0.62, 3.7) and 1.4 (95% CI 0.46, 3.4), respectively. Including 2 deaths (0.11 expected) among females attributed to combined multiple myeloma and immunoproliferative neoplasms, resulted in an SMR of 2.0. Death from non-cancer blood and blood-forming diseases had an SMR of 3.0 (95% CI 0.95, 6.9).

The SMR for diabetes deaths (N = 12) was 1.6 (95% CI 0.81, 2.75). The SMR for acute myocardial infarction was 1.4 (95% CI 1.2, 1.6), based on 126 cases and the SMR for atherosclerosis and aneurysm was 2.0 (95% CI 1.2, 3.1), based on 18 cases, respectively. There was no analysis by exposure measures (job, serum PFOA, or duration) or personal lifestyle, BMI or SES.

In addition, there was an elevated incidence of carcinoid tumor at the Washington Works (Morel-Symons et al., 2007).

Epidemiological investigations at the 3M Decatur plant also included a health claims study. Analysis of 1993-1998 health claims compared workers at the POSF (“chemical”) plant with workers at the film plant (Olsen et al., 2004). (This time frame is prior to the start of PFOA production, but biomonitoring in 1998 (Olsen et al., 2003b) showed serum PFOA levels as high as PFOS levels.) There were 652 and 659 workers, respectively, included in the analysis, including 211 and 345 workers employed for ≥ 10 years before 1993. Some workers had worked in both plants, but were not analyzed separately, which might mask associations. The expected number was based on “a normative database, which consisted of the remainder of the 3M manufacturing population” in the U.S. (approximately 20,000 workers) and calculated with an “employee health claim grouper (EHCG) software used by the Ingenix Employer Group.

It found that among male workers (N = 530) there were 5 prostate cancer “episodes of care” (involving 5 unique individuals) versus an age-adjusted expected number of 3.1, an RR = 1.6. (In this instance that means 5 unique cases.) A relative comparison with male workers at the neighboring “film” facility, which did not have direct exposure to POSF,

yielded an RR of 7.7 (95% CI 0.9, >100). Among long-term workers, the RRs were increased: RR = 2.7 (based on 4 unique cases) and employment in the chemical versus the film plant, RR = 8.2 (95% CI 0.8, >100). In addition, there were 59 episodes of care for enlarged prostate (involving 53 unique individuals) versus an expected 40.6, an RR = 1.5. Likewise, the number of acute prostatitis episodes was increased, 73 versus 39.2 expected based on 55 unique individuals. However, these latter two conditions were also elevated among male workers at the neighboring "film" facility. Therefore, it is possible that the workplace population in that location was more prone to prostate ailments. An important limitation is that the analysis was not adjusted for possible confounders, including smoking.

Gastrointestinal tract problems that were increased among long-term chemical plant versus film plant workers included malignant and benign colon cancer. There were 3 unique malignant cases (versus an expected 0.8) in the chemical plant compared to zero cases (versus an expected 1.6) in the film plant. Among long-term workers, the RR for benign colon cancer in the chemical plant was 2.4, based on 20 unique individuals, while it was approximately 1.0 in the film plant, based on 18 unique individuals. The internal comparison RR was 2.4 (95% CI 1.3, 4.5).

Page 116 Oral: Hepatic Effects.

The low participation, 30-50% in the randomly selected portion of the Emmett et al. (2006) study subjects (N = 343 in 161 households) and the additional group of subjects (N = 54 in 35 households) who were volunteers selected by lottery potentially allows for significant selection bias.

The median serum PFOA concentration, 354 ng/mL, was much higher in this study than in the C8 Health Project (28 ng/mL, see below). (Eighteen subjects were occupationally exposed and probably accounted for the top 5% of the serum PFOA levels.)

Despite those negative findings of the small Emmett study, descriptive statistics from the large, high participation C8 Health Project (2009) showed that serum levels of the liver enzymes, AST and ALT, are elevated with increasing serum PFOA levels in the C8 Health Project, while in the Emmett et al. study the slope estimates are negative. However, in the Emmett study the AST and ALT levels over the serum PFOA interquartile range (25%-ile - 75%-ile, 184 – 571 ng/mL) are 18 and 27 IU/L and 15 and 27 IU/L, respectively. In addition, serum levels of the liver enzyme, GGT, over the interquartile range of serum PFOA were 14 and 27 IU/L. Similarly, the interquartile range for total cholesterol was 172 and 220 mg/dL. These results were univariate (i.e., not adjusted by age, gender or medications).

Recently, analysis of total cholesterol by the C8 Science Panel (Steenland et al., 2009a) showed that the OR for cholesterol levels being above the clinical reference range (>240 mg/dL) in adults in the C8 Health Project were 1.2, 1.3 and 1.4 for the second, third and fourth quartiles, respectively, of serum PFOA versus the first quartile. All ORs were statistically significant. Similar results were seen for PFOS. In addition, extensive regression analyses showed statistically significant associations of both PFOA and PFOS

with total cholesterol, LDL cholesterol, total non-HDL cholesterol, triglycerides and the total cholesterol/HDL cholesterol ratio. Analysis only of subjects taking lipid control medications results in similar, though muted, associations with PFOA, but there was “no consistent trend” for PFOS. All analyses were adjusted for age, gender, BMI, education, exercise level and current alcohol consumption.

Also recently, Steenland et al. (2009b) found that uric acid was associated in a dose-response manner with increasing deciles of both PFOA and PFOS. Elevated uric acid has been linked to hypertension, and with less evidence to stroke, diabetes and metabolic disease. They also showed a dose response by quartile categories set up within the ≤ 20 ug/L subgroup, i.e., the response is present within the range of general population exposure.

These results have also been found in children (C8 Science Panel, 2009b).

One question that arises is whether the relationships that seem obvious in the much larger C8 Health Project, a clear dose-response, are not observed in the Emmett et al. study because the effects (e.g., total serum cholesterol) occurred within the lower exposure ranges and plateaued at higher serum PFOA concentrations. This is especially significant because the associations exhibited no threshold down to the lowest deciles of exposure (see figure in Steenland paper), and the serum levels in the lower deciles in the C8 study population are within the range of exposures of the general US population (Calafat et al., 2007).

Page 124 Oral: Renal Effects

While it is not clear whether renal function was affected even though creatinine levels were not changed (Steenland et al., 2009b), certain serum electrolytes, calcium, iron, magnesium, sodium among adults, and potassium among women, had higher serum levels with increasing serum PFOA in the preliminary descriptive statistics (C8 Health Project, 2009). This finding is consistent with that observed by Sakr et al. (2007a) at the DuPont Washington Works. No other study reported on that, though the data was probably collected.

Page 125 Oral: Endocrine Effects.

Regarding the overall negative findings in the Emmett et al. (2006) study, the low participation, 30-50% in the randomly selected portion of the study subjects (N = 343 in 161 households) and the additional group of subjects (N = 54 in 35 households) who were volunteers selected by lottery potentially allows for significant selection bias.

Regarding the lack of effect on thyroid hormones, iodine sufficiency (urinary iodide) should also be measured in any study of potential thyroidal impact. In addition, the pulsatile nature of protein or peptide hormone release means that multiple blood sample should be taken for greater accuracy.

Recently, Lin et al. (2009) examined a subpopulation of NHANES participants at least 12 years old (N = 3,685) tested for perfluoroalkyl chemicals. This study had a great amount of biochemical, health behavior and body measurement data available for inclusion in the analysis, as well as diabetes diagnostic methods. However, NHANES is a cross-sectional study and it cannot be easily determined whether the diabetes symptoms preceded the exposure or the reverse.

Serum PFOA was significantly associated with pancreatic beta-cell function (all three step-wise statistical models), and with blood insulin measurement (in the fully saturated model). Covariates included age, gender, BMI, family history of diabetes, and use of relevant medicines. PFOS was associated with both measures and with the calculated measure, homeostasis model assessment – insulin resistance (HOMA-IR). Since the authors chose to show probabilities only for statistically significant associations, there may be more diabetes diagnostic indicators that have marginal statistical significance.

Also recently, MacNeil et al. (2009) reported on the incidence of self-reported adult-onset diabetes (diabetes 2) that had been validated by medical record check and its relationship to serum PFOA in the C8 Study population. The data was analyzed as a case-control study, and controls were non-cases among the eligible population. The study population was restricted to a subset with at least a 20-year residency in the area prior to diagnosis, though the entire group (without restrictions) was also examined. No association was found in any decile of serum PFOA. Fasting blood glucose levels were also not associated with serum PFOA, though properly treated individuals would be less likely to show elevated glucose levels.

There are several limitations. Cases were lost because of missing residency data even though the serum PFOA and PFOS were used in the analysis. This could have introduced an ascertainment bias. In addition, since the study group is based on self-reporting before medical record validation, that may exclude many who are unaware of their adult-onset diabetes, since there is evidence that insulin-resistance is significantly under-diagnosed in the general population, depending on access to health care (U.S. Preventive Services Task Force, 2008). The proportion of unidentified cases was estimated to be 30-50% of the total number of cases. Another concern, which the authors also noted, is that the covariates they used in their analysis “may be intermediates on the pathway from exposure to disease, and therefore arguably should not be controlled in the analysis”. Lastly, the authors also noted that since the study was cross-sectional in nature (even though they used a case-control type of analysis), it cannot be used for causality, i.e., one can’t determine whether “exposure preceded disease”.

In the crude descriptive data for estradiol, testosterone and prolactin (C8 Health Project, 2009), there appear to be notable changes with serum PFOA, especially in the tables and figures divided by age and gender.

Page 131 Oral: Immunological and Lymphoreticular Effects.

The C8 Health Project (2009a) descriptive statistics and the C8 Science Panel (2009) Status Report on immunological effects showed increased levels of anti-nuclear

antibodies (suggestive of autoimmune disease) as well as occurrence of self-reported scleroderma and Sjögren's syndrome (autoimmune diseases) in women with higher serum PFOA.

In addition, it is interesting that C-reactive protein levels are notably decreased with increasing PFOA. The change in CRP is of large magnitude and indicates that PFOA at these levels is having a biological effect consistent with known effects of PPAR alpha activators, such as the fibrates, in humans.

Serum levels of immunoglobulins A and E also showed a steady, though small, decrease with increasing serum PFOA.

Page 135 Oral: Reproductive Effects.

The C8 Health Project (2009) descriptive statistics showed notable effects on estradiol and prolactin levels in females with higher serum PFOA. In both girls and women estradiol was lower with higher PFOA, while lower prolactin was associated with higher serum PFOA in females over the 16 years old.

The new study by Fei et al., (2009) showed a longer time to conception with increasing maternal serum PFOA and PFOS in the general population. Women in each of the three highest quartiles of each chemical exhibited approximately one-third greater risk of having a time-to-pregnancy >12 months than those in the respective lowest quartile.

The new study by Joensen et al. (2009) showed an association between serum PFOA and spermatozoa quality and number in young Danish men.

Page 141 Oral: Developmental Effects.

In the Washino et al. (2009) study maternal serum PFOS was statistically significantly associated with birth weight of females, but not males. Maternal PFOA was not associated with birth weight. However, adjustment only for gestational age, the most significant confounder, resulted in a statistically significant slope coefficient for PFOA versus birth weight of all infants and of female infants and a marginally significant slope coefficient for PFOA versus head circumference among males. One potential major limitation of this study was the low participation rate, 29%, which could have resulted in selection bias. In addition, maternal age, parity and BMI, included as covariates in the fully adjusted models, were also related to serum PFOA level (i.e., they are probably intermediate variables). This could have reduced the regression coefficients in the fully adjusted models. Lastly, the relatively low levels of PFOA in serum in this study may have limited the accuracy of the exposure assessment, given the detection limit of 0.5 ug/L (7% of women had no detectable PFOA).

The new study by Monroy et al. (2008) was a small hospital-based prospective study (N = 101) that was part of a larger Family Study cohort recruited during 2004-2005 in Hamilton, Ontario. A significant limitation of this study was the very low (10%) recruitment rate, which could allow substantial selection bias. No association was found

between PFOA or PFOS and birth weight, but no detail was reported on the regression analysis to find out whether there was a trend that would have been statistically significant in a larger study.

Page 142 Oral: Developmental Effects.

In addition to the extensive limitations of the Nolan et al. (2009) study discussed in the Toxicological Profile, including the lack of any individual-based data on exposure or key confounders known to influence birth weight and gestational age (e.g., parity, smoking status, nutrition, and socioeconomic status), one should also include potential misclassification of residential history related to moving to a residence more appropriate to a larger family prior to the birth, but with a different PFOA exposure level). This is more important for this study since serum PFOA data was not available for incorporation into the analysis.

The C8 Science Panel (Stein et al., 2009) reported results of a case-control study on the outcome of pregnancies during the 5 years before enrollment (August, 2005 through July, 2006) among women whose residence during their live or stillborn singleton pregnancy was completely in one of the water districts targeted by the C8 Health Project or whose residence during the 90 days before their miscarriage was in one of the targeted water districts. In addition, there was a separate analysis of serum PFOS that was not focused on water districts, which looked at all pregnancies regardless of drinking water source. There were 5262 singleton pregnancies in women whose serum was analyzed for PFCs among 3996 unique women. The water system-based PFOA study excluded 3290 pregnancies mostly due to missing data on water district, for a total of 1972. That analysis centered on white women with no history of pre-pregnancy diabetes for whom there was a complete set of data, 1845 pregnancies. The PFOS analysis included all 5262 pregnancies.

Preeclampsia, a potentially dangerous syndrome that can occur late in pregnancy, was marginally associated with serum PFOA above the median (adjusted OR = 1.3, 95% CI 0.9, 1.9), compared to those below the median, but the risk was lower above the 75th percentile. Miscarriage, low birth weight (LBW, < 5.5 pounds) and preterm birth (≥ 3 weeks early) were not associated. Neither birth weight nor gestational age at birth was analyzed as a continuous variable. Serum PFOS level above the 90th percentile was associated with preterm birth. The 75th – 90th and the 90th percentile of PFOS were associated with a higher risk of LBW in comparison to PFOS less than the median. Preeclampsia was also associated with PFOS, both above versus below the median and above the 90th percentile versus below the median. Birth defects were not associated with PFOS.

Important limitations are 1) the quality of the self-reported information, especially since birth records had not been accessed for this study, 2) the PFOA study design that excluded approximately 60% of pregnancies mostly because of incomplete data on residency in water system of concern during pregnancy even though the analysis was based on the serum PFOA level, and 3) lack of data on maternal BMI and infant gender.

The study did not conduct a sensitivity analysis by examining the full group, i.e., the same set of subjects analyzed for PFOS. The investigators are developing exposure reconstruction models, which will allow inclusion of greater numbers of pregnancies

Page 148 Oral: Cancer.

As noted above, the occupational exposures were thought to be primarily from inhalation. However, this has not been studied and at least one author has suggested that oral exposure may have accounted for a significant amount of the absorbed perfluoroalkyl chemicals.

Cancer incidence was prospectively studied in a subset of a cohort (N = 57,000) assembled from 50-65 year olds in the Danish general population during December, 1993, through May, 1997 (Eriksen et al., 2009). Cancer cases (713 prostate, 332 bladder, 128 pancreas and 67 liver) that occurred in this cohort were ascertained from the Danish Cancer Registry and the Danish Pathology Data Bank after a median 7 years of follow-up ending at the start of July, 2006. Those cases (N = 1111 males and 129 females) and a random sample (N = 680 males and 92 females) of those not diagnosed with cancer were tested for serum PFOA and PFOS.

PFOA and PFOS were highly correlated ($R = 0.70$), and median levels were 6.9 and 35 ug/L, respectively, among control males, and 5.4 and 29 ug/L, respectively, among control females. Females with cancer had slightly higher PFOA, 6.0 ug/L.

Only pancreatic cancer exhibited a notably increased, but not statistically significant, RR = 1.6 among those in the fourth quartile of PFOA. Bladder and liver cancer cases had a reduced incidence with higher PFOA, while prostate cancer incidence was slightly elevated. However, PFOS was marginally associated with increased prostate cancer in the 2nd, 3rd and 4th quartiles. The RR for the 4th quartile was 1.4 (95% CI 0.99, 1.9).

Page 190 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models. Risk Assessment.

Extrapolations based on serum levels, as discussed by Post et al. (2009) and Tardiff et al. (2009) avoids the limitations of extrapolating between pharmacokinetic models for different species.

Page 198 Animal-to-Human Extrapolations.

The text states that “No significant health conditions have been associated with the serum levels of perfluoroalkyls...” and “Health evaluations of perfluoroalkyl workers ... or of people undergoing high environmental exposure ... have **not provided evidence of adverse effects**”. The summary of human health and serum chemistry results should reflect the concordances noted in these Comments. The weight of evidence is not that clear cut.

In addition, there is little rationale for the statement,

“Thus, the lack of reported health effects at the reported body burdens precludes identifying the animal model that would be most appropriate for human risk assessment based on similar toxic effects.”.

The epidemiology has numerous limitations, as discussed in this document; however, as also noted here, the health effects reported in the epidemiological literature are more concordant, given those limitations, than the opinion expressed in the Toxicologic Profile. ATSDR should not use that rationale to avoid development of Maximum Risk Levels (MRLs).

In addition, as noted in the comments by Dr. Post, the public health logic of this sentence is unclear:

“As a result of these large differences in kinetics, internal doses (i.e., serum concentrations of PFOA) achieved during intermediate-duration exposures in rats or monkeys would not represent steady-state internal doses that might be achieved in humans over longer exposure durations.”

Page 198-200 Toxicities Mediated through the Neuroendocrine Axis.

The Toxicological Profile correctly notes that among male workers, estradiol and testosterone were elevated with higher serum PFOA in both the 3M and the DuPont cross-sectional studies. (Unfortunately, the DuPont study (Sakr et al., 2007a) did not give the units or further elaborate, so it is difficult to further interpret those findings.)

It is interesting that the C8 Health Project findings suggest that estradiol decreased among females with increasing serum PFOA.

Page 203 Children's Susceptibility.

The ongoing C8 Health Study will also provide information on associations of many endpoints with PFOA exposure in children. Notably, children exposed to PFOA in drinking water had higher serum PFOA levels than adults (Emmett et al., 2006, Steenland et al., 2009c). This could be due to greater water consumption per kilogram body and/or differences in the toxicokinetics.

Page 207 Biomarkers Used to Characterize Effects Caused by Perfluoroalkyls.

The following sentence should be deleted, based on the comments provided here:

“Health evaluations of workers exposed to perfluoroalkyl compounds or of subjects environmentally exposed via their drinking water have not provided evidence of adverse health effects in the groups studied (Emmett et al. 2006a; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1999, 2003a; Sakr et al. 2007a, 2007b).”

Page 207 Populations that are Unusually Susceptible.

As mentioned in Steenland et al. (2009a), several studies have shown associations with increased liver enzymes, so it is agreed that people with compromised liver function may be particularly susceptible.

Page 212 Existing Information of Health Effects of Perfluoroalkyls.

A variety of C8 Science Panel studies have recently been published in peer-reviewed publications and more are expected. As well, studies based on the NHANES are being published. It can no longer be said that there are “limited” data on environmental exposures.

Page 213 Identification of Data Needs.

There is currently sufficient information with a “sufficient degree of certainty” to develop a chronic oral MRL for PFOA. This is also addressed in the comments on the Minimal Risk Levels portion of the Relevance to Public Health section.

Page 214 Chronic-Duration Exposure and Cancer.

I disagree with the statement that “for the most part, no significant adverse effects have been identified”, as outlined in the General Comments here and in the Specific Comments. This section should also discuss the DuPont incidence study (Leonard, 2003) the recent occupational 3M mortality study of Lundin et al. (2009), the blood chemistry study of Miteni workers in Italy, as well studies of chronic exposure in the community (Lin et al., 2009; MacNeil et al., 2009; Steenland et al., 2009a,b). There is more concordance among the studies than discordance.

Page 216 Reproductive Toxicity.

Both the study on spermatozoa quality and number (Joensen et al., 2009) and the study by Fei et al. (2009) on increased time to pregnancy found associations with PFOA and PFOS.

Page 218 Developmental Toxicity.

In addition to the extensive limitations of the Nolan et al. (2009) study discussed in the Toxicological Profile, including the lack of any individual-based data on exposure or key confounders known to influence birth weight and gestational age (e.g., parity, smoking status, nutrition, and socioeconomic status), one should also include potential misclassification of residential history related to moving to a residence more appropriate to a larger family prior to the birth, but with a different PFOA exposure level). This is

more important for this study since serum PFOA data was not available for incorporation into the analysis.

In the Washino et al. (2009) study adjustment only for gestational age, the most significant confounder, resulted in a statistically significant slope coefficient for PFOA versus birth weight and a marginally significant slope coefficient versus head circumference among males. A major limitation of this study was the low participation rate, 29%, which could have resulted in selection bias. In addition, maternal age, parity and BMI, included as covariates in the fully adjusted models, were also related to serum PFOA level (i.e., they are intermediate variables). This could have reduced the regression coefficients in the fully adjusted models.

The C8 Science Panel study of low birth weight, preterm birth, birth defects, miscarriage and preeclampsia of pregnancy by Stein et al. (2009) observed associations between PFOS and low birth weight, preterm birth and preeclampsia and marginally between PFOA and preeclampsia. However, neither birth weight nor gestational age at birth was analyzed as a continuous variable. Important limitations are 1) the quality of the self-reported information, especially since birth records had not been accessed for this study, 2) the PFOA study design that excluded approximately 60% of pregnancies mostly because of incomplete data on residency in water system of concern during pregnancy even though the analysis was based on the serum PFOA level, and 3) lack of data on maternal BMI and infant gender. The study did not conduct a sensitivity analysis by examining the full group, i.e., the same set of subjects analyzed for PFOS. The investigators are developing exposure reconstruction models, which will allow inclusion of greater numbers of pregnancies

Page 219 Immunotoxicity.

The C8 Health Project (2009) descriptive statistics and the C8 Science Panel (2009) Status Report on immunological effects showed increased levels of anti-nuclear antibodies (suggestive of autoimmune disease) as well as occurrence of self-reported scleroderma and Sjögren's syndrome (autoimmune diseases) in women with higher serum PFOA.

Page 220 Epidemiological and Human Dosimetry Studies.

I disagree with the statement that "No significant health conditions have been associated with the serum levels of perfluoroalkyls measured in these studies,..." as outlined in the General Comments here and in the Specific Comments. My disagreement stems from a critical review of old and new studies.

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October 27, 2009

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
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RE: Comments on Draft Toxicological Profile for Perfluoroalkyls
Docket Control Number ATSDR-253

To Whom It May Concern:

I appreciate the opportunity to comment on the Draft Toxicological Profile for Perfluoroalkyls (Profile) dated May 2009. I have served and am currently serving as a toxicology consultant to plaintiffs in litigation involving perfluoroalkyl chemical issues. I have the following comments on the profile.

On page 21 the Profile states the following.

In the cohort studied by Emmett et al. (2006b), the average concentration of PFOA in water that the subjects may have consumed over a period of 3 years before the health assessment was conducted was 3.5 ug/L. Median serum PFOA levels in residents were 105 times the level in their residential drinking water. Blood levels of perfluoroalkyl compounds have been measured both in workers and in members of the general population. As indicated in the preceding section, no significant health effects have been associated with specific serum levels of perfluoroalkyl compounds, although minor alterations in serum lipids and in serum estradiol levels in male workers have been reported (Costa 2004; Olsen et al. 1998; Sakr et al. 2007b).

There are a number of problems with these statements. First, the elevations in liver enzymes associated with PFOA serum concentration in studies of worker populations are not included (Olsen et al. 2003; Sakr et al. 2007). Second, the elevations of serum lipids and serum estradiol (and presumably liver enzymes had they been included) are described as "minor alterations." These alterations are likely not minor for the subset of individuals experiencing them. While the mean, median, or geometric mean serum levels are not pushed into a clinically unacceptable range by the association with PFOA in these studies, the alterations in central tendencies for these parameters are very likely the result of a larger impact on a small subset of susceptible individuals whose elevations may well be clinically adverse. While the characterization of these elevations as "minor alterations" may be somewhat consistent with those of the industry authors of these studies, the Profile description should represent an independent critique of study data. Accepting the assessment of the industry study authors without an independent assessment of study data is a criticism voiced by Dr. Lynn Goldman who peer reviewed an earlier draft of the Profile. The problem remains.

An illustration of the subset effect is the association of PFOA or PFOS with liver enzyme elevations for the Olsen et al. (2003) study of workers in two facilities producing PFOA and PFOS containing products.

Tetra Tech Inc.

The liver enzyme alanine aminotransferase (ALT) is significantly elevated in the fourth serum PFOS/PFOA quartile versus the first quartile. The magnitude of the elevation is 7 IU/L (33 versus 26, respectively). The upper bound of the reference range for ALT is 40 IU/L so the elevated value of 33 IU/L for the fourth quartile is within the reference range and an individual with such a level would not be considered to be exhibiting signs of liver toxicity. If, however, one considers the small portion of workers that were actually pushed into the clinically excessive ALT range by the association of ALT with PFOS/PFOA, it is apparent that adverse effects likely occurred. The number of individuals exceeding the reference range for the fourth quartile was 13 of 105 while the number for the first quartile was 4 of 105. The difference between first and fourth quartiles is an indicator of the impact of PFOA on ALT. Nine workers (8.6 percent) may have experience elevated liver enzyme levels beyond the reference range as a result of their exposure to PFOA. ALT values for quartile three are also elevated (7 IU/L) but less so than for the fourth quartile.

The analysis shown above for liver enzymes cannot be done for lipids or estradiol because the individual serum data for workers were not included in the reported studies. It is likely that the modestly elevated mean values for these parameters would also be the result of more extreme alterations in a subset of workers.

The other problem with the Profile statement shown above is that declares the Emmett et al. (2006b) study to have resulted in “no significant health effects” and then goes on to suggest that a no-observed-adverse-effect-level (NOAEL) could possibly be established based on the PFOA human body burden observed in this study. This statement is troubling as the Emmett 2006b study has a serious weakness that would limit its ability to detect a positive association between serum PFOA and any outcome assessed. The major limitation of the Emmett et al. (2006b) study is the participation rate which is only 37 percent. This very low participation rate results in likely self-selection bias. The process normally used to address a low participation rate is a follow up on a sample of nonparticipants to determine if their outcome response would be different from that of participants. No such follow up was done by Emmett (2006b). There is a large literature on self-selection bias, sometimes referred to as volunteer bias, that indicates that individuals with conditions that make them more susceptible to adverse effects tend to participate in health surveillance studies to a lesser extent than do healthy individuals and that the absence of these less healthy study subjects will bias the study results toward the null. Such a bias in the relationship between exposure and health outcomes may underestimate or fail to detect an adverse effect when one exists. Cross sectional volunteer studies have been reported to average 74 percent participation (Morton et al. 2005. *Amer J Epidem* 163:197-203). Self-selection bias has been detected with participation rates as high as 93 percent (Lyngbye et al. 1988. *Scand J Soc Med* 16:209-215). The 37 percent participation rate of the Emmett et al. (2006b) study is very low and likely biased the results of that study toward the null. Emmett et al. (2006b) should not be considered for use as a NOAEL and should not be considered convincing evidence of the absence of an association between PFOA body burden and adverse effects in the general population.

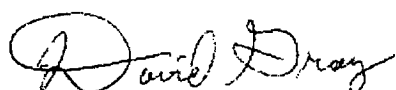
The participation rate limitation of the Emmett et al. (2006b) study is also present in most of the occupational studies although to a lesser extent. Many of the occupational studies have participation rates of 55 percent or less.

Finally, the Profile does not include a number of important recent reports relating to PFCs and human health. Studies by Lundin et al. (2009)¹ and Steenland et al. (2009)² need to be included. Steenland et al. (2009) was conducted in 46,294 members of the general population with an estimated 81 percent participation rate. The Steenland et al. (2009) findings conflict with those of the much smaller Emmett et al. (2006b) study. Steenland et al. (2009) state the following.

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 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): 1.21, 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.

The negative findings of the Emmett et al. (2006b) study are cited in many locations in the Profile. The Profile concludes that there is an absence of observed health effects in PFOA community studies. This conclusion should be modified given the more recent human studies.

Sincerely,



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¹ Lundin J.I. et al. 2009. Ammonium perfluorooctanoate production and occupational mortality. *Epidemiol.* 20:921-28.

² Steenland K. et al. 2009. Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. *Am J Epidemiol.* DOI: 10.1093/aje/kwp279.

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Agency for Toxic Substances and Disease Registry (ATSDR)
 Toxicological Profile for Perfluoroalkyls
 Draft for Public Comment

Comments of Olga V. Naidenko, Ph.D.
 Senior Scientist
 Environmental Working Group

“ATSDR needs to protect people and the environment from contamination with perfluoroalkyls”

October 30, 2009

Environmental Working Group (EWG) is a non-profit public health and environmental research and advocacy organization based in Washington, DC. We focus much of our research on potential health risks from chemical contamination of food, water, consumer products, and the environment.

EWG appreciates this opportunity to comment on the Agency for Toxic Substances and Disease Registry (ATSDR) draft toxicological profile for perfluoroalkyl compounds. We are very concerned, however, with several significant shortcomings of the proposal, most notably that the Agency has decided not to develop minimum risk levels (MRLs) for this entire class of extraordinarily problematic chemicals.

For several critical perfluoroalkyl compounds, including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), there is a rich scientific literature that both supports the need and provides the basis for establishing an MRL. Several states, including New Jersey, North Carolina and Minnesota, have developed risk-based levels for PFOA in drinking water (MDH 2007; NCDENP 2008; NCSAB 2009; NJDEP 2007). The Agency’s decision not to publish an MRL forces state agencies and public health officials across the country to employ their limited resources on developing their own guidance levels for PFOA and PFOS.

Perfluoroalkyls contaminate food, water, wildlife, consumer products, and have been detected in every corner of the globe. They have been found in the blood of virtually all Americans tested over the last decade (Calafat 2007). In the human body, these chemicals are persistent, bioaccumulative and toxic to numerous organs.

PFOA and PFOS are associated with a broad range of developmental effects, including developmental delays, and organ abnormalities (Lau 2007); liver toxicity (Guruge 2006); suppression of the immune system and predisposition to allergies (DeWitt 2008; Fairley 2007; Peden-Adams 2008; Yang 2002; Yang 2000); behavioral effects (Johansson 2008); altered hormonal function (Biegel 1992; Bookstaff 1990; Cook 1992; Liu 2007) as well as liver, pancreatic, testicular, and mammary cancers (Sibinski 1987).

EPA researchers have recently developed provisional drinking water guideline levels for PFOA and PFOS (U.S. EPA 2009c), and the agency is currently engaged in developing drinking water standards for both chemicals (Hegstad 2009). EPA Administrator Lisa Jackson recently announced that perfluorinated chemicals are one of the six chemicals or chemical classes of concern that EPA is considering for “action plan development” for targeted risk management (U.S. EPA 2009b). It makes no sense for ATSDR to claim that it is currently impossible to estimate minimal risk levels for people while the EPA is engaged in that very task – and both agencies are looking at the same basic set of data. Perfluoroalkyl chemicals present a significant, well-characterized risk to human health. There is no reason to delay setting MRLs for both PFOS and PFOA.

With this letter, we make three key points regarding the Agency’s proposal:

- The latest science points to the health risks associated with the PFOA and PFOS levels found in the general population;
- Determining minimal risk levels for two perfluoroalkyls, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), is scientifically feasible;
- The Agency must develop minimal risk levels in order to protect human health from multiple sources of PFOA and PFOS exposure.

Details and rationale for these recommendations are provided below.

1. Latest science points to the health risks associated with the PFOA and PFOS levels found in the general population.

In its draft, ATSDR states (p. 22): “*It could be proposed that measured serum levels of perfluoroalkyls in the populations for whom health data are available be considered body burdens corresponding to no-observed-adverse-effect levels (NOAELs) or perhaps lowest-observed-adverse-effect levels (LOAELs) if the alterations reported in workers are considered adverse.*”

EWG strongly disagrees with this statement. Instead, the Agency should determine NOAELs and LOAELs using standard scientific practice that incorporates safety margins to account for uncertainties and variable susceptibility in the population and that are based on the most recent scientific findings, which, in this case, have found evidence of adverse health effects at the levels of PFOA and PFOS that are found in the general population.

Key studies are listed below:

- A recent study found an association between PFOA and PFOS levels in the blood and delayed time to pregnancy, a well-established indicator of fertility problems. Analyzing data from a cohort of 1,240 women enrolled in a Danish longitudinal study, a team of scientists based at the University of California-Los Angeles found that women with elevated blood levels of PFOA experienced more difficulties in conceiving and were twice as likely to be diagnosed with infertility as women with lower PFOA body burdens. For women with more than 3.9 parts per billion (ppb) of PFOA in their bodies, the risk of infertility increased by 60 to 150 % (Fei 2009).

- Study by Danish scientists associated PFOA and PFOS with lower sperm quality in otherwise healthy young men (Joensen 2009). This study included 105 Danish men (median age 19 years) from the general population; the median levels of PFOA in this population were 4.9 ppb; the median levels of PFOS were at 24.5 ppb. Researchers observed that men with high combined levels of PFOS and PFOA had a median of 6.2 million normal spermatozoa in their ejaculate compared to 15.5 million normal spermatozoa counts among men with low PFOS-PFOA. The authors of the study hypothesized that “high levels of PFAAs may contribute to the otherwise unexplained low semen quality seen in many young men” (Joensen 2009).
- An association of the PFOA and PFOS with serum lipids was reported in a multi-year study of 69,000 West Virginians and Ohioans whose drinking water was contaminated by a fluorochemical manufacturing plant in Washington, W.Va., along the Ohio River (Steenland, Tinker, Frisbee 2009; West Virginia University School of Medicine 2008). These findings of elevated cholesterol and other lipids in people exposed to PFOA in drinking water are in agreement with the increased lipid levels in PFOA-exposed workers in fluorochemical plants (Costa 2009; Sakr, Kreckmann 2007; Sakr, Leonard 2007). The authors of the study concluded: “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” (Steenland, Tinker, Frisbee 2009).
- In the same study, known as the C8 Health Project, greatly decreased concentrations of estradiol were observed in women and in girls with higher serum levels of PFOA (West Virginia University School of Medicine 2008). Adverse effects on the immune system have also been noted (Frisbee 2008). The immune system changes included a significant decrease in serum levels of two immune defense proteins, immunoglobulins IgA and IgE, that correlated with increasing PFOA serum levels (C8 Science Panel 2009).
- The latest publication from the C8 Health Project found that both PFOA and PFOS were significantly associated with elevated levels of uric acid in serum (Steenland, Tinker, Shankar 2009); similar results have been reported in cross-sectional studies of PFOA-exposed workers (Costa 2009; Sakr, Kreckmann 2007). Increased uric acid is a risk factor for hypertension; it may also be associated with stroke and diabetes (Heinig 2006; Steenland, Tinker, Shankar 2009).

These studies are only the latest addition to the rapidly growing body of data indicating that the levels of PFOA and PFOS in the general population cannot be considered LOAELs or NOAELs. On the contrary, present levels of contamination are associated with a range of adverse health effects. To declare current body burden of perfluoroalkyls as either LOAEL or NOAEL would be irresponsible and indefensible from the scientific perspective. We strongly urge the Agency to re-consider this important point and make the final decision that will protect the health of the American public and help in setting standards for these contaminants rather than condone the persistent perfluoroalkyl pollution in people and the environment.

2. Determination of the minimal risk levels for two perfluoroalkyls, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), is scientifically feasible.

In its draft, the Agency decided not to derive the minimal risk levels (MRLs) for perfluoroalkyls (p. 21), citing insufficient human data and large differences in the metabolism of perfluoroalkyls in humans and various laboratory species as the reasons for not developing the MRLs. This decision seems to be in contradiction with another, very clear, statement in the ATSDR draft that *“inspection of the animal database would suggest that there are studies, particularly by the oral route, of PFOS and PFOA in animals that established dose-response relationships that could be used for MRL derivation.”* (p. 23)

Currently, EPA is engaged in developing drinking water standards for PFOA and PFOS; both chemicals have been listed in the final Contaminant Candidate List 3 (CCL3) of water contaminants that may require regulation under the Safe Drinking Water Act (U.S. EPA 2009a). Furthermore, EPA Administrator Lisa Jackson recently announced that perfluorinated chemicals are one of the six chemicals or chemical classes of concern that EPA is considering for “action plan development” for targeted risk management (U.S. EPA 2009b).

In light of these simultaneous developments at EPA, EWG finds it incomprehensible that ATSDR refuses to acknowledge that robust and sufficient data are available to develop MRLs for PFOA and PFOS. The recommendation to develop NOAELs and LOAELs was also given to ATSDR by one of the four peer reviewers of the initial draft, Dr. Edward Emmett, a recognized expert in this field and the author of several studies of perfluoroalkyls in people (Emmett 2006). EWG is very concerned that ATSDR’s decision leaves public health at risk and would slow down rather than facilitate human and environmental health protection.

Below we highlight several studies that jointly provide sufficient toxicological data for determining minimal risk exposure levels for people. The list below primarily addresses the case of PFOA; however, a similar dataset is available for PFOS (see item 6) and we urge the Agency to take a focused look at both of these highly toxic chemicals.

1. Research by EPA scientists demonstrating developmental toxicity at low doses of PFOA exposure in mouse developmental studies (Lau 2007; Lau, Butenhoff 2004). These developmental effects include full litter resorptions, postnatal mortality, decreased birth weight, delayed growth and development, effects on mammary gland development; increased pup liver weight, structural changes in the uterus and metabolic effects in adulthood after prenatal exposures (reviewed in (Post 2009)). Some of these developmental changes are observed at doses as low as 0.1 mg PFOA/kg body weight/day (LOAEL) (Abbott 2007).
2. In follow up studies, EPA scientists observed that in mice, developmental exposure to even lower doses of PFOA, 0.01 mg/kg/day, lead to significant increases in body weight and levels of serum insulin and leptin hormones in mid-life (Hines 2009). These results indicate that fetal exposure to PFOA, similar to fetal exposure to other toxic chemicals, may predispose towards obesity in adulthood (Hines 2009).

3. Chronic dietary exposure to PFOA has been associated with liver, pancreatic, testicular, and mammary cancers in laboratory animals (Sibinski 1987). These results prompted the U.S. EPA's Science Advisory Board to classify PFOA as a "likely human carcinogen" (SAB 2006).
4. Chronic dietary exposure to PFOA in adult female rats was associated with decreased body weight and blood changes; this study reported NOAEL at 1.6 mg/kg/day dose of PFOA (U.S. EPA 2005).
5. A study in Cynomolgus monkeys linked oral PFOA exposure with sudden mortality; this study reported a LOAEL of 3 mg/kg/day of PFOA (U.S. EPA 2005).
6. For PFOS, U.S. EPA scientists recently identified the subchronic toxicity study in Cynomolgus monkeys (Seacat 2003) as acceptable and "critical" for the derivation of the Provisional Health Advisory value for PFOS contamination of drinking water (U.S. EPA 2009c). In this study, effects of PFOS on liver, thyroid hormones and serum lipids have been observed, with a NOAEL of 0.03 mg/kg/day (U.S. EPA 2009c).

Overall, the existing data provide a strong foundation for deriving MRLs for PFOA and PFOS. EWG urges the ATSDR to recognize that this important next step is scientifically feasible and should be done to provide the necessary guidance to state agencies and public health officials across the country.

3. The Agency should develop minimal risk levels in order to protect human health from multiple sources of PFOA and PFOS exposure.

Perfluoroalkyl chemicals are found in a wide range of consumer products, including water, stain and grease repellants, cookware, food wrap, carpeting, furniture and clothing. Perfluoroalkyls contaminate food because of bioaccumulation in the food supply (Martin 2004; Tittlemier 2007) and due to leaching from food packaging materials (Begley 2008; Begley 2005; Deon 2007). Furthermore, according to recently published EPA research, degradation of perfluorochemical-based polymers, like those used in grease-proof food packaging or waterproofing clothing, releases stable short-chain perfluoroalkyl compounds that are exceptionally persistent in the environment (Renner 2009; Washington 2009).

Children and infants are at particular risk from widespread presence of perfluoroalkyl pollutants. Scientists have found that children tend to have elevated exposure to PFOA, PFOS, perfluorohexansulfonate (PFHxS) and related perfluoroalkyls (Emmett 2006; Olsen 2004). Moreover, PFOA and PFOS have been found in maternal and umbilical cord blood, so there is transplacental exposure whereby these pollutants cross the placenta and transfer from mother's body to the fetus (Apelberg, Goldman 2007; Fei 2007; Inoue 2004; Midasch 2007). Perfluoroalkyls have been also found in breast milk, so infants are exposed to these chemicals via lactational transfer (Karrman 2007; Kuklenyik 2004; Tao 2008; Volkel 2008).

Two large cohort studies have found an association between PFOA levels in umbilical cord or maternal blood and smaller weight and size in newborn infants, indicating the human health risks of gestational

exposure to perfluoroalkyls (Apelberg, Witter 2007; Fei 2007). Low birth weight is a well-known indicator of potentially serious medical problems later in life (Lau and Rogers 2004).

In addition to other sources of exposure, perfluoroalkyl contamination of drinking water is a problem that needs urgent attention from the federal agencies. EWG's review of water quality data from both scientific literature and government dockets found that PFOA and PFOS pollute drinking water sources in at least 11 states and the District of Columbia (EWG 2009). The true number of states with PFOA- and PFOS-contaminated water is probably higher, since no nation-wide surveillance has been conducted as of now. Meanwhile, research by scientists in the New Jersey Department of Environmental Protection demonstrates both the feasibility and the great need for developing the MRLs for PFOA in drinking water (Post 2009).

It is a standard ATSDR practice to develop MRLs as an integral part of toxicological profiles for hazardous substances. EWG analyzed the existing ATSDR toxicological profiles and the list of MRLs that the Agency has developed in the past (ATSDR 2009a, b). Specifically, the latest update of ATSDR's Toxicological Profile Information Sheet, published on October 19, 2009, includes 190 entries for Finalized Toxicological Profiles (ATSDR 2009b). For comparison, the last list of MRLs, last updated on January 14, 2009, included 173 entries (ATSDR 2009a).

Based on this review, EWG confirmed that for the majority of cases, ATSDR has developed an MRL, making the present decision not to develop MRLs for perfluoroalkyls very unusual. We agree that for some perfluoroalkyls, such as six- and four- carbon fluorinated chemicals, the data are currently limited. This is, indeed, a problem that should be resolved by the manufactures who should be responsible for generating and publishing data for these chemicals as soon as possible. However, we already know enough about PFOA and PFOS to carry out comprehensive risk assessments for these chemicals on the basis of extensive toxicological data from animal studies and the growing number of human epidemiological studies.

In conclusion, EWG urges ATSDR to strengthen and improve its draft toxicological profile for perfluoroalkyls by developing the minimal risk levels for PFOA and PFOS. The development of the MRLs will address a severe gap in our current public health policy and protect the health of millions of Americans who may be exposed to perfluoroalkyls from a variety of sources.

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October 30, 2009

VIA ELECTRONIC AND REGULAR U.S. MAIL

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Re: Docket ATSDR-253: Comment On Draft Toxicological Profile For
Perfluoroalkyls

Ms. Roney:

On behalf of our clients in various States whose residential drinking water is contaminated with one or more perfluoroalkyls, including PFOA and/or PFOS, and in response to ATSDR's July 23, 2009, Federal register notice, we are submitting the following comments on ATSDR's Draft Toxicological Profile for Perfluoroalkyls (the "Profile"). In general, we believe that the current draft Profile inappropriately down-plays the significance of the available data confirming significant risks of adverse health effects among humans exposed to one or more perfluoroalkyls, particularly among perfluoroalkyl workers and those living near industrial sources of perfluoroalkyls that have contaminated nearby drinking water supplies.

Although we recognize that research relating to the potential adverse health effects of perfluoroalkyls is on-going and will be continuing for quite some time, we believe that there is a considerable amount of recent data that does not appear to have been considered within the scope of the existing draft Profile that should be before the Profile is finalized. In particular, recently-published studies of perfluoroalkyl workers have strengthened and reaffirmed the consistency of associations previously reported between perfluoroalkyl exposure and adverse health outcomes, and new studies of tens of thousands of community residents exposed to perfluoroalkyls in their drinking water, including new published, peer-reviewed articles, confirm similar and additional associations at even lower internal serum levels. We believe this additional data renders inaccurate and misleading statements in the current draft Profile such as "long-term exposure to perfluoroalkyls at work has not been associated with significant

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adverse health effects"¹ and that the available data on "people whose drinking water contained perfluoroalkyls did not find problems."² On behalf of our clients, we request that all portions of the draft Profile be revised to the extent necessary to thoroughly and properly reflect the impact of this more-recent data now available through the following publications, studies, and reports:³

1. Lundin, J.I., et al., "Ammonium Perfluorooctanoate Production and Occupational Mortality." 20 *Epidem.* 921-28 (Nov. 2009);
2. West Virginia University, "C-8 Health Project Results," (available online Oct. 30, 2009 at www.hsc.wvu.edu/som/cmed/c8/results/index.asp);10/
3. C-8 Science Panel, "Status Report: Association of Perfluorooctanoic Acid (C8/PFOA) and Perfluorooctane Sulfonate (PFOS) With Lipids Among Children in the Mid-Ohio Valley," (available online at www.c8sciencepanel.org) (Oct. 28, 2009);
4. Steenland, K., et al., "Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with Uric Acid Among Adults with Elevated Community Exposure to PFOA," *Environ. Health Persp.* (online doi: 10.1289/ehp/0900940 (Oct. 22, 2009));
5. Bartell, S.M., et al., "Rate of Decline in Serum PFOA Concentrations After Granular Activated Carbon Filtration at Two Public Water Systems in Ohio and West Virginia," *Environ. Health Persp.* (online doi: 10.1289/ehp.0901252 (Oct. 22, 2009));
6. 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 doi:10.1093/aje/kwp279 (Oct. 21, 2009));
7. Dallaire, R., et al., "Thyroid Function And Plasma Concentrations Of Polyhalogenated Compounds In Inuit Adults," 117(9) *Environ. Health Persp.* 1380-86 (Sept. 2009);

¹ Draft Profile, at 4.

² *Id.*

³ Because all of these materials are available either in the published literature, have been submitted into public files (including USEPA public dockets EPA-HQ-OPPT-2203, AR-226, EPA-HQ-ORD-2003-0016, and/or TSCA 8(e)), or are available through public websites sponsoring the work (such as the DuPont PFOA MOU peer review work), we have not enclosed additional copies of any of these materials. Please let us know, however, if the Agency is unable to locate any of the documents and would like for us to forward a copy.

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8. Stein, C.R., et al., "Serum Levels of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and Pregnancy Outcome." *Am. J. Epidemiol.* (online doi:10.1093/aje/kwp212 (Aug. 19, 2009));
9. MacNeil, J., et al., "A Cross-Sectional Analysis of Type II Diabetes In A Community With Exposure To Perfluorooctanoic Acid (PFOA)," *Environ. Res.* (online doi:10.1016/j.envres.2009.08.002 (Aug. 2009));
10. Minnesota Department of Health, "East Metro Perfluorochemical Biomonitoring Pilot Project" (available online at www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/index.html) (July 21, 2009);
11. "Final Report of the Peer Consultation Panel: Scientific Peer Consultation Process For A Site Environmental Assessment Program as Part of the DuPont-EPA Memorandum of Understanding and Phase II Workplan" (available online at <http://itp-pfoa.ce.cmu.edu/>) (July 15, 2009);
12. Steenland, K., et al., "Predictors of PFOA Levels In A Community Surrounding A Chemical Plant." 117 *Environ. Health Persp.* 1083-88 (July 2009);
13. Frisbee, S.J., et al., "The C8 Health Project: Design, Methods, and Participants," *Environ. Health Persp.* (online doi:10.1289/ehp.0800379 (July 13, 2009));
14. Sakr, C.J., et al., "Ischemic Heart Disease Mortality Study Among Workers With Occupational Exposure To Ammonium Perfluorooctanoate," *Occup. Environ. Med.* (online doi:10.1136/oem.2008.041582 (June 23, 2009));
15. Fenton, S.E., et al., "Analysis Of PFOA In Dosed CD-1 Mice Part 2: Disposition Of PFOA In Tissues And Fluids From Pregnant And Lactating Mice And Their Pups," *Reprod. Toxicol.* (online doi:10.1016/j.reprotox.2009.02.012 (2009));
16. von Ehrenstein, O.S., et al., "Perfluoroalkyl Chemicals In The Serum And Milk Of Breastfeeding Women," *Reprod. Toxicol.* (online doi:10.1016/j.reprotox.2009.03.001 (2009));
17. Hines, E.P., et al., "Phenotypic Dichotomy Following Developmental Exposure To Perfluorooctanoic Acid (PFOA) In Female CD-1 Mice: Low Doses Induce Elevated Serum Leptin And Insulin, And Overweight In Mid-Life." 304 *Molecular & Cellular Endocrinology* 97-105 (2009);
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20. C-8 Science Panel, "Status Report: PFOA And Immune Biomarkers In Adults Exposed To PFOA In Drinking Water In The Mid Ohio Valley" (available online at www.c8sciencepanel.org) (March 16, 2009);
21. Costa, G., et al., "Thirty Years Of Medical Surveillance In Perfluorooctanoic Acid Production Workers," 51 *J.O.E.M.* 1-9 (March 2009);
22. Joensen, U.N., et al., "Do Perfluoroalkyl Compounds Impair Human Serum Quality?" *Environ. Health Persp.* (online doi:10.1289/ehp.0800517 (March 2, 2009));
23. Kato, K., et al., "Polyfluoroalkyl Compounds In Pooled Sera From Children Participating In The National Health And Nutrition Examination Survey 2001-2002," *Environ. Sci. Technol.* (online doi/abs/10.1021/es803156p (Feb. 19, 2009));
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In addition to the health and toxicology data referenced above, we recognize that the Agency also has specifically requested "any additional studies, particularly unpublished data" that might be of use to the Agency as it finalizes its Profile. In that regard, we believe the Agency should consider and incorporate all available data reflecting levels of perfluoroalkyls in the serum/blood of residents exposed to the chemicals in their drinking water, even if that data is not formally published or peer-reviewed. On that issue, our law firm has submitted voluminous data to USEPA over the last several years confirming the levels of PFOA, PFOS, and other perfluoroalkyls detected in the serum/blood of residents in West Virginia, Ohio, Minnesota, and New Jersey whose residential source of drinking water has been contaminated with one or more perfluoroalkyls. A listing of several of those letters to USEPA (each of which is publicly-available in one or more USEPA public dockets, such as AR-226, EPA-HQ-OPPT-2003, and/or TSCA 8(e), along with the supporting analytical data sheets (with names redacted for privacy)) follows⁴:

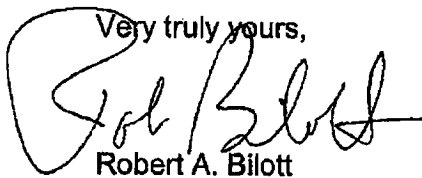
1. Letter from R. Bilott to C. Auer, et al. Re: PFOA-Exposed Community Blood Sample Results – Lubeck PSD, Washington, County, West Virginia (Sept. 15, 2004);
2. Letter from R. Bilott to C. Auer, et al. Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota (May 12, 2005);
3. Letter from R. Bilott to C. Auer, et al. Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota (Oct. 20, 2005);
4. Letter from R. Bilott to C. Auer, et al. Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota (Jan. 13, 2006);
5. Letter from R. Bilott to C. Auer, et al. Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota (Feb. 2, 2007);
6. Letter from R. Bilott to C. Auer, et al. Re: Perfluorochemical Blood Exposure Data For New Jersey (April 16, 2007); and

⁴ To assist in retrieving the letters and supporting data from the public files, we have enclosed additional copies of the text of these letters.

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Page 6

7. Letter from R. Bilott to C. Auer, et al. Re: PFOA/C-8 Blood Levels From Ohio/West Virginia Drinking Water Contamination (April 9, 2008).

We appreciate the opportunity to provide these comments and to submit this additional data for consideration and incorporation into any final Profile released by the Agency for perfluoroalkyls. We hope that such information will assist the Agency in promptly developing and releasing to the public a Minimal Risk Level to help ensure the protection and safety of our clients' drinking water.

Very truly yours,

Robert A. Bilott

RAB:mdm
Enclosures

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September 15, 2004

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Re: PFOA-Exposed Community Blood Sample Results
(For AR-226 And OPPT-2003-0012)

Ladies and Gentlemen:

In response to USEPA's previous requests for information relating to the threat to human health and the environment involving PFOA/C-8, we have enclosed the results of PFOA serum testing performed through DuPont and its contractor, Exygen, for twelve members of the general population living near DuPont's Washington Works facility in Wood County, WV. All twelve of the individuals tested have been exposed to PFOA/C-8 through drinking water provided by the Lubeck Public Service District where, according to DuPont, the level of PFOA/C-8 in the drinking water has averaged approximately 0.5 ppb over the last several years. These individuals also claim to have stopped using the contaminated public drinking water as their primary source of drinking water approximately three years ago, and switched to alternative sources, such as bottled water. Only one of the individuals (with a PFOA serum result of 90.4 ppb) ever worked

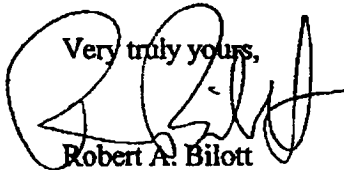
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 Mary Dominiak
 September 15, 2004
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at the DuPont Washington Works Plant. A chart summarizing the results from the enclosed lab report (EID871401-10) is presented below. Please include this information in AR-226 and OPPT-2003-0012.

<u>SEX</u>	<u>AGE</u>	<u>PFOA SERUM (PPB)</u>	<u>APPROX. YEARS ON WATER</u>
F	55	128	>20
M	52	103/103	>20
M	70	90.4	>20
F	80	83.1	10-20
M	63	78.5/73.7	10-20
F	46	65	5-10
M	69	61.3	<5
M	36	56.4/50.8	>20
M	57	51.2	10-20
F	55	42.6	10-20
F	48	40.1	10-20
M	57	15.7	<5

Very truly yours,


 Robert A. Bilott

RAB/mdm
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May 12, 2005

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Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota

Ladies and Gentlemen:

We serve as counsel for Plaintiffs in a lawsuit that is currently pending against the 3M Company in State Court in Minnesota involving claims arising from exposures to perfluorochemicals released by or otherwise attributable to 3M. The lawsuit is styled, *Palmer, et al. v. 3M Company* (Minn. Dist. Ct. Court File No. C2-04-6309). 3M owns and operates a manufacturing facility in Cottage Grove where various perfluorochemicals, including PFOS and PFOA, were manufactured, released, and disposed for several decades. In the context of

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Plaintiffs' investigation of their claims, Plaintiffs' counsel arranged for sampling of private water wells and soil in the vicinity of 3M's Cottage Grove operations, along with blood sampling of individuals residing in areas that may have been impacted from perfluorochemical wastes attributable to 3M's Cottage Grove operations. In recognition of the potential threat to human health and the environment revealed by this data, and in response to USEPA's prior public requests for perfluorochemical monitoring data, we are providing copies of this initial round of data to you for inclusion in USEPA's Administrative Record 226 and OPPT-2003-0012.

The PFOS and PFOA results for the serum, whole blood, water, and soil samples collected and analyzed to date on behalf of Plaintiffs are summarized below. Please note that all results were provided by Axys Analytical Services LTD in Canada and were obtained, arranged for, and paid for without any involvement by 3M.

I. PFOA/PFOS SERUM/WHOLE BLOOD DATA

The following charts present summaries of the PFOA and PFOS serum and whole blood data collected from residents of Washington County, Minnesota. Please note that whole blood results were obtained for only 2 of the individuals tested (as indicated in the chart). We have grouped the available serum and whole blood data by drinking water source.

The first chart (Chart A) summarizes the blood data obtained from individuals consuming drinking water provided by the City of Oakdale, Minnesota, where recent testing has confirmed PFOS in 2 of the City's water supply wells in levels exceeding the State of Minnesota's recommended Health Based Value of 1 part per billion (1 ppb), and levels of PFOA just below 1 ppb. (See AR-226-1929, 1933, and 1935) 3M has reported detecting PFOS in tap samples collected from a 3M/Dyneon facility in Oakdale as high as 0.9 ppb and PFOA as high as 0.8 ppb. (See AR-226-1934)

The second chart (Chart B), summarizes blood data obtained from individuals whose drinking water is provided by either the City of Lake Elmo, Minnesota, the City of Cottage Grove, Minnesota, or the City of Hastings, Minnesota, where it has been reported that the levels of both PFOS and PFOA in those municipalities' water supplies are either not-detectable or below quantification levels. (See AR-226-1929, 1931, and 1932. See also Exhibit A) In regard to Hastings water, 3M has reported having detected PFOA in a municipal water supply well

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above the detection limit of 0.025 ppb but below the laboratory quantification limit of 0.05 ppb.
 (See AR-226-1929 and 1931)

The third chart (Chart C), summarizes data obtained from individuals consuming drinking water from private wells, the vast majority of which have not yet been analyzed for perfluorochemicals. To the extent information is available regarding the level of perfluorochemicals actually detected in the specific private well providing water to the individuals whose blood was sampled, that information is provided in Chart C. Maps showing the general residential location of those whose blood was sampled are attached at Exhibit B.

The lab results for each of the serum and whole blood results are attached at Exhibit C. For privacy reasons, the names, addresses, and specific ages of each of those sampled are not provided with this submission. Also enclosed at Exhibit A are copies of materials, including materials distributed by the Minnesota Department of Health ("MDH"), discussing the levels of perfluorochemicals recently detected by MDH in the City of Oakdale municipal water supply and private Lake Elmo area wells, including detections of PFOS in both private and public water supply wells in levels exceeding the State's current recommended Health Based Value of 1 ppb for PFOS in water. We understand that MDH already is arranging for users of some of the contaminated private wells to begin receiving bottled water and water treatment. (See Exhibit A)

CHART A - OAKDALE CITY WATER CUSTOMERS

<u>SEX</u>	<u>AGE</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>YEARS ON WATER</u>
M	41-50	121.0	109.0	N/A
F	51-60	117.0	91.8	>30
M	>70	82.3	118.0	N/A
M	>70	78.6	112.0	>30
F	41-50	77.5	78.4	N/A
F	51-60	74.9	61.1	20-30

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<u>SEX</u>	<u>AGE</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>YEARS ON WATER</u>
F	>70	69.3	102.0	>30
F	61-70	59.9	71.0	N/A
M	61-70	58.7	61.7	<10
F	61-70	58.3	68.1	20-30
F	41-50	57.8	70.4	20-30
M	51-60	44.6	60.4	10-20
M	41-50	44.1	55.2	<10
M	61-70	39.8	46.5	20-30
F	18-30	38.8	47.6	20-30
M	51-60	37.1	51.1	>30
F	51-60	33.2	59.5	10-20
M	41-50	32.1	57.6	10-20
M	51-60	24.5	37.2	10-20
F	18-30	23.1	29.2	20-30
F	51-60	22.2	46.1	20-30
F	<18	19.1	42.9	10-20
F	61-70	6.96	22.6	>30
F	18-30	6.09	17.7	10-20

N/A=data not available

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**CHART B - LAKE ELMO/COTTAGE GROVE/ HASTINGS
 CITY WATER CUSTOMERS**

<u>SEX</u>	<u>AGE</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>YEARS ON WATER</u>
F	51-60	42.3	49.5	<10
F	N/A	6.9	19.6	N/A
M	31-40	6.78 (4.22*)	10.5 (7.95*)	10-20
M	31-40	6.13	13.5	>30
M	>70	4.34	14.0	>30
F	51-60	4.10	17.3	10-20
M	51-60	3.89	21.2	10-20
F	N/A	3.36	21.4	N/A
F**	51-60	2.21	7.88	>30

* = whole blood analysis

**= former 3M employee

N/A=data not available

CHART C - WASHINGTON COUNTY PRIVATE WELL USERS

1. Lake Elmo Area Private Wells

<u>SEX</u>	<u>AGE</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>YEARS ON WATER</u>	<u>PFOA IN WATER</u>	<u>PFOS IN WATER</u>
M	41-50	45.7	19.7	20-30	N/A	N/A

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<u>SEX</u>	<u>AGE</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>YEARS ON WATER</u>	<u>PFOA IN WATER</u>	<u>PFOS IN WATER</u>
F	51-60	24.0	17.0	>30	N/A	N/A
M	N/A	16.4	22.1	N/A	N/A	N/A
F	41-50	15.7	9.27	10-20	N/A	N/A
F	>70	14.3	8.90	>30	N/A	N/A
M	61-70	12.1	9.78	>30	N/A	N/A
M	18-30	7.56	17.3	20-30	N/A	N/A
M	61-70	6.95	43.1	20-30	N/A	N/A
M	51-60	6.78	21.0	20-30	N/A	N/A
M	61-70	6.1	43.7	>30	N/A	N/A
M	51-60	5.35	20.4	N/A	N/A	N/A
F	41-50	3.14	11.2	N/A	N/A	N/A
F	61-70	2.4	12.0	>30	N/A	N/A

N/A=data not available

2. Cottage Grove/Hastings Area Private Wells

<u>SEX</u>	<u>AGE</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>YEARS ON WATER</u>	<u>PFOA IN WATER (ppb)</u>	<u>PFOS IN WATER (ppb)</u>
M**	>70	19.7	108.0	20-30	N/A	N/A

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<u>SEX</u>	<u>AGE</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>YEARS ON WATER</u>	<u>PFOA IN WATER (ppb)</u>	<u>PFOS IN WATER (ppb)</u>
F	31-40	17.1	16.9	<10	0.02	ND
F	61-70	7.38	32.5	>30	N/A	N/A
F	51-60	9.12	42.8	20-30	N/A	N/A
M	>70	6.42	32.5	>30	N/A	N/A
F	41-50	4.97	16.3	20-30	0.003	ND
F	41-50	4.68	12.0	<10	N/A	N/A
F	<18	3.87	15.8	<10	N/A	N/A
F	N/A	3.54 (2.98*)	8.51 (8.3*)	N/A	N/A	N/A
F	41-50	3.39	14.9	>30	N/A	N/A
M	<18	2.83	14.8	<10	N/A	N/A
M	41-50	2.01	22.4	<10	0.004	ND

*=whole blood analysis

**=former 3M employee

N/A=data not available

ND=not detected

II. PRIVATE WATER WELL DATA

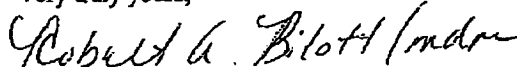
Attached at Exhibit D are the private water well water results obtained to date. For privacy reasons, the specific addresses and names of the owners of the wells tested have been redacted. A map showing generally where the wells are located is attached at Exhibit E.

Dr. Charles M. Auer
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James Kelly
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III. PRIVATE PROPERTY SOIL RESULTS

Attached at Exhibit F are the private property soil results obtained to date. For privacy reasons, the specific addresses and names of the owners of the properties tested have been redacted. A map showing generally where the soil results were obtained is attached at Exhibit G.

Very truly yours,


Robert A. Bilott

RAB/mdm

Attachments

cc: Gale D. Pearson, Esq. (w/ attachments)
Stephen J. Randall, Esq. (w/ attachments)
Rhon E. Jones, Esq. (w/ attachments)
J. Mark Englehart, Esq. (w/ attachments)
David B. Byrne III, Esq. (w/ attachments)
R. Edison Hill, Esq. (w/ attachments)
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October 20, 2005

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Land & Water Quality Section
Minnesota Pollution Control Agency
520 Lafayette Road North
St. Paul, MN 55155Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota

Ladies and Gentlemen:

In a letter dated May 12, 2005, we provided information regarding levels of various perfluorochemicals, including PFOA and PFOS, detected in blood, soil, and water in the vicinity of 3M's perfluorochemical operations in Minnesota. Since that submission, we have arranged for additional blood samples of individuals residing in communities that may have been impacted

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Dr. Charles M. Auer
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 October 20, 2005
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from perfluorochemical wastes attributable to 3M's Minnesota operations. In recognition of the potential threat to human health and the environment revealed by this data, and in response to USEPA's prior public requests for perfluorochemical monitoring data, we are providing copies of this additional data to you for inclusion in USEPA's Administrative Record 226 and OPPT-2003-0012.

The perfluorochemical (including PFOS and PFOA) results for serum samples collected and analyzed on behalf of Plaintiffs are summarized below. Please note that all results were provided by Axys Analytical Services LTD in Canada and were obtained, arranged for, and paid for without any involvement by 3M.

In our May 12, 2005, letter, we presented charts summarizing the PFOA and PFOS serum and whole blood data collected from residents of Washington County, Minnesota, with the data organized by drinking water source. Since our May 12, 2005, submission, additional blood data has been collected from individuals consuming water provided by the City of Oakdale, Minnesota, where testing of the City's water supply wells has, on occasion, confirmed PFOS in levels exceeding the State of Minnesota's recommended Health Based Value ("HBV") of 1 part per billion (1 ppb), and levels of PFOA just below 1 ppb. (See AR-226-1929, 1933, and 1935) 3M also has reported detecting PFOS in tap samples from Oakdale as high as 0.95 ppb and PFOA as high as 0.71 ppb, indicating that the combined level of PFOS and PFOA in Oakdale water has exceeded the State's Hazard Index ("HI") of 1 for drinking water containing both PFOS and PFOA. (See AR-226-2737-39; AR-226-1945-46; Exhibit A (3M's HI calculations)) As 3M explained in its June 14, 2005, letter to USEPA, such cumulative amounts of PFCs in tap water exceeding the HI of 1 represent a level of PFCs that also exceeds the State's current, recommended HBVs, which the State uses to assess whether there is an unreasonable risk to human health. (See *id.*)

There are now also data suggesting the possibility of additional perfluorochemicals, including PFBS (C-4) (a chemical 3M uses in on-going manufacturing processes), in the water near the impacted public water supplies. The presence of these other perfluorochemicals in water already contaminated with both PFOS and PFOA contributes to the threat of even greater cumulative toxicity concerns. (See Exhibit B) Some of these other PFCs, including PFBS (C-4), already have been detected in the blood of area residents, leading to very high cumulative PFC levels in their blood. (See Exhibit D; May 12, 2005, Letter (attached lab sheets)) Chart A below

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includes all of the original and new blood data for City of Oakdale water customers, including the cumulative, total amount of various perfluorochemicals detected in the blood samples.¹⁷ The new data are in bold type.

In our May 12, 2005, submission, we also provided data regarding the level of perfluorochemicals found in the blood of individuals consuming drinking water from private wells in the area of 3M's Minnesota operations. Since that submission, we have collected additional blood data from private well users in the Lake Elmo, Minnesota, area and have obtained some additional information from 3M and MDH regarding the level of PFOS and PFOA in some of those wells. (See Exhibit C (Excerpts from 3M's September 2, 2005, Answers to Plaintiffs' Interrogatories))²². Chart B below provides a summary of all of the original Lake Elmo area private well blood and water data (now with cumulative totals for the perfluorochemical blood data), plus the new data obtained since May 12, 2005. The new data is in bold type. In order to avoid identification of individual identities, we have provided available private water well PFC data in a general range, as opposed to specific results.

The lab results for the blood results are attached at Exhibit D. For privacy reasons, the names, addresses, and specific ages of each of those sampled are omitted from this submission.

¹⁷ Although the individual blood test result sheets attached to our May 12, 2005, letter referenced the levels of various perfluorochemicals detected in the individual blood samples, we did not include the cumulative totals in the charts set forth in our original, May 12, 2005, letter. We have now included the cumulative total PFC results from those lab sheets in the current charts.

²² The Minnesota Department of Health is currently using detection/reporting limits of 0.5 ppb and 1.0 ppb for PFOS and PFOA, respectively. (See Exhibit C)

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CHART A - OAKDALE CITY WATER CUSTOMERS

<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*</u>
M	41-50	N/A	121.0	109.0	267.12
F	51-60	>30	117.0	91.8	240.06
M	>70	>30	105.0	113.0	241.45
M	51-60	20-30	104.0/103.0	70.3/72.7	192.44/195.54
M	61-70	20-30	100.00	131.0	293.08
F	51-60	20-30	96.1	67.8	180.2
F	41-50	<10	95.1/89.1	85.9/79.8	200.71/186.15
M	51-60	20-30	86.8	125.0	248.01
M	>70	N/A	82.3	118.0	221.79
F	61-70	20-30	80.5	163.0	212.40
M	>70	>30	78.6	112.0	210.63
F	41-50	N/A	77.5	78.4	178.51
F	51-60	20-30	74.9	61.1	152.72
M	31-40	10-20	74.6	91.0	182.36
F	>70	>30	69.3	102.0	191.84
F	41-50	N/A	69.0	77.2	163.79
M	<18	<10	68.3	50.1	134.12
M	41-50	10-20	63.3	76.7	158.88

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*</u>
F	41-50	<10	63.3	73.1	150.11
F	61-70	N/A	59.9	71.0	145.61
F	61-70	>30	58.7	73.4	149.48
M	61-70	<10	58.7	61.7	134.64
F	61-70	20-30	58.3	68.1	154.95
F	41-50	20-30	57.8	70.4	146.46
F	31-40	10-20	48.4	71.9	132.83
M	51-60	10-20	44.6	60.4	115.40
M	41-50	<10	44.1	55.2	114.29
M	18-30	10-20	43.5	54.4	107.12
M	<18	10-20	42.4	51.1	107.84
M	61-70	20-30	39.8	46.5	104.37
F	18-30	20-30	38.8	47.6	96.33
M	51-60	>30	37.1	51.1	102.01
F	51-60	10-20	33.2	59.5	105.24
F	41-50	<10	32.7	41.5	89.66
M	41-50	10-20	32.1	57.6	103.35
F	<10	<10	30.7	56.8	99.11
F	<10	<10	27.5	62.0	98.63

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*</u>
M	51-60	10-20	24.5	37.2	69.72
F	18-30	20-30	23.1	29.2	59.83
F	51-60	20-30	22.2	46.1	74.88
F	31-40	N/A	21.1/19.6	12.8/8.81	29.64/36.80
F	<18	10-20	19.1	42.9	71.21
F	<18	<10	17.1	20.1	43.08
M	31-40	<10	15.5	12.7	29.31
M	41-50	<10	14.6	30.8	49.49
F	18-30	<10	13.3	12.3	27.14
F	18-30	<10	10.7	23.1	35.87
M	>70	20-30	10.2	24.2	35.31
F	18-30	<10	7.35	10.5	19.39
M	51-60	<10	7.21	38.9	57.56
F	61-70	>30	6.96	22.6	36.00
F	18-30	10-20	6.09	17.7	26.79

N/A=data not available

*Total of detected levels of PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDoA, PFBS, PFHxS, PFOS, and PFOSA in the blood sample

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CHART B - LAKE ELMO AREA PRIVATE WELL USERS

<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb) /Dup.</u>	<u>PFOS (ppb) /Dup.</u>	<u>PPB PFOA IN WATER</u>	<u>PPB PFOS IN WATER</u>	<u>TOTAL PFCs (ppb)*</u>
F	<18	<10	110.0	111.0	1.0-1.4	0.5-0.9	247.19
F	41-50	10-20	72.9	87.6	1.0-1.4	0.5-0.9	175.25
F	<18	10-20	55.4	60.8	1.0-1.4	0.5-0.9	124.35
M	41-50	20-30	45.7	19.7	ND	ND	72.11
F	61-70	20-30	30.9	88.6	0.5-0.9	ND	128.93
M	51-60	10-20	27.0/26.7	28.5/32.7	1.0-1.4	0.5-0.9	62.32/65.74
M	61-70	20-30	24.2	38.0	0.5-0.9	ND	69.91
F	51-60	>30	24.0	17.0	ND	ND	50.96
M	N/A	N/A	16.4	22.1	ND	ND	44.43
F	41-50	10-20	15.7	9.27	N/A	N/A	27.68
F	>70	>30	14.3	8.90	ND	ND	26.27
M	61-70	>30	12.1	9.78	ND	ND	24.89
M	41-50	10-20	9.66	26.6	ND	ND	42.51
F	41-50	<10	9.25	28.4	N/A	N/A	41.58
M	18-30	20-30	7.56	17.3	N/A	N/A	33.70
M	61-70	20-30	6.95	43.1	N/A	N/A	55.00
M	51-60	20-30	6.78	21.0	N/A	N/A	36.91

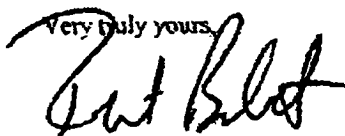
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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/ Dup.</u>	<u>PFOS (ppb) /Dup.</u>	<u>PPB PFOA IN WATER</u>	<u>PPB PFOS IN WATER</u>	<u>TOTAL PFCs (ppb)*</u>
M	61-70	>30	6.1	43.7	N/A	N/A	54.19
F	51-60	10-20	5.92	29.5	ND	ND	41.26
M	51-60	N/A	5.35	20.4	N/A	N/A	29.02
F	41-50	N/A	3.14	11.2	N/A	N/A	16.29
F	18-30	<10	2.63	17.4	N/A	N/A	26.09
F	61-70	>30	2.4	12.0	N/A	N/A	17.91

N/A=data not available

ND= not detected above reported detection limits

*Total of detected levels of PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDoA, PFBS, PFHxS, PFOS, and PFOSA in the blood sample

Very truly yours,

 Robert A. Bilotti

RAB/mdm
 Enclosures

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January 13, 2006

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Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota

Ladies and Gentlemen:

In letters dated May 12, 2005, October 20, 2005, and November 10, 2005, we provided information regarding levels of various perfluorochemicals (PFCs), including PFOA and PFOS, detected in blood, soil, and water in the vicinity of 3M's perfluorochemical operations in Minnesota. In recognition of the potential threat to human health and the environment revealed

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by this data, and in response to USEPA's prior public requests for perfluorochemical monitoring data, we are providing additional data to you for inclusion in USEPA's Administrative Record 226 and EPA-HQ-OPPT-2003-0012 relating to cumulative perfluorochemical levels detected in tap water samples obtained from areas serviced by the City of Oakdale, Minnesota, and the City of Lake Elmo, Minnesota^{1/}, along with additional data relating to the cumulative level of PFCs detected in the blood of residents consuming drinking water supplied by the City of Oakdale, Minnesota. We are also providing this data to the Minnesota Department of Health, the Minnesota Pollution Control Agency, and to the Cities of Oakdale, Minnesota, and Lake Elmo, Minnesota, to enhance understanding of the potential impact of cumulative PFC levels in drinking water.

The individual tap water results are summarized below in Chart A. Three tap water samples were obtained and analyzed from three different residences served by the City of Oakdale and two tap water samples were obtained from two different residences served by the City of Lake Elmo.^{2/} A map showing the general location of the tap water samples in relation to the City of Oakdale's municipal wells is attached at Exhibit A. Copies of the lab sheets (with specific addresses redacted) are enclosed at Exhibit B. For privacy reasons, the specific

^{1/} We understand that there is a plan to connect certain properties with PFC-contaminated private water wells in the Lake Elmo area to the City of Lake Elmo public water supply. We understand that, in the meantime, MDH is arranging for bottled water to be provided to certain users of some of these PFC-contaminated private wells. Based on the recent detection of PFOA in certain bottled water supplied to those using PFOA-contaminated water supplies in Ohio (see Exhibit D), we request clarification from MDH as to whether the bottled water being supplied in the Lake Elmo area has been tested for PFCs, which PFCs were included in any such analysis, and what the detection limits are for any such analysis that has been performed.

^{2/} The tap samples identified in Chart A as "Oakdale City 1," "Oakdale City 2," and "Oakdale City 3" correspond to the tap water sample locations identified in approximate terms on the map attached at Exhibit A with diamonds labeled "O1," "O2," and "O3" respectively. The tap samples identified in Chart A as "Lake Elmo City 1" and "Lake Elmo City 2" correspond to the tap water sample locations identified in approximate terms on the map attached at Exhibit A with diamonds labeled "LE1" and "LE2" respectively. The stars on the map attached at Exhibit A are the approximate locations of certain City of Oakdale municipal water supply wells.

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addresses where the tap samples were collected have been omitted from this submission. Please note that all results were provided by Axys Analytical Services Ltd. in Canada, and were obtained, arranged for, and paid for without any involvement by 3M.

CHART A - CITY TAP WATER RESULTS (PARTS PER BILLION)

	<u>OAKDALE CITY 1</u>	<u>OAKDALE CITY 2</u>	<u>OAKDALE CITY 3</u>	<u>LAKE ELMO CITY 1</u>	<u>LAKE ELMO CITY 2</u>
PFBA	0.3800/0.4390	0.4760	1.7200	0.0920	0.0865
PFPeA	0.0202/0.0188	0.0239	0.0834	ND	ND
PFHxA	0.0543/0.0515	0.0588	0.1970	ND	ND
PFHpA	0.0226/0.0181	0.0251	0.1020	ND	ND
PFOA	0.1140/0.1120	0.1360	0.6260	ND	ND
PFNA	ND/ND	ND	0.00245	ND	ND
PFDA	ND/ND	ND	0.00309	ND	ND
PFUnA	ND/ND	ND	ND	ND	ND
PFDoA	ND/ND	ND	ND	ND	ND
PFBS	0.00676/0.00744	0.00915	0.0386	ND	ND
PFHxS	0.0133/0.0108	0.0149	0.0663	ND	ND
PFOS	0.0508/0.0509	0.0632	0.7550	ND	ND
PFOSA	ND/ND	ND	0.00341	0.00126	ND
TOTAL PFCs	0.66196/0.70854	0.80705	3.59725	0.09326	0.0865

ND=not detected

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The updated PFC results for serum samples collected and analyzed from City of Oakdale water customers (including total PFCs and individual PFOA and PFOS levels) are summarized below in Chart B. The new data are in bold type. The lab results for the new blood results are attached at Exhibit C. For privacy reasons, the names, addresses, and specific ages of each of those sampled are omitted from this submission. Please note that all results were provided by Axyx Analytical Services LTD in Canada and were obtained, arranged for, and paid for without any involvement by 3M.

CHART B - OAKDALE CITY WATER CUSTOMERS

<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/Dup.</u>
M	<18	<10	155.0	180.0	371.35
M	41-50	N/A	121.0	109.0	267.12
F	51-60	>30	117.0	91.8	240.06
F	51-60	10-20	113.0	167.0	357.34
M	>70	>30	105.0	113.0	241.45
F	51-60	10-20	104.0	108.0	252.23
M	51-60	20-30	104.0/103.0	70.3/72.7	192.44/195.54
M	61-70	20-30	100.00	131.0	293.08
M	41-50	10-20	97.9	121.0	244.71
F	51-60	20-30	96.1	67.8	180.2
F	41-50	<10	95.1/89.1	85.9/79.8	200.71/186.15
M	51-60	10-20	92.7/92.5	88.0/111.0	211.78/240.23

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
M	51-60	20-30	86.8	125.0	248.01
F	61-70	>30	85.7	121.0	232.86
M	>70	N/A	82.3	118.0	221.79
F	61-70	20-30	80.5	163.0	212.40
M	>70	>30	78.6	112.0	210.63
F	41-50	N/A	77.5	78.4	178.51
F	31-40	10-20	75.9	103.0	196.84
F	51-60	20-30	74.9	61.1	152.72
M	31-40	10-20	74.6	91.0	182.36
F	18-30	N/A	70.9	112.0	200.91
F	>70	>30	69.3	102.0	191.84
F	41-50	N/A	69.0	77.2	163.79
M	<18	<10	68.3	50.1	134.12
M	10-30	<10	67.4	83.3	167.12
M	41-50	10-20	63.3	76.7	158.88
F	41-50	<10	63.3	73.1	150.11
F	51-60	10-20	60.6	92.5	184.71
F	61-70	N/A	59.9	71.0	145.61

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
F	61-70	>30	58.7	73.4	149.48
M	61-70	<10	58.7	61.7	134.64
F	61-70	20-30	58.3	68.1	154.95
F	41-50	20-30	57.8	70.4	146.46
M	41-50	10-20	56.2	116.0	193.95
F	31-40	10-20	48.4	71.9	132.83
M	<18	<10	45.4/46.4	68.2/71.7	130.85/132.92
M	51-60	10-20	44.6	60.4	115.40
M	41-50	<10	44.1	55.2	114.29
M	18-30	10-20	43.5	54.4	107.12
M	<18	10-20	42.4	51.1	107.84
M	61-70	>30	40.7	80.3	137.38
M	61-70	20-30	39.8	46.5	104.37
F	41-50	10-20	39.3	46.3	94.34
F	41-50	<10	39.0	57.4	112.63
F	18-30	20-30	38.8	47.6	96.33
M	51-60	>30	37.1	51.1	102.01
F	41-50	10-20	33.8	46.4	91.07

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/Dup.</u>
F	51-60	10-20	33.2	59.5	105.24
F	41-50	<10	32.7	41.5	89.66
M	41-50	10-20	32.1	57.6	103.35
F	<10	<10	30.7	56.8	99.11
F	<10	<10	27.5	62.0	98.63
F	51-60	10-20	26.2	104.0	149.68
F	51-60	<10	25.2	46.2	77.18
M	51-60	10-20	24.5	37.2	69.72
F	41-50	10-20	23.6	72.9	107.32
F	18-30	20-30	23.1	29.2	59.83
F	51-60	20-30	22.2	46.1	74.88
F	31-40	N/A	21.1/19.6	12.8/8.81	29.64/36.80
F	51-60	10-20	19.7	52.6	76.87
F	<18	10-20	19.1	42.9	71.21
F	<18	<10	17.1	20.1	43.08
M	<18	<10	16.1	24.3	51.95
M	31-40	<10	15.5	12.7	29.31
F	31-40	10-20	14.6	37.4	59.61

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
M	41-50	<10	14.6	30.8	49.49
M	<18	<10	13.4	50.1	83.18
F	18-30	<10	13.3	12.3	27.14
M	41-50	<10	12.8	30.1	47.16
M	18-30	10-20	11.4	50.8	72.75
M	<18	<10	11.2	27.7	57.94
F	18-30	<10	10.7	23.1	35.87
M	>70	20-30	10.2	24.2	35.31
F	31-40	<10	8.76	30.1	45.35
F	18-30	<10	7.35	10.5	19.39
M	51-60	<10	7.21	38.9	57.56
F	61-70	>30	6.96	22.6	36.00
M	31-40	<10	6.16	16.1	26.90
F	18-30	10-20	6.09	17.7	26.79
M	41-50	<10	5.52	8.27	15.82

N/A=data not available

*Total of detected levels of PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDaA, PFBS, PFHxS, PFOS, and PFOSA in the blood sample

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Donald Kriens
January 13, 2006
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Very truly yours,



Robert A. Bilott

RAB/mdm

Enclosures

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Re: Perfluorochemical Residential Exposure Data For Washington County, Minnesota

Ladies and Gentlemen:

In letters dated May 12, October 20, November 10, 2005, and January 13, 2006, we provided information regarding levels of various perfluorochemicals (PFCs), including PFOA and PFOS, detected in blood, soil, and water in the vicinity of 3M's perfluorochemical operations in Washington County, Minnesota. In recognition of the potential threat to human health and the environment revealed by the data, and in response to USEPA's prior public requests for perfluorochemical monitoring data, we are providing additional data to you for inclusion in USEPA's Administrative Record 226 and EPA-HQ-OPPT-2003-0012 to supplement the data we provided previously.

In particular, we are providing clarification with respect to the extent of our available data regarding detections of PFBA in the blood of residents exposed to PFBA in their drinking water. We thought this information might be of value in connection with the recent disclosure by the Minnesota Department of Health ("MDH") that PFBA has now been found in additional public water supply wells in Washington and Dakota Counties at levels exceeding the State's current guideline of 1.0 part per billion. (See Exhibit A) In our last letter on this topic dated January 13, 2006, we provided our own tap water sampling data confirming that PFBA had been found in tap water supplied by the City of Oakdale, Minnesota, at a level exceeding 1.0 part per billion, and that the level of PFBA in that water was actually more than double the amount of either PFOA and PFOS in the tap water. MDH's own recent sampling confirms that similar, if not higher, PFBA concentrations are present in additional public water supplies serving tens of thousands of additional residents of Washington and Dakota Counties. (See *id.*) Data independently collected and provided to us recently by an area resident reveal similarly elevated PFBA

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concentrations in water from three wells identified to us as "Old Cottage Grove wells" (1.83 ppb, 1.85 ppb, and 1.25 ppb) and from tap water identified to us as being supplied by the City of South St. Paul (1.64 ppb).^{1/} (See Exhibit B) These levels all also exceed the current 1.0 ppb well guideline for PFBS in drinking water.

Although a substantial number of the area blood samples referenced in our earlier letters were not analyzed for PFBA, some of the later samples included PFBA analysis and reveal detections as high as 2.92 ppb in the blood of an exposed individual. We have highlighted the available PFBA blood results in the following charts. We thought data confirming detections of PFBA in any exposed individuals would be of use to regulatory agencies evaluating this issue, particularly in light of MDH's current understanding that "PFBA does not appear to accumulate in animals or people." (Exhibit A)

Updated PFC results for serum samples collected and analyzed from Washington County, Minnesota, residents (this time, also noting PFBA blood results, if any) are summarized in the charts below. New serum data not included with our previous letters or included in 3M's August 4, 2006, letter forwarding some of our additional sampling information are highlighted below in bold type. The lab results for the new blood data are attached as Exhibit C. For privacy reasons, the names, addresses, and specific ages of those sampled are omitted from this submission. Please note that all results were provided by Axys Analytical Services LTD in Canada and were obtained, arranged for, and paid for without any involvement by 3M.

CHART A - OAKDALE CITY WATER CUSTOMERS

<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>PFBA (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
M	<18	<10	155.0	180.0	1.16	371.35
M	41-50	N/A	121.0	109.0	N/T	267.12
F	51-60	>30	117.0	91.8	N/T	240.06

^{1/} We understand that the private citizen who reported these data to us arranged and paid for this testing and analysis through Axys Analytical Services, LTD in Canada.

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>PFBA (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
F	51-60	10-20	113.0	167.0	N/D	357.34
M	>70	>30	105.0	113.0	N/T	241.45
F	51-60	10-20	104.0	108.0	N/D	252.23
M	51-60	20-30	104.0/103.0	70.3/72.7	N/T	192.44/195.54
M	61-70	20-30	100.00	131.0	N/T	293.08
M	41-50	10-20	97.9	121.0	N/D	244.71
F	51-60	20-30	96.1	67.8	N/T	180.2
F	41-50	<10	95.1/89.1	85.9/79.8	N/T	200.71/186.15
M	51-60	10-20	92.7/92.5	88.0/111.0	2.92	211.78/240.23
M	51-60	20-30	86.8	125.0	N/T	248.01
F	61-70	>30	85.7	121.0	N/D	232.86
M	>70	N/A	82.3	118.0	N/T	221.79
F	61-70	20-30	80.5	163.0	N/T	212.40
M	>70	>30	78.6	112.0	N/T	210.63
F	41-50	N/A	77.5	78.4	N/T	178.51
F	31-40	10-20	75.9	103.0	N/D	196.84
F	51-60	20-30	74.9	61.1	N/T	152.72
M	31-40	10-20	74.6	91.0	N/T	182.36
F	18-30	N/A	70.9	112.0	N/D	200.91
F	>70	>30	69.3	102.0	N/T	191.84
F	41-50	N/A	69.0	77.2	N/T	163.79

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>PFBA (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
M	<18	<10	68.3	50.1	N/T	134.12
M	10-30	<10	67.4	83.3	N/D	167.12
M	41-50	10-20	63.3	76.7	N/T	158.88
F	41-50	<10	63.3	73.1	N/T	150.11
F	51-60	10-20	60.6	92.5	N/D	184.71
F	61-70	N/A	59.9	71.0	N/T	145.61
F	N/A	10-20	59.8	109.0	N/D	183.42
F	61-70	>30	58.7	73.4	N/T	149.48
M	61-70	<10	58.7	61.7	N/T	134.64
F	61-70	20-30	58.3	68.1	N/D	154.95
F	41-50	20-30	57.8	70.4	N/T	146.46
M	41-50	10-20	56.2	116.0	N/D	193.95
F	31-40	10-20	48.4	71.9	N/T	132.83
M	61-70	>30	46.1	85.3	N/D	131.40
M	<18	<10	45.4/46.4	68.2/71.7	N/D	130.85/132.92
M	51-60	10-20	44.6	60.4	N/T	115.40
M	41-50	<10	44.1	55.2	N/T	114.29
M	18-30	10-20	43.5	54.4	N/T	107.12
M	<18	10-20	42.4	51.1	N/T	107.84
M	61-70	>30	40.7	80.3	N/D	137.38
M	61-70	20-30	39.8	46.5	N/D	104.37

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>PFBA (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
F	41-50	10-20	39.3	46.3	N/D	94.34
F	18-30	20-30	38.8	47.6	N/T	96.33
M	51-60	>30	37.1	51.1	N/T	102.01
F	41-50	10-20	33.8	46.4	N/D	91.07
F	51-60	10-20	33.2	59.5	N/T	105.24
F	41-50	<10	32.7	41.5	N/T	89.66
M	41-50	10-20	32.1	57.6	N/T	103.35
F	<10	<10	30.7	56.8	N/T	99.11
F	<10	<10	27.5	62.0	N/T	98.63
F	51-60	10-20	26.2	104.0	1.06	149.68
F	51-60	<10	25.2	46.2	N/D	77.18
M	51-60	10-20	24.5	37.2	N/D	69.72
F	41-50	10-20	23.8	40.3	N/D	74.18
F	41-50	10-20	23.6	72.9	N/D	107.32
F	18-30	20-30	23.1	29.2	N/T	59.83
F	51-60	20-30	22.2	46.1	N/T	74.88
F	31-40	<10	21.1/19.6	12.8/8.81	N/T	29.64/36.80
M	41-50	10-20	20.3	32.5	N/D	60.23
F	51-60	10-20	19.7	52.6	N/D	76.87
F	<18	10-20	19.1	42.9	N/T	71.21
F	41-50	<10	18.6	21.0	N/D	43.83

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>PFBA (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
F	<18	<10	17.1	20.1	N/T	43.08
M	<18	<10	16.1	24.3	N/D	51.95
M	31-40	<10	15.5	12.7	N/T	29.31
F	41-50	<10	14.9	23.6	N/D	42.94
F	31-40	10-20	14.6	37.4	N/D	59.61
M	41-50	<10	14.6	30.8	N/T	49.49
M	<18	<10	13.4	50.1	N/D	83.18
F	18-30	<10	13.3	12.3	N/T	27.14
M	41-50	<10	12.8	30.1	N/D	47.16
M	41-50	<10	11.2	27.7	N/D	57.94
F	18-30	<10	10.7	23.1	N/T	35.87
M	41-50	10-20	10.5	35.2	N/D	52.66
M	>70	20-30	10.2	24.2	N/T	35.31
F	31-40	<10	8.76	30.1	N/D	45.35
F	18-30	<10	7.35	10.5	N/T	19.39
F	61-70	>30	6.96	22.6	N/T	36.00
M	31-40	<10	6.16	16.1	N/D	26.90
F	18-30	10-20	6.09	17.7	N/D	26.79

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)/Dup.</u>	<u>PFOS (ppb)/Dup.</u>	<u>PFBA (ppb)/Dup.</u>	<u>TOTAL PFCs(ppb)*/ Dup.</u>
M	41-50	<10	5.52	8.27	N/D	15.82

N/T=not tested

N/A=data not available

N/D=not detected above laboratory detection limits

*Total of detected levels of PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDaA, PFBS, PFHxS, PFOS, PFBA, and PFOSA in the blood sample

**CHART B - LAKE ELMO/COTTAGE GROVE/ HASTINGS
CITY WATER CUSTOMERS**

<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>PFBA (ppb)</u>	<u>TOTAL PFCs(ppb)***</u>
F	51-60	<10	42.3	49.5	N/T	106.04
M	18-30	10-20	11.4	50.8	N/T	72.75
M	<18	<10	7.89	19.0	N/D	29.72
M	51-60	<10	7.21	38.9	N/T	57.56
F	N/A	N/A	6.9	19.6	N/T	33.04
M	31-40	10-20	6.78 (4.22*)	10.5 (7.95*)	N/D	24.07
M	31-40	>30	6.13	13.5	N/D	22.77
F	41-50	<10	4.97	12.9	N/D	21.57
M	>70	>30	4.34	14.0	N/D	21.99
F	51-60	10-20	4.10	17.3	N/T	26.12
M	51-60	10-20	3.89	21.2	N/T	29.84

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>PFBA (ppb)</u>	<u>TOTAL PFCs(ppb)***</u>
M	31-40	<10	3.79	14.9	N/D	24.16
F	N/A	N/A	3.36	21.4	N/D	29.36
F**	51-60	>30	2.21	7.88	N/T	18.27
F	<18	<10	1.95	N/D	N/D	1.95

* = whole blood analysis

**= former 3M employee

N/T=not tested

N/A=data not available

N/D=not detected above laboratory detection limits

***Total of detected levels of PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDaA, PFBS, PFHxS, PFOS, PFBA, and PFOSA in the blood sample

CHART C - WASHINGTON COUNTY PRIVATE WELL USERS**1. Lake Elmo Area Private Wells**

<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>PFBA (ppb)</u>	<u>TOTAL PFCs(ppb)*</u>
M	41-50	<10	133.0	155.0	N/D	322.93
F	<18	<10	110.0	111.0	N/T	247.19
F	41-50	10-20	72.9	87.6	N/T	175.25
F	<18	10-20	55.4	60.0	N/T	124.35
M	41-50	20-30	45.7	19.7	N/D	72.11
F	41-50	<10	39.0	57.4	N/D	112.63
F	61-70	20-30	30.9	88.6	N/T	128.93

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>PFBA (ppb)</u>	<u>TOTAL PFCs(ppb)*</u>
M	61-70	20-30	24.2	38.0	N/T	69.91
M	51-60	10-20	27.0	28.5	N/T	62.32
F	51-60	>30	24.0	17.1	N/D	50.96
M	51-60	10-20	20.1	53.5	N/D	86.21
M	N/A	N/A	16.4	22.1	N/D	44.43
F	41-50	10-20	15.7	9.27	N/D	27.68
F	>70	>30	14.3	8.90	N/D	26.27
M	61-70	>30	12.1	9.78	N/D	24.89
M	61-70	10-20	10.4	42.0	N/D	61.40
M	41-50	10-20	9.66	26.6	N/T	42.51
M	18-30	20-30	7.56	17.3	N/T	33.70
M	61-70	20-30	6.95	43.1	N/T	55.00
M	51-60	20-30	6.78	21.0	N/T	36.91
M	61-70	>30	6.10	43.7	N/T	54.19
F	61-70	10-20	6.06	36.9	N/D	49.09
F	51-60	10-20	5.92	29.5	N/T	41.26
M	51-60	N/A	5.35	20.4	N/T	29.02
F	41-50	N/A	3.14	11.2	N/T	16.29
F	61-70	>30	2.4	12.0	N/T	17.91

N/T=not tested

N/A=data not available

N/D=not detected above laboratory detection limits

*Total of detected levels of PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDoA, PFBS, PFHxS, PFOS, PFBA, and PFOSA in the blood sample

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2. Cottage Grove/Hastings Area Private Wells

<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>PFBA (ppb)</u>	<u>TOTAL PFCs(ppb)***</u>
M**	>70	20-30	19.7	108.0	N/T	151.41
F	31-40	<10	17.1	16.9	N/D	45.18
F	61-70	10-20	14.2	35.6	2.34	57.93
F	61-70	<10	10.3	28.7	N/D	45.53
F	51-60	20-30	9.12	42.8	N/D	57.61
M	61-70	<10	9.40	39.0	N/D	61.40
M	31-40	10-20	8.80	40.6	N/T	61.82
F	61-70	>30	7.38	32.5	N/T	66.46
M	>70	>30	6.42	32.5	N/T	45.32
M	<18	<10	5.75	14.9	N/D	27.01
F	41-50	20-30	4.97	16.3	N/D	25.08
F	41-50	<10	4.68	12.0	N/D	20.71
F	41-50	<10	4.31	23.5	N/D	32.92
F	51-60	10-20	4.12	12.4	N/T	18.60
M	61-70	10-20	3.88	38.6	N/D	49.39
F	<18	<10	3.87	15.8	N/T	28.51
F	N/A	N/A	3.54 (2.98*)	8.51 (8.3*)	N/D	15.76
F	41-50	>30	3.39	14.9	N/T	21.83
F	41-50	10-20	3.24	24.5	N/T	35.27
M	<18	<10	2.83	14.8	N/T	23.53

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<u>SEX</u>	<u>AGE</u>	<u>YEARS ON WATER</u>	<u>PFOA (ppb)</u>	<u>PFOS (ppb)</u>	<u>PFBA (ppb)</u>	<u>TOTAL PFCs(ppb)***</u>
M	41-50	<10	2.01	22.4	N/D	29.52

*=whole blood analysis

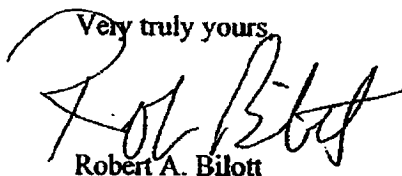
**=former 3M employee

N/A=data not available

N/T=not tested

N/D=not detected above laboratory detection limits

***Total of detected levels of PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnA, PFDaA, PFBS, PFHxS, PFOS, PFBA, and PFOSA in the blood sample

Very truly yours,


Robert A. Bilott

RAB/mdm

Enclosures

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Stephen J. Randall, Esq. (w/o encls.)
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April 16, 2007

FEDERAL EXPRESS

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Gloria Post
New Jersey DEP
401 East State Street, 1st Floor
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Re: Perfluorochemical Blood Exposure Data For New Jersey

Ladies and Gentlemen:

We serve as counsel for Plaintiffs in a lawsuit that is currently pending against E.I. duPont de Nemours and Company ("DuPont") in Federal Court in New Jersey involving claims arising from exposures to perfluorochemicals released by or otherwise attributable to DuPont. The lawsuit is styled *Rowe, et al. v. E.I. duPont de Nemours and Company*, Civil Action No. 06-1810 (RBK), USDC, Camden Vicinage, New Jersey.

DuPont owns and operates a manufacturing facility in New Jersey known as the Chambers Works Plant where perfluorochemicals, including PFOA, were handled, released, and/or disposed for several decades. In the context of Plaintiffs' investigation of their claims, Plaintiffs' counsel arranged for sampling of private water wells in the vicinity of DuPont's Chambers Works Plant, along with blood sampling of individuals whose private or public source of drinking water is contaminated by perfluorochemicals attributable to the plant. In recognition of the potential threat to human health and the environment revealed by the results, and in response to USEPA's prior public requests for perfluorochemical monitoring data, we are

{W0950088.1}

April 10, 2007

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providing copies of this initial data to you for inclusion in USEPA's Administrative Record 226 and public docket EPA- HQ-OPPT-2003-00012.

The PFOA, PFOS and total perfluorochemical ("total PFCs") results for the blood and water samples collected and analyzed to date on behalf of Plaintiffs are summarized below. Please note that all results were provided by Axys Analytical Services Ltd. in Canada and were obtained, arranged for, and paid for without any involvement by DuPont.¹ The PFC blood data is divided into the following categories: (1) customers of the Penns Grove Water Supply Company (Chart A)²; and (2) individuals whose drinking water is obtained from private drinking water wells (Chart B). The lab results for each of the blood results presented below are attached at Exhibit A. For privacy reasons, the names, addresses and specific ages of each of those sampled are not provided with this submission. The lab results for the private water well sampling are attached at Exhibit B. All blood and water results are presented in parts per billion (ppb).

CHART A - PENNS GROVE PUBLIC WATER CUSTOMERS

<u>SEX</u>	<u>AGE</u>	<u>PFOA</u>	<u>PFOS</u>	<u>TOTAL PFCs</u>	<u>YEARS ON WATER</u>
*M	41-50	421.00	16.6	444.86	<10
M	<18	24.3	22.8	59.94	<10
*M	41-50	23.5	21.4	58.10	N/A
F	41-50	12.9	22.4	44.84	10-20
F	51-60	12.8	13.7	32.23	20-30
*M	51-60	10.3	14.0	30.98	N/A
M	31-40	9.65	44.5	63.08	10-20
F	61-70	9.58	36.8	55.04	21-30
F	51-60	9.56	14.8	30.20	N/A
F	>70	9.45	34.1	60.65	N/A
F	61-70	8.04	26.2	42.65	<10
F	41-50	7.51	11.8	20.74	10-20
M	51-60	7.48	24.1	37.64	N/A
M	<18	7.4	14.6	26.71	10-20
M	51-60	6.6	27.4	46.93	N/A
M	<18	6.32	9.95	21.06	<10
M	18-30	6.31	8.45	19.01	10-20
F	51-60	5.61	25.3	34.77	N/A
F	<18	4.83	10.8	18.55	<10
F	18-30	2.72	6.61	10.44	20-30
M	51-60	2.55	8.39	13.10	10-20

* = DuPont Chambers Works Employee

NA = Data not currently available

¹ Blood results were, however, previously reported to DuPont by Plaintiffs' Counsel

² PFOA has been detected in the Penns Grove public water supply at levels exceeding the current 0.04 ppb guideline for PFOA developed by the New Jersey Department of Environmental Protection.

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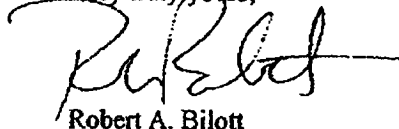
CHART B - PRIVATE WELL USERS

<u>SEX</u>	<u>AGE</u>	<u>PFOA</u>	<u>PFOS</u>	<u>TOTAL</u>	<u>PFOA/ WATER</u>	<u>PFOS/ WATER</u>	<u>TOTAL PFCs IN WATER</u>	<u>YEARS</u>
M	51-60	11.9	16.8	39.25	0.041	ND	0.041	20.30
F	51-60	11.2	66.4	89.54	0.041	ND	0.041	20-30
F	51-60	11.1	76.2	91.24	0.28	0.02	0.30	10-20
M	<18	9.36	24.6	38.32	0.28	0.02	0.30	10-20
F	61-70	5.1	12.3	22.07	ND	ND	ND	N/A
F	18-30	2.82	11.1	18.03	ND	ND	ND	N/A

ND = Not detected at laboratory detection limits

N/A = Data not currently available

Very truly yours,



Robert A. Bilott

RAB:itc

Attachments (Exhibit A and B)

cc: R. Edison Hill, Esq.
Larry A. Winter, Esq.
Rhon E. Jones, Esq.
David B. Byrne, III, Esq.
Shari M. Blecher, Esq.

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April 9, 2008

VIA ELECTRONIC MAIL AND REGULAR U.S. MAIL

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Lara Werner
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Philadelphia, PA 19103

Re: PFOA/C-8 Blood Levels From Ohio/West Virginia Drinking Water
Contamination: For Ar-226/OPPT-2003-0012/TSCA 8(e)/IRIS

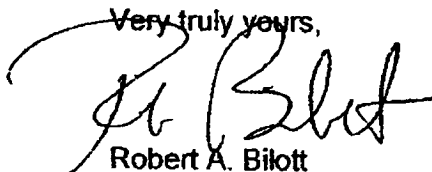
Ladies and Gentlemen:

Enclosed is information relating to the levels of PFOA/C-8 detected in the blood of tens of thousands of people who used for at least one year drinking water from one or more public and/or private drinking water supplies in West Virginia and/or Ohio contaminated with PFOA/C-8 at or above 0.05 parts per billion. This information was collected through the Health Project implemented under a 2005 settlement of a class action lawsuit against E.I. du Pont de Nemours and Company. Additional information relating to this data and health effects reported among those tested (and other information) can be found at the following Web site hosted by West Virginia University: <http://www.hsc.wvu.edu/som/cmed/c8/>. We understand that additional data will be posted on this Web site in the future.

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We request that USEPA include this information in its AR-226, OPPT-2003-0012, TSCA 8(e), and IRIS dockets and databases for PFOA/C-8, except any portion that EPA is prohibited by law from including in its public files.

Very truly yours,

A handwritten signature in black ink, appearing to read "R. Bilott", written over the typed name.

Robert A. Bilott

RAB:mdm

Enclosure

cc: Chris Korleski, OEPA (w/ encl.)
Lisa McClung, WVDEP (w/ encl.)
Gloria Post, NJDEP (w/ encl.)
John Linc Stine, MDH (w/ encl.)
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November 3, 2009

VIA ELECTRONIC AND REGULAR U.S. MAIL

Ms. Nickolette Roney
Division of Toxicology and Environmental Medicine
Agency For Toxics Substances and Disease Registry
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1600 Clifton Road, NE
Atlanta, GA 30333

Re: Docket ATSDR-253: Supplemental Comment On Draft
Toxicological Profile For Perfluoroalkyls

Ms. Roney:

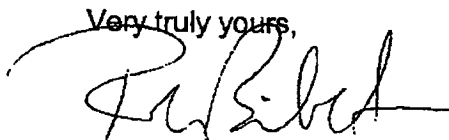
As a supplement to our October 30, 2009, comments on the referenced draft Toxicological Profile For Perfluoroalkyls, we wish to include references to three additional documents that we believe should be reviewed and considered before finalizing the current draft Profile:

1. Nelson, J.W., "Exposure to Polyfluoroalkyl Chemicals and Cholesterol, Body Weight, and Insulin Resistance in the General U.S. Population," *Environ. Health Persp.* (online doi: 10.1289/ehp.0901165 (Nov. 2, 2009));
2. Hoffman, K., et al., "Exposure to Polyfluoroalkyl Chemicals and Attention Deficit Hyperactivity Disorder in U.S. Children Aged 12-15 Years," 20 (6) *Epidem.* S70 (Nov. 2009) (ISEE 2009 Conference Abstract/Poster); and
3. Pinney, S.M., et al., "Perfluorooctanoic Acid (PFOA) and Pubertal Maturation in Young Girls," 20 (6) *Epidem.* S80 (Nov. 2009) (ISEE 2009 Conference Abstract/Poster).

Although these materials became available after the October 30, 2009, public comment deadline, we note that ATSDR has committed to consider "comments received after the public comment period" on "the basis of what is deemed to be in the best interest of the general public." As these new materials relate to potential health risks to people exposed to perfluoroalkyls, we believe that consideration of these materials is in the

Ms. Nickolette Roney
November 3, 2009
Page 2

best interest of the general public and that ATSDR should afford the information due consideration prior to any finalization of the current draft Profile. Thank you.

Very truly yours,

Robert A. Bilott

RAB:mdm
Enclosures

ehp

ehponline.org

ENVIRONMENTAL HEALTH PERSPECTIVES

Exposure to Polyfluoroalkyl Chemicals and Cholesterol, Body Weight, and Insulin Resistance in the General U.S. Population

Jessica W. Nelson, Elizabeth E. Hatch, and Thomas F. Webster

doi: 10.1289/ehp.0901165 (available at <http://dx.doi.org/>)

Online 2 November 2009



NIEHS

National Institute of
Environmental Health Sciences

National Institutes of Health
U.S. Department of Health and Human Services

**Exposure to Polyfluoroalkyl Chemicals and Cholesterol, Body Weight, and Insulin
Resistance in the General U.S. Population**

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Running Title: PFCs and Cholesterol in the General U.S. Population

Key words: body mass index (BMI), cholesterol, insulin resistance, National Health and Nutrition Examination Survey (NHANES), polyfluoroalkyl chemicals (PFCs), perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), waist circumference (WC)

Article Descriptor: Cardiovascular, Obesity

Acknowledgements and grant information:

We acknowledge the invaluable work of the National Center for Health Statistics and the National Center for Environmental Health of the U.S. Centers for Disease Controls and Prevention in conducting the National Health and Nutrition Examination Survey, and the contributions of Lynn L. Moore, Mustafa Qureshi, Martha Singer, and Janice Weinberg. This work was supported in part by grant R21ES013724 from the National Institute of Environmental Health Sciences (NIEHS). Jessica Nelson was supported in part by Award Number T32ES014562 from NIEHS. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIEHS or the National Institutes of Health. The authors declare they have no competing financial interests.

Abbreviations and acronyms:

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CHD	Coronary heart disease
CI	Confidence interval
HDL	High-density lipoprotein
HOMA	Homeostatic model assessment
LDL	Low-density lipoprotein
LOD	Limit of detection
NCEH	National Center for Environmental Health
NHANES	National Health and Nutrition Examination Survey
Non-HDL	Non-high-density lipoprotein
PFCs	Polyfluoroalkyl chemicals
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PPARs	Peroxisome proliferator-activated receptors
SES	Socioeconomic status
TC	Total cholesterol
VLDL	Very low-density lipoprotein
WC	Waist circumference

Outline of section headers:

Abstract

Introduction

Materials and Methods

Study Population

PFC Concentrations

Outcomes

Covariates

Statistical Analysis

Results

Cholesterol

Body Weight

HOMA

Discussion

Previous Studies in Humans

Previous Studies in Animals

Possible Modes of Action

Implications for the Current Study

Limitations and Strengths

Conclusion

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Abstract

Background. Polyfluoroalkyl chemicals (PFCs) are used commonly in commercial applications and are detected in humans and the environment world-wide. Concern has been raised that they may disrupt lipid and weight regulation.

Objectives. We investigated the relationship between PFC serum concentrations and lipid and weight outcomes in a large publicly-available dataset.

Methods. We analyzed data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES) for participants aged 12-80. Using linear regression to control for covariates, we studied the association between serum concentrations of perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS), and measures of cholesterol, body size, and insulin resistance.

Results. We observed a positive association between concentrations of PFOS, PFOA, and PFNA and total and non-HDL-cholesterol. We found the opposite for PFHxS. Those in the highest quartile of PFOS exposure had total cholesterol levels 13.4 mg/dL (95% CI, 3.8, 23.0) higher than those in the lowest. For PFOA, PFNA, and PFHxS, this effect estimate was 9.8 (95% CI, -0.2, 19.7), 13.9 (95% CI, 1.9, 25.9), and -7.0 (95% CI, -13.2, -0.8), respectively. A similar pattern emerged when exposures were modeled continuously. We saw little evidence of a consistent association with body size or insulin resistance.

Conclusions. This exploratory cross-sectional study is consistent with other epidemiologic studies in finding a positive association between PFOS and PFOA and

cholesterol, despite much lower exposures in NHANES. Results for PFNA and PFHxS are novel, emphasizing the need to study PFCs other than PFOS and PFOA.

Introduction

Polyfluoroalkyl chemicals (PFCs) are a class of highly stable compounds used widely in commercial and industrial applications as surfactants, paper and textile coatings, and in food packaging (Calafat et al. 2007). Numerous chemicals belong to this class, including the products used industrially, by-products of manufacturing, and degradation products. They are composed of a fluorinated carbon backbone of varying length terminated by a carboxylate or sulfonate functional group. This amphipathic structure provides them the properties of water and oil repellency and stain resistance (Conder et al. 2008). The perfluorinated carboxylates include perfluorooctanoic acid (PFOA) and perfluorononanoic acid (PFNA), and the perfluorinated sulfonates include perfluorooctane sulfonic acid (PFOS) and perfluorohexane sulfonic acid (PFHxS).

Biomonitoring studies have documented human exposure to PFCs, both in occupationally-exposed cohorts (Costa et al. 2009; Olsen and Zobel 2007; Sakr et al. 2007a) and in the general population (Apelberg et al. 2007; Calafat et al. 2007; Fei et al. 2007). While the major sources of human exposure are poorly known, possibilities include diet (either directly from food or migration from food packaging), drinking water, and house dust (reviewed in Lau et al. 2007).

Once taken into the human body, PFCs are slowly eliminated and are not known to undergo biotransformation (Lau et al. 2007). They bioaccumulate, but not in lipid like many other persistent organic pollutants. Instead, they have been shown to bind to proteins in the liver and serum (Conder et al. 2008). Mean serum half lives in humans are estimated as 5.4 years for PFOS and 3.8 years for PFOA (Olsen et al. 2007). Shorter-chain compounds are generally assumed to have shorter half lives, though PFHxS is an

exception with an estimated mean half life of 8.5 years (Olsen et al. 2007). The half life for PFNA in humans has not been estimated.

Various adverse health effects have been observed in animal studies of PFOS and PFOA, including tumors in certain organs and developmental delays (Biegel et al. 2001; White et al. 2007). The structural resemblance of PFCs to fatty acids and the discovery that they bind to peroxisome proliferator-activated receptors (PPARs), nuclear receptors that play a key role in lipid metabolism and adipogenesis, have raised the concern that PFCs may disrupt lipid and weight regulation. Indeed, among the early reported health effects in animal studies that administered high PFC doses was hypolipidemia (Seacat et al. 2002). However, several studies in humans suggest that exposure to PFOA, and possibly to PFOS, may be associated with increased cholesterol in people (C8 Science Panel 2008; Costa et al. 2009; Sakr et al. 2007a). The evidence for an association between PFC exposure and body size and insulin resistance is much weaker (Lin et al. 2009).

The rising prevalence of the metabolic syndrome, which includes obesity, dyslipidemia, and insulin resistance, is of increasing public health concern in the U.S. and globally, and is linked closely with coronary heart disease (CHD) and related disorders (Ramos and Olden 2008). While changes in diet and lifestyle are undoubtedly important factors in this trend, there is growing interest in the hypothesis that endocrine disrupting chemicals may be playing a role (Grun and Blumberg 2009).

This exploratory, cross-sectional epidemiologic study investigated the relationship between exposure to four PFCs, including two compounds that have been little studied in humans, and cholesterol levels, obesity, and insulin resistance.

Materials and Methods

Study Population. The National Health and Nutrition Examination Survey (NHANES) is an ongoing survey of the civilian non-institutionalized U.S. population conducted by the U.S. Centers for Disease Control and Prevention (CDC) that gathers data on dietary and health factors. Participants are selected using a complex multistage probability sampling design, and come to a mobile examination center for a physical examination and to provide blood and urine samples. Various questionnaires are administered by trained interviewers (CDC 2008). The survey also includes biomonitoring for different environmental chemicals, including PFCs, of a random one-third subsample of participants by the National Center for Environmental Health (NCEH). NHANES obtained informed consent from all participants.

PFC Concentrations. PFCs were measured in serum of participants aged 12 and older by the NCEH using automated solid-phase extraction coupled to isotope dilution-high-performance liquid chromatography-tandem mass spectrometry; details of laboratory methods are available elsewhere (Calafat et al. 2007). Our study examined the four PFCs detected in greater than 98 percent of people: PFOS, PFOA, PFHxS, and PFNA. The other eight PFCs measured were detected in less than 28 percent of people. Values below the limit of detection (LOD) were reported by NHANES as the LOD divided by the square root of two.

Outcomes. Several cholesterol measures are commonly used in clinical and epidemiologic studies. Cholesterol is carried in plasma within different lipoproteins, including low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) which carry cholesterol to peripheral tissues and are considered “bad” cholesterol, and high-density lipoproteins (HDL) which transport cholesterol back to the liver for excretion and are considered “good” cholesterol. LDL carries around 70 percent of total plasma cholesterol, and HDL 20 to 30 percent (Tietz et al. 2006). Total cholesterol (TC) is the sum of the cholesterol content of LDL, HDL, and VLDL. The non-HDL cholesterol fraction, which includes LDL and VLDL cholesterol, has been shown to be a better predictor of CHD risk than LDL alone (Liu et al. 2006).

We studied TC, HDL, non-HDL, and LDL. TC and HDL were measured by NHANES directly in serum of all participants; TC was measured enzymatically through coupled reactions that hydrolyze cholesteryl esters, and HDL after the precipitation of apolipoprotein B lipoproteins with a blocking agent (CDC 2007b). We calculated non-HDL by subtracting HDL from TC. LDL was available only for the subsample of fasting participants and was not measured directly in serum, but estimated by NHANES using the widely-accepted Friedewald formula (CDC 2007c).

Body size outcomes considered include body mass index (BMI, weight (kg) divided by height (m)-squared) and waist circumference (WC, in cm). Weight, height, and WC were measured during the examination using standard protocols (CDC 2007d). To assess insulin resistance, we studied homeostatic model assessment (HOMA), used in epidemiologic studies as a simple, inexpensive, and reliable alternative to more complicated methods (Bonora et al. 2000). We calculated HOMA using the method of

Matthews et al.: $\text{HOMA} = [\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)}] / 22.5$
 (Matthews et al. 1985). Plasma insulin and glucose were measured enzymatically by
 NHANES in the fasting subsample of participants (CDC 2007a).

Covariates. NHANES collected data on potential confounding variables through questionnaires. As we had a large sample size, our models included a priori a number of covariates that are important predictors of cholesterol and body weight: age, gender, race/ethnicity, socioeconomic status (SES, a dichotomous indicator which combined income, education, and food insecurity to minimize missing data), saturated fat intake (tertiles, as percent of total caloric intake), exercise (performed moderate or vigorous physical activity in the past 30 days), and time in front of a TV or computer (categories of hours per day in the past 30 days). For those aged 20 and older, we also included alcohol consumption (categories of drinks per week), smoking, and, for women, parity. For the cholesterol analyses, we included continuous BMI as a covariate, and tested for confounding by continuous serum albumin. See Supplemental Material, Table 1 for details on covariates.

Statistical Analysis. We performed regression analyses in gender and age (12-19, 20-59, 60-80) subgroups for each PFC separately. When results showed similar trends by age and gender, we combined groups. Cholesterol and weight outcomes were analyzed as continuous variables; HOMA was log-transformed as it was log-normally distributed. For the main analysis, exposure was modeled in quartiles of PFC concentration, with quartiles formed in the population overall and separately for the age/gender group used in

the analysis. We present effect estimates for each quartile compared to the reference group (the first quartile) and their corresponding 95% confidence intervals (CIs). Tests for trend in the quartile analyses were performed by treating PFC category as a linear predictor in the models.

In addition, for cholesterol outcomes in adults, we performed a sensitivity analysis that modeled exposure as a continuous predictor. We identified influential points and outliers by examining studentized residuals, predicted values, and scatterplots, and excluded them from the analysis if they changed the effect estimates by 5 percent or more.

All analyses excluded those over age 80, pregnant, breastfeeding, on insulin, or undergoing dialysis. Cholesterol analyses also excluded those who reported current use of cholesterol-lowering medications in the blood pressure portion of the questionnaire or who were missing this variable. See Supplemental Material, Figure 1 for the number of people in each exclusion group. Covariates described above were used in all models for which they were available, depending on age group and gender.

To perform analyses, we used the SAS 9.1 Proc SURVEYREG procedure, which takes into account possible correlation between the strata and clusters by which NHANES samples the population. Models were adjusted for relevant covariates instead of using NHANES sampling weights; this adjustment is regarded as a good compromise between efficiency and bias (Korn and Graubard 1991).

Results

PFC concentrations were available for 2,094 participants of the original subsample of 2,368 people. PFOS levels were an order of magnitude higher than the other PFCs, with a median of 19.9 $\mu\text{g/L}$ serum compared to 3.8 for PFOA. Similar to results in the same dataset reported by Calafat et al. (2007), concentrations were higher in males compared to females, non-Hispanic whites compared to Mexican Americans and non-Hispanic blacks, and people of higher SES compared to lower SES. There were no striking concentration differences by age. The four PFCs were log-normally distributed, and were moderately correlated with one another. PFOA and PFOS were most strongly correlated, with a Spearman correlation coefficient of 0.65; PFHxS and PFNA were the least correlated at 0.12. Cholesterol, body weight, and insulin resistance outcomes varied with age, gender, and race/ethnicity, and were correlated with one another in predictable ways.

The number of participants in each analysis depended on the outcome and missing data. We present results for the cholesterol analyses among adults (20-80 year-olds) in Tables 1 and 2 and Figure 1. Supplemental Material, Figure 1 illustrates how we arrived at our final sample size, which does not include 12-19 year-olds ($n=640$). Of adults with PFC and cholesterol measures ($n=1310$), we excluded the 20% who reported using cholesterol-lowering medications and the 3% who were missing this variable. None of the covariates were missing in more than 9% of people. Table 1 shows the distribution of outcomes and PFC concentrations in this sub-population, including PFC range and number of people in each quartile. In all cases, the PFC range in the fourth quartile is much wider than in the other three quartiles. Supplemental Material, Table 1 provides information on the distribution of covariates.

Cholesterol. Figure 1 presents the adjusted associations between the four cholesterol measures and PFC serum concentrations for adults (Supplemental Material, Table 2 presents crude associations). We omitted 12-19 year-olds because no data were available for two important covariates, alcohol and smoking. See Supplemental Material, Table 3 for results stratified by age (including 12-19 year-olds) and gender.

We found a positive association between TC and PFOS, PFOA, and PFNA concentrations (Figure 1A). Adults in the highest PFOS quartile had TC levels 13.4 mg/dL (95% CI, 3.8, 23.0) higher than those in the lowest quartile. For PFOA, there was a 9.8 mg/dL (95% CI, -0.2, 19.7) increase, and for PFNA, 13.9 mg/dL (95% CI, 1.9-25.9). TC appeared to increase linearly across the quartiles of PFC exposure, particularly for PFNA (p-value for trend = 0.04). When examined in age and gender subgroups, results were similar, with associations of greater magnitude among 60-80 year-olds. Associations were fewer and of smaller magnitude among 12-19 year-olds. In contrast, results for PFHxS indicated an inverse trend among adults (p-value for trend = 0.07). Those in the top PFHxS quartile had TC levels that were lower than those in the lowest quartile by -7.0 mg/dL (95% CI, -13.2, -0.8) . The same pattern held in the female age subgroups in particular.

We found fewer consistent trends in the HDL analyses. We observed differences by age and gender; results for all adults (Figure 1B) may in some cases mask these findings (see Supplemental Material, Table 3). PFOA and PFOS were associated with higher HDL in adolescent girls (effect estimates for the top quartile compared to lowest of 4.3 (95% CI, 0.1, 8.5) and 3.7 (95% CI, -0.5, 7.9), respectively), with some evidence

of the opposite in the older age group (in 60-80 year-old males, effect estimate for the top PFOA quartile compared to lowest of -8.7 (95% CI, -16.3, -1.1)). No meaningful associations were observed between PFNA and PFHxS concentration and HDL.

Results for non-HDL were similar to those for TC, as would be expected because the non-HDL fraction makes up 70 to 80 percent of TC (Figure 1C). The magnitude of effect increased slightly for PFNA and PFHxS. LDL results (Figure 1D) should mirror those for non-HDL; however, the sample size for LDL analyses was half as large. We found a somewhat similar pattern for PFNA and PFHxS, but no association with PFOA and PFOS concentration.

We repeated all cholesterol models adjusting for albumin. Results were substantively the same as those presented above (data not shown). Results were similar as well in models that considered PFC concentration as a continuous predictor (Table 2). PFOS, PFOA, and PFNA were all positively associated with TC and non-HDL (effect estimates were statistically significant for PFOS and PFOA). The opposite was seen for PFHxS, which was negatively associated with TC, non-HDL, and LDL.

In addition, we performed a number of sensitivity analyses that also had no qualitative effect on results from the quartile analysis: the inclusion of adults missing data on use of cholesterol-lowering medication, the inclusion of all adults (even those who reported taking medications), the exclusion of points identified as outliers in the continuous models from Table 2, and use of NHANES sampling weights.

Body Weight. We found fewer meaningful associations between body weight and PFC concentrations (see Supplemental Material, Table 3). The strongest effects were

seen with PFOS among males. In 12-19 and 20-59 year-olds, BMI decreased with increasing PFOS exposure. Teenage boys in the highest PFOS quartile had BMIs that were 2.8 points (95% CI, -4.1, -1.4) lower than those in the lowest quartile (p-value for trend = 0.004). In 60-80 year-old men, on the other hand, increasing PFOS exposure was associated with increased BMI (effect estimate for the top quartile compared to lowest of 1.6 (95% CI, 0.14, 3.0)). We did not see evidence of a relationship in the female age groups. Results for the other PFCs were less consistent, and those for WC were similar to BMI.

HOMA. On the whole, we found no association between PFC concentrations and HOMA. Although there were isolated suggestive trends, such as a significant positive trend with PFNA in adult females and a negative one with PFHxS in adolescent females, effects were not consistent (see Supplemental Material, Table 3).

Discussion

This exploratory study examined associations between serum concentrations of four PFCs and cholesterol levels, body size, and insulin resistance in a sample of the general U.S. population. Most striking were the findings for TC and non-HDL. These outcomes were positively associated with PFOS, PFOA, and PFNA and negatively associated with PFHxS after controlling for numerous covariates in categorical and continuous models. The LDL analyses were more limited by study size, but, for PFHxS and PFNA, revealed similar trends, though of less consistency and magnitude. No strong trends emerged in the HDL analyses. These results suggest that exposure to background

levels of certain PFCs may exert effects on the non-HDL fraction of cholesterol. We did not find consistent associations between PFCs and BMI, WC, or HOMA.

Previous Studies in Humans: Studies of the association between cholesterol levels and PFCs are found primarily in the occupational health literature. While results are not entirely consistent, the general trend is one of positive associations between PFOA concentration and cholesterol levels. Results for PFOS are less clear as it has been less-studied. Sakr et al. studied a large cohort of DuPont workers (n=454 for a longitudinal study and 1,025 for a cross-sectional study) (Sakr et al. 2007a; Sakr et al. 2007b). In both, PFOA was positively associated with TC, but not with HDL. A positive association was observed with LDL in the cross-sectional study only. When restricted to those not taking cholesterol-lowering medications, the magnitude of effect in the cross-sectional study increased. A study of a smaller group of Italian workers (n=53), which included a sub-study excluding those being treated for hyperlipidemia, found a similar positive association between TC and PFOA (Costa et al. 2009). Findings from studies of workers at different 3M Company locations are more mixed. The most recent study conducted by Olsen et al. did not find evidence of an association between serum PFOA and TC or LDL among 506 employees at three facilities (Olsen and Zobel 2007). An earlier study of the same workers at two of those locations, which did not adjust for use of cholesterol-lowering medications, found a positive association between serum PFOS and PFOA and TC in a cross-sectional analysis (n=421) and PFOA in a longitudinal analysis (n=174) (Olsen et al. 2003).

Exposure levels in these workers are much higher than in NHANES participants. Median serum concentrations in the 3M cohort were 1100 µg/L for PFOA and 720 µg/L for PFOS (Olsen and Zobel 2007). The mean PFOA level was 4300 µg/L in the DuPont studies (Sakr et al. 2007a); the median was 3890 µg/L in 2007 measurements from the Italian cohort (Costa et al. 2009). In comparison, median serum concentrations in NHANES were 4 and 20 µg/L for PFOA and PFOS, respectively.

Two studies have also been conducted on PFCs and cholesterol outcomes in communities surrounding a DuPont plant who have much higher exposures than the general population. Emmett et al. examined PFOA concentrations among 371 residents of a water district area bordering the plant (Emmett et al. 2006). While the study found no association between PFOA and total cholesterol, the analyses neither controlled for possible confounders nor excluded people on cholesterol-lowering medications. The C8 Health Project, a much larger study conducted in relation to a legal case, has released preliminary, non-peer reviewed findings from its analysis of 46,294 people living in six water districts near the plant (C8 Science Panel 2008). The study, which excluded those on cholesterol medications and controlled for confounding, found significant positive associations between PFOA and PFOS concentrations and TC and LDL.

A recent study using NHANES data examined the relationship between PFCs and components of the metabolic syndrome in 1999-2000 and 2003-2004 participants (Lin et al. 2009). It is difficult to compare our study to these results, as the authors examined an additional two years of data, did not report results for TC, non-HDL, or LDL, and conducted logistic regression analyses for two of the outcomes. They found a significant positive association between HOMA and PFOS concentrations in adults, similar to the

direction of association we observed (though, in our study, the trend did not come close to statistical significance). PFNA concentrations were found to have a protective effect on the odds of having low HDL in adolescents and adults, with the opposite seen for PFOS in adults. Our study did not observe these relationships with HDL as a continuous outcome. Finally, the authors found that higher PFHxS, PFOA, and PFOS concentrations in adolescents were associated with decreased WC, findings we also observed for PFOS.

There have been few studies of non-developmental PFC exposure and body size. A cross-sectional study of 3M workers found BMI to be slightly higher in the highest category of PFOA exposure, although there was no adjustment for confounding (Olsen et al. 1998). Another study found that mothers who were overweight or obese before pregnancy had higher plasma levels of PFOS and PFOA (Fei et al. 2007), and a third observed higher PFOS and PFOA levels in cord blood of both overweight and underweight women (Apelberg et al. 2007).

Previous Studies in Animals: Unlike in humans, studies in rodents found consistent inverse associations between cholesterol levels and exposure to PFOS and PFOA, though doses administered were much higher than typical human exposure levels (Martin et al. 2007; Thibodeaux et al. 2003). In cynomolgus monkeys, decreased total cholesterol was reported as the earliest reliable measure of a clinical response following PFOS exposure (Seacat et al. 2002). This hypolipidemic effect in primates has not been seen with PFOA exposure, however (Butenhoff et al. 2002). We are not aware of similar animal studies of PFNA or PFHxS exposure.

Weight loss has also been a common finding in high dose animal studies of PFOS and PFOA (Seacat et al. 2002; Thibodeaux et al. 2003). A recent study in mice of PFOA exposure and body weight tested a wide range of doses and looked at both adult and developmental exposure (Hines et al. 2009). Exposure during adulthood was not associated with later-life body weight effects, whereas low-dose developmental exposure led to greater weight in adulthood and increased serum leptin and insulin levels. Animals exposed to higher doses of PFOA, on the other hand, had decreased weight.

Possible Modes of Action. The hypothesized mode of action for the hypolipidemic effects of PFCs in animals is through activation of PPAR-alpha, the PPAR isoform involved in lipid homeostasis and peroxisome proliferation (Wolf et al. 2008). Multiple in vitro studies have shown PFCs to be PPAR-alpha ligands in rodent and human cells (Vanden Heuvel et al. 2006; Wolf et al. 2008). Activation is greater as carbon backbone length increases, and carboxylates (PFOA and PFNA) have higher activation than sulfonates (PFOS and PFHxS). PFCs may also indirectly activate PPAR-alpha by interacting with fatty acid binding proteins (Luebker et al. 2002). PPAR-alpha ligands, such as the fibrate class of cholesterol-lowering medications, inhibit secretion of cholesterol from the liver, reducing cholesterol in the serum (Kennedy et al. 2004). PPAR-gamma is another PPAR isoform more closely involved in adipogenesis (Grun and Blumberg 2009). Some PFCs weakly activate PPAR-gamma in certain human cell lines (Vanden Heuvel et al. 2006).

PPAR-independent mechanisms could be involved as well. PFOS and PFOA have been shown to interact with other nuclear receptors, including the constitutive activated receptor (CAR) and pregnane X receptor (PXR) (Ren et al. 2009).

Interspecies differences may partly explain the inconsistent cholesterol findings between animal and human studies. Humans are less sensitive to PPAR-alpha-related effects than rodents, with approximately 10-fold lower expression of PPAR-alpha in liver compared to mice (Tilton et al. 2008). There are also major differences in PFC half-life and metabolism. While the half-life of PFOA in human serum is estimated to be 3.8 years, in mice it is around 18 days (Lau et al. 2007). Finally, rodents and humans have different plasma lipid profiles, with HDL, rather than LDL, predominating in rodents (Lima et al. 1998).

Implications for the Current Study. The positive associations we observed between serum concentrations of PFOS, PFOA, and PFNA and TC are consistent with much of the occupational health literature regarding PFOA, even though serum concentrations in studies of workers were at least one order of magnitude higher than in NHANES. Our findings for PFOA and PFOS are also consistent with emerging results from the very large C8 Health Study cohort. Although hyperlipidemia is not consistent with the animal literature, this may be explained by differences between species and/or doses studied.

The strongest, most consistent cholesterol results were seen for PFNA despite lower serum concentrations in the NHANES population. This is biologically plausible given that PFC toxicity seems to increase with carbon chain length. Correlation with

PFOS and/or PFOA could also partly explain the results, though PFNA is only moderately correlated with them ($r=0.5$). Very few studies have been conducted on the possible health effects of PFNA. Another notable finding was that PFHxS consistently acted in the opposite direction of the other PFCs in the cholesterol analyses. Of the compounds studied, PFHxS has the shortest carbon chain and the longest estimated half life. This differential effect of PFHxS is not found in the literature; more research is needed to assess possible mechanisms of PFHxS action that may differ from longer-chain PFCs.

The lack of consistent findings regarding body size is not entirely surprising. While interesting findings have been recently published on developmental exposures in both humans and animals (Fei et al. 2007, Hines et al. 2009), adult exposures appear to be less of a concern. Effects on insulin resistance have been very little studied.

Limitations and Strengths. Our study has a number of limitations that make it exploratory in nature. The NHANES data are cross-sectional, limiting our ability to rule out reverse causality. It is possible that PFCs behave differently in the bodies of people who have higher cholesterol levels. In addition, the hypothesis has been raised that the positive associations observed here and in occupational health studies between PFCs and TC may be due to the fact that PFCs bind to beta-lipoproteins and albumin in the blood (Olsen and Zobel 2007). Han et al. concluded that, in human and rat serum, more than 90 percent of PFOA would be bound to albumin (Han et al. 2003). The only report regarding PFC binding to beta-lipoproteins is a short non-peer reviewed document found in a U.S. Environmental Protection Agency docket that found that PFOS, PFOA, and PFHxS all

bind tightly to albumin, but that differences exist in binding to beta-lipoproteins, with 96 percent of PFOS binding compared to 64 percent of PFHxS and 40 percent of PFOA (Kerstner-Wood 2003). The authors conclude, "The data...shows that albumin is by far the largest single protein binder for three of the four compounds tested...The fourth compound, PFOS, was found to be highly bound by both albumin and beta-lipoproteins."

To address these concerns, we showed that controlling for serum albumin did not affect associations between serum PFCs and cholesterol. Confounding by PFC binding to beta-lipoproteins is still an issue, though we would expect this to be most striking for PFOS, which binds most highly. The fact that we see similar results for PFOS, PFOA, and PFNA is somewhat reassuring, as is the fact that we see an inverse association with PFHxS. If major confounding by beta-lipoprotein binding were occurring, we would expect to see a stronger positive association between cholesterol and PFHxS than PFOA. Our results for PFOA are also consistent with occupational studies that were able to model longitudinal data.

Additional limitations of our study include the fact that we have only one measurement of PFC and cholesterol concentrations. As PFCs have relatively long half lives, we can be fairly confident that blood concentrations reflect longer-term exposure, but cholesterol levels have significant variability and multiple measures are ideal (Tietz et al. 2006). If this measurement error is random and not related to PFC level, which seems likely, it should not bias the estimate, but rather increase the standard deviation. There is also the potential for residual confounding by diet or other factors. Because NHANES measures different classes of environmental chemicals in different subsamples of the

population, we were unable to consider co-exposure to other chemicals suspected to disrupt weight and lipid regulation.

Despite these limitations, our study has a number of strengths. It has a relatively large sample size and the ability to account for key covariates such as alcohol consumption and use of cholesterol-lowering medications. The large population also allows for consideration of modification by age and gender. In addition to PFOA and PFOS, we examined PFNA and PFHxS, compounds that have received less scientific attention but appear important to study further.

Conclusion

Though these results are based on cross-sectional data and are exploratory, they are consistent with much of the human epidemiologic literature, and indicate that PFCs may be exerting an effect on cholesterol metabolism at environmentally-relevant exposures. Our study affirms the importance of investigating PFCs other than PFOS and PFOA, particularly as industrial uses of PFOS and PFOA decline and other PFCs are substituted. PFNA may be of particular concern, as the chemical was detected in 98 percent of NHANES participants and serum concentrations rose between the time periods of 1999-2000 and 2003-2004 (Calafat et al. 2007). In some cases, PFNA had a greater magnitude of effect on cholesterol levels than PFOS and PFOA.

While this study does not demonstrate a causal association between PFC exposure and serum cholesterol levels, it provides clues about where to focus future epidemiologic and toxicology research. In particular, additional studies are needed to shed light on explanations for the opposite associations with cholesterol observed for PFHxS compared

to the other PFCs studied, and on the relationship between PFC binding to proteins in the blood, particularly beta-lipoproteins, and cholesterol levels. Despite its limitations, this study contributes to the literature suggesting that PFC exposure may disrupt cholesterol metabolism or homeostasis in humans.

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Table 1. Distribution of cholesterol outcomes and PFC concentrations, 20-80 year-olds^a

	N	Median	Mean (SD)	Range
TC (mg/dL)	860	199.0	202.1 (42.3)	86 - 394
HDL (mg/dL)	860	53.0	54.6 (15.4)	23 - 122
Non-HDL (mg/dL)	860	143.0	147.5 (43.4)	52 - 361
LDL (mg/dL)	416	115.0	117.1 (35.6)	21 - 252
PFOA (µg/L)	860	3.9	4.6 (3.0)	0.1 - 37.3
Quartile 1	223	2.1	1.9 (0.6)	0.1 - 2.7
Quartile 2	211	3.4	3.4 (0.4)	2.8 - 3.9
Quartile 3	186	4.6	4.6 (0.4)	4.0 - 5.4
Quartile 4	240	6.9	8.0 (3.3)	5.5 - 37.3
PFOS (µg/L)	860	21.0	25.3 (20.6)	1.4 - 392.0
Quartile 1	193	9.9	9.6 (2.9)	1.4 - 13.6
Quartile 2	198	17.3	17.0 (1.8)	13.8 - 19.7
Quartile 3	211	23.5	23.6 (2.4)	19.8 - 28.1
Quartile 4	258	37.5	44.8 (28.0)	28.2 - 392.0
PFNA (µg/L)	860	1.0	1.3 (1.2)	0.1 - 10.3
Quartile 1	170	0.4	0.4 (0.1)	0.1 - 0.5
Quartile 2	183	0.7	0.7 (0.1)	0.6 - 0.8
Quartile 3	246	1.0	1.1 (0.1)	0.9 - 1.3
Quartile 4	261	2.0	2.5 (1.5)	1.4 - 10.3
PFHxS (µg/L)	860	1.8	2.6 (2.7)	0.2 - 27.1
Quartile 1	217	0.8	0.7 (0.3)	0.2 - 1.1
Quartile 2	239	1.5	1.5 (0.2)	1.2 - 1.9
Quartile 3	233	2.4	2.6 (0.5)	2.0 - 3.5
Quartile 4	171	5.3	6.7 (3.7)	3.6 - 27.1

^a This table presents data for the population analyzed in Figure 1 and Table 2: 20-80 year-olds with full information on outcomes, exposures, and covariates. Quartiles of PFC exposure were calculated in the overall population (which included 12-19 year-olds and people missing covariate information). Therefore, the number of people in each PFC quartile is unequal.

Table 2. Change in cholesterol measure (mg/dL) per $\mu\text{g/L}$ increase in PFC, 20-80 year-olds^a

	TC Coefficient (95% CI)	HDL Coefficient (95% CI)	Non-HDL Coefficient (95% CI)	LDL Coefficient (95% CI)
PFOS	0.27 (.05, .48)	0.02 (-0.05, 0.09)	0.25 (0, 0.50)	0.12 (-0.17, 0.41)
PFOA	1.22 (.04, 2.40)	-0.12 (-0.41, 0.16)	1.38 (0.12, 2.65)	-0.21 (-1.91, 1.49)
PFNA	2.01 (-1.16, 5.18)	-0.40 (-0.90, 0.09)	2.56 (-1.19, 6.30)	0.50 (-3.94, 4.93)
PFHxS	-0.93 (-1.80, -0.06)	0.19 (-0.18, 0.55)	-1.13 (-1.90, -0.35)	-2.06 (-3.54, -0.58)

^a All models are adjusted for age, gender, race/ethnicity, socioeconomic status, saturated fat intake, exercise, time in front of a TV or computer, BMI, alcohol consumption, and smoking. We excluded values identified as influential points and outliers from the population of adults (n=860) in Table 1 and Figure 1. Most analyses excluded one or two points except: PFNA and TC (4), PFNA and HDL (6), PFNA and non-HDL (4), PFHxS and non-HDL (0), and PFHxS and LDL (5). See Supplemental Material, Table 4 for a full listing of the number of outliers excluded in each analysis.

Figure Legend

Figure 1. Differences in cholesterol levels, 20-80 year-olds, with increasing quartile of PFC exposure. Figure 1A presents change in total cholesterol (n=860), Figure 1B change in HDL (n=860), Figure 1C change in non-HDL (n=860), and Figure 1D change in LDL (n=416). All models control for age, gender, race/ethnicity, socioeconomic status, saturated fat intake, exercise, time in front of a TV or computer, alcohol consumption, smoking, and BMI. Median PFC levels ($\mu\text{g/L}$) for each quartile are shown below/above the bar. Error bars represent standard errors of the effect estimates (i.e. the difference between the quartile and the reference group), and p-values for trend are presented. 95% confidence intervals for each effect estimate are available in Supplemental Material, Table 3.

Figure 1A (n=860)

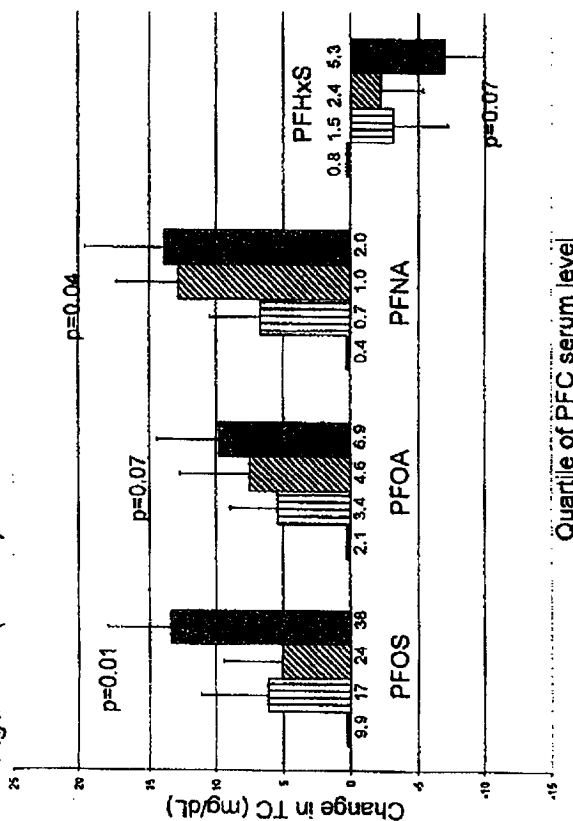


Figure 1B (n=860)

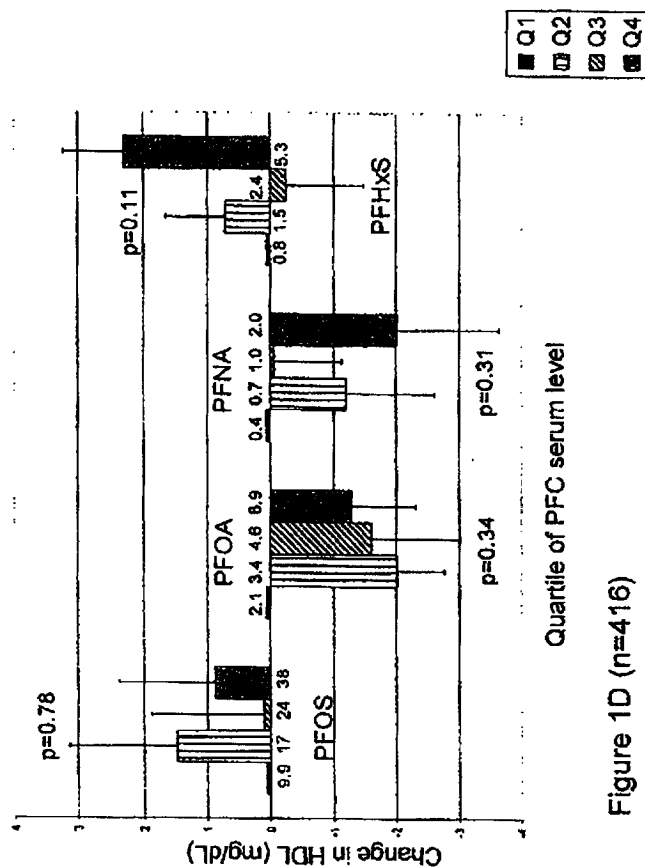


Figure 1C (n=860)

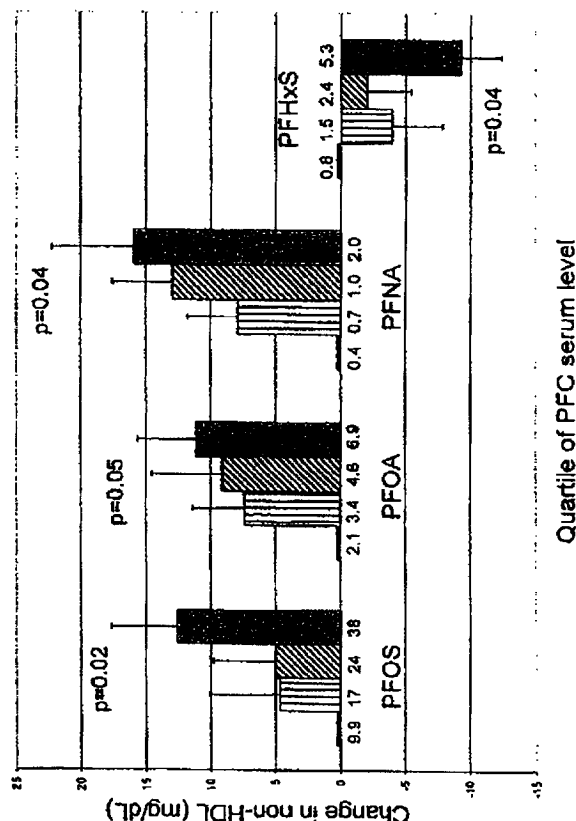
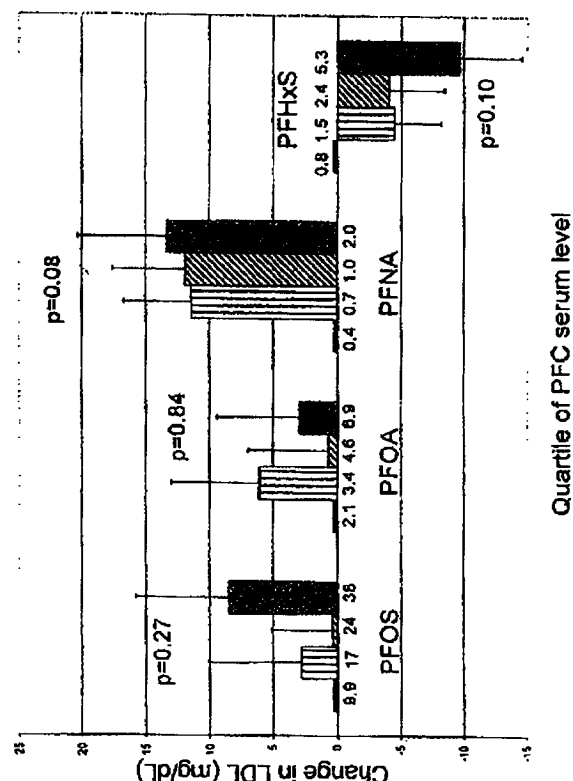


Figure 1D (n=416)



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Abstracts: ISEE 21st Annual Conference, Dublin, Ireland, August 25-29, 2009: Poster Presentations

Exposure to Polyfluoroalkyl Chemicals and Attention Deficit Hyperactivity Disorder in U.S. Children Aged 12-15 Years**Hoffman, Kate; Vieira, Veronica; Webster, Thomas; White, Roberta****Abstract**

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OS2.2.5**Exposure to polyfluoroalkyl chemicals and attention deficit hyperactivity disorder in U.S. children aged 12-15 years.**

Kate Hoffman, Veronica Vieira, Thomas Webster, Roberta White

Department of Environmental Health, Boston University School of Public Health, United States

Background and Objective: Polyfluoroalkyl chemicals (PFCs) have been widely used in consumer products. Exposures in the U.S. and world populations are widespread. Associations between exposures to four common PFCs and parental report of diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) were evaluated.

Methods: Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2003-2004 for children aged 12-15. Parental report of a previous diagnosis by a doctor or healthcare professional of ADHD in the child was the outcome measure. PFOA, PFOS, PFNA, and PFHS levels were measured in serum samples from each child. The association between each PFC and ADHD was examined using smoothing, categories, and linear models. All analyses were adjusted for age, sex, race, maternal smoking during pregnancy, and environmental tobacco smoke. Confounding by variables such as lead and socioeconomic status was also assessed but associations were not altered.

Results: Of the 586 children aged 12 to 15 in the sample, 51 were reported by their parents to have been diagnosed with ADHD. When PFOS was entered into analyses as a continuous predictor, a 1.22 fold increased odds was observed for each 10 $\mu\text{g/L}$ increase (95% CI 1.03-1.45). Similarly, compared to the first quartile of PFOS exposure, individuals in the fourth quartile were 1.92 times more likely to have ADHD (95% CI 0.82-4.51; p-value for trend=0.039). There were also significant dose response relationships between PFHS and PFOA exposures and ADHD. For each $\mu\text{g/L}$ increase, the odds of ADHD increased 1.06 and 1.09 times respectively (95% CI 1.02-1.11 and 1.00-1.18). Similarly, children with higher PFNA levels were more likely to have ADHD (OR=1.33 for $\mu\text{g/L}$ increase; 95% CI 0.91-1.95).

Conclusions: These results are consistent with an affect of PFCs on ADHD risk. Follow-up of these cross-sectional data with cohort studies is needed.

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Perfluorooctanoic Acid (PFOA) and Pubertal Maturation in Young Girls

Pinney, Susan M.; Windham, Gayle C.; Biro, Frank M.; Kushi, Larry H.; Yaghjian, Lusine; Calafat, Antonia; Kato, Kayoko; Succop, Paul; Brown, M Kathryn; Hernick, Ann; Bornschein, Robert



Abstract

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OS10.5.4

Perfluorooctanoic acid (PFOA) and Pubertal Maturation in Young Girls

Susan M. Pinney¹, Gayle C. Windham², Frank M. Biro^{3,4}, Larry H. Kushi⁵, Lusine Yaghjian¹, Antonia Calafat⁶, Kayoko Kato⁶, Paul Succop¹, M. Kathryn Brown¹, Ann Hernick¹, Robert Bornschein¹

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Background: Polyfluoroalkyl compounds (PFCs) and their salts, such as perfluorooctanoic acid (PFOA), have been reported to change mammary gland structure and function in laboratory animals. We explored the relationship between serum PFOA concentration and timing of pubertal maturation in young girls.

Methods: Within the NIH Breast Cancer and the Environment Research Centers (BCERC), we conducted a study of multiple environmental biomarkers, including PFOA and other PFCs in serum of young girls (age 6-7 years at entry) from two sites (N=689 girls). Pubertal staging (breast (B) and pubic hair (PH)) has been conducted by clinicians or trained research staff, every year or more frequently, for as long as four years. After calculating adjusted geometric means for all PFCs, we examined the relationship between PFOA serum concentration at the beginning of the study with body mass index (BMI) and pubertal Stage 2 at baseline and one year follow-up.

Results: Detectable serum levels of five PFCs, including PFOA, were found in >95% of the girls. The PFOA median was 6.4 ng/ml (range < LOD 0.1 to 55.9 ng/ml), with 24.9% having values above the 95th percentile for children 12-19 years (NHANES 2003-2004 population (8.6 ng/ml)). At the follow-up visit, 28.3% of girls had reached Tanner stage B2+, 19.2% were PH2+ and 30.3% had a BMI percentile for age >85. In analyses where serum PFOA was modeled as a continuous variable, we found a direct relationship with pubertal breast status and an inverse relationship with BMI percentile at the follow-up visit, with adjustment for age, race, site and caregiver education.

Conclusions: It appears that PFOA acts as an endocrine disruptor although perhaps not by the usual mechanism. Although the relationship with BMI was inverse, there was a direct relationship with breast maturation. We continue to explore these complex relationships in models including other covariates.

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