



LITTLE HOCKING WATER ASSOCIATION, INC.

3998 St. Rt. 124 • P.O. Box 188 • Little Hocking, OH 45742
(740) 989-2181 Fax (740) 989-5543
Website: www.littlehockingwater.org

U.S. EPA PUBLIC SCIENCE ADVISORY PANEL EPA 2007 REPORT ON THE ENVIRONMENT REVIEW PANEL July 10-12, 2007

COMMENTS

THE LITTLE HOCKING WATER ASSOCIATION, INC. LITTLE HOCKING, OHIO

My name is Bob Griffin. I want to thank the Science Advisory Board for this opportunity to comment. I am a civil engineer, who is the general manager of a non-profit rural water system located in southeast Ohio. The Little Hocking Water Association (LHWA) serves approximately 12,000 people from an approximately 45-acre wellfield adjacent to the Ohio River. In 2002, we first learned that PFOA or C-8, a perfluorinated compound (used in industry and the manufacture of consumer products) had contaminated our drinking water supply. We now know that our wellfield has the dubious distinction of having the highest level of C-8 measured in a public water system of which we are aware. In addition, LHWA customers have C-8 blood levels as high as 390 times the nationwide blood level of approximately 5 ppb. The average LHWA members C-8 blood levels are 70-80 times the national average. As a result of C-8 in our drinking water, over 80 percent of our customers are using bottled water as part of an emergency bottled water program.

According to US EPA, PFOA is of concern because:

- PFOA is persistent in the environment;
- PFOA bioaccumulates in living organisms;
- PFOA remains in the human body for years;
- Exposure to PFOA has caused adverse effects in laboratory studies in animals; and
- The multiple sources and pathways of PFOA exposure are not understood, making reductions difficult.

The presence of PFOA and other perfluorinated chemicals is not limited to just Ohio. Perfluorinated compounds have been found worldwide – in such wide-ranging venues as polar bears in Greenland to pandas in China. They are found in surface water and ground water in Europe and Japan. To date, in the United States, PFOA has been detected in ground water in Minnesota, New Jersey, Virginia, North Carolina, Alabama, West Virginia and Ohio. Public and private drinking water wells are affected.

In order to protect the health and welfare of the consumers of the LHWA water, the LHWA has closely followed relevant regulatory efforts and public recognition that PFOA may pose a threat to human health and the environment. LHWA actively participated in the ECA process (started in June 2003 by US EPA) that highlighted the importance of understanding pathways for exposure to PFOA. Although many studies spawned from this process are ongoing, formal ECA meetings were discontinued in 2006. Among other actions taken by US EPA on PFOA, a draft risk assessment was prepared and a SAB panel was formed to review the document. This SAB review was completed in May 2006 and recommended that PFOA be classified as a “likely carcinogen”. There is currently no US EPA-promulgated drinking water standard for PFOA or any related compound. Neither is there a TSCA reference dose for any of these compounds. However, in November, 2006 the US EPA announced an interim “action level” of 0.50 ppb. In February, 2007 the State of New Jersey announced a 0.04 ppb preliminary guidance level for C8.

As a result of the scope and complexity of these science and health issues, we are struck by the absence of PFOA and other perfluorinated compounds in the list of “Emerging Issues” in Chapter 7 of the 2007 Science Report on the Environment. PFOA and other perfluorinated compounds have been recognized by US EPA and other federal agencies as emerging issues. The public needs scientific guidance that is not subject to interference by those who have a financial interest in the outcome of the research. We urge you to update this report with this new information and references to make this document reflect the current importance of these contaminants. I am here to ask the Science Advisory Board to include a recommendation under either Charge Question 3 or 6 that PFOA and other perfluorinated compounds be included as an “Emerging Issue” in Chapter 7.

In support of this request, I have included the following annotated history and references for consideration by the Science Advisory Board in formulating their recommendation:

- 1) On April 16, 2003, the USEPA announced the beginning of the Environmental Consent Agreement process (known as ECA) to look at PFOA. The attached Federal Register notice summarizes the basis for concern about PFOA, but specifically excludes discussions of blood levels during this process.¹ The ECA process is a voluntary effort by industry in concert with the Agency.
- 2) In November and December 2005, the Little Hocking Water Association tested blood of some of its customers for PFCs. The results show levels of PFOA ranging from 112 ppb to 1040 ppb as compared to the national average of approximately 5 ppb.² The results also show the presence of other perfluorinated compounds.

¹ Environmental Protection Agency, 2003. Perfluorooctanoic Acid (PFOA), Fluorinated Telomers; Request for Comment, Solicitation of Interested Parties for Enforceable Consent Agreement Development, and Notice of Public Meeting, Federal Register 68 (73):18626-18633. April 16.

² <http://www.regulations.gov/fdmspublic/component/main> USEPA Docket EPA-HQ-OPPT-2003-0012-0990.

- 3) On August 8, 2006, Dr. Emmett et al. published the PFOA results of blood testing for residents primarily in the LHWA service area in the *Journal of Occupational and Environmental Medicine*.³ This study was funded by the National Institute of Health Sciences. The highest median blood level was 374 ppb for customers drinking Little Hocking water. The study concluded that drinking water was the primary source of PFOA in the blood.
- 4) After three years of negotiation under the ECA process, EPA had not received commitments by industry to perform studies in all desired arenas. At the June 8, 2006 Non-ECA PFOA Information Forum, USEPA provided updates on Agency-led initiatives including: the Office of Research and Development (ORD) telomer biodegradation research on soil and sewage sludge; ORD research in toxicity testing and pharmacokinetics; the Center for Disease Control's inclusion of PFOA and PFOS in the National Biomonitoring Program with data to be included in the 2007 National Report; and the National Toxicology Program's tiered research on perfluorochemicals with chain lengths from C-4 to C-12, including pharmacokinetics, mechanistic studies, reproductive toxicity and carcinogenicity. The agenda for that meeting is attached.⁴
- 5) On June 1, 2007, Benjamin Apelberg et al. published the results of a study by Johns Hopkins University and the Centers for Disease Control in *Environmental Science and Technology*.⁵ This study showed the ubiquitous presence of PFOA in babies cord blood. Nine other PFCs were also detected. Of particular significance, the study showed a negative correlation between birth weight and head circumference and PFOA and PFOS concentrations in the cord blood.
- 6) In May 2007, Kellyn Betts published an article in *Environmental Health Perspectives on Perfluoroalkyl Acids*.⁶ This article summarizes many of the research studies and presents many of the yet-to-be answered questions about these chemicals.

³ Emmett, E.A., Shofer, F.S., Zhang, H., Freeman, D., Desai, C., and Shaw, L.M. 2006. Community Exposure to Perfluorooctanoate: Relationships Between Serum Concentrations and Exposure Sources. *Journal of Occupational Environmental Medicine* 48 (8):759-770.

⁴ U.S. EPA, June 8, 2006. Agenda for Perfluorooctanoic Acid (PFOA) Enforceable Consent Agreement (ECA) Process Ninth Plenary Session and Non-ECA PFOA Information Forum, 2 pages.

⁵ Apelberg, B.J., Goldman, L.R., Calafat, A.M., Herbstman, J.B., Kuklennyik, Z., Heidler, J., Needham, L.L., Halden, R.U., and Witter, F.R. 2007. Determinants of Fetal Exposure to Polyfluoroalkyl Compounds in Baltimore, Maryland. *Environmental Science and Technology* 41(11):3891-3897.

⁶ Betts, K.S. 2007. Perfluoroalkyl Acids. What is the Evidence Telling Us? *Environmental Health Perspectives* 115 (5):A250-A256.

In summary, PFOA and other perfluorinated compounds have been recognized as chemicals of concern that have recently garnered much attention. We acknowledge that a brief reference is made in the 2007 Science Report in the discussion section on “Trends in Human Exposure to Environmental Contaminants” stating that the National Biomonitoring Program now includes PFOA and PFOS. However, we feel that this passing reference does not adequately reflect the “Emerging Issue” status of this chemical. Once again, I respectfully request that the SAB recommend that PFOA and other perfluorinated compounds be included in Chapter 7 as an “Emerging Issue”.

Thank you for carefully considering the comments of the Little Hocking Water Association.

A handwritten signature in black ink that reads "Robert L. Griffin". The signature is written in a cursive style with a prominent initial 'R'.

Robert L. Griffin, General Manager

Attachments (5)

ATTACHMENT 1

categorically excluded from the preparation of an environmental assessment or an environmental impact statement.

Determination Under Executive Order 12866

Western has an exemption from centralized regulatory review under Executive Order 12866. This notice is not required to be cleared by the Office of Management and Budget.

Dated: March 27, 2003.

Michael S. HacsKaylo,
Administrator.

[FR Doc. 03-9325 Filed 4-15-03; 8:45 am]

BILLING CODE 6450-01-P

ENVIRONMENTAL PROTECTION AGENCY

[OPPT-2003-0012; FRL-7303-8]

Perfluorooctanoic Acid (PFOA), Fluorinated Telomers; Request for Comment, Solicitation of Interested Parties for Enforceable Consent Agreement Development, and Notice of Public Meeting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA has identified potential human health concerns from exposure to perfluorooctanoic acid (PFOA) and its salts, although there remains considerable scientific uncertainty regarding potential risks. EPA is requesting public comment on pertinent topics of interest, as discussed in this document, and the submission of additional data concerning these chemicals. EPA is also soliciting the identification of interested parties who want to monitor or participate in negotiations on one or more enforceable consent agreements (ECAs) under section 4 of the Toxic Substances Control Act (TSCA) concerning PFOA and fluorinated telomers which may metabolize or degrade to PFOA, and is announcing the first public meeting for these ECA negotiations.

DATES: Comments on this notice must be received on or before May 16, 2003.

Notify EPA in writing on or before May 16, 2003 of your desire to be accorded "interested party" status for the purpose of participating in or monitoring the negotiations for development of ECAs concerning PFOA and telomers.

A public meeting has been scheduled to initiate negotiations on an ECA for PFOA and telomers, from 1 p.m. to 5 p.m., on Friday, June 6, 2003.

ADDRESSES: Submit your comments, identified by docket ID number OPPT-2003-0012, online at <http://www.epa.gov/edocket/> (EPA's preferred method), or by mail to EPA Docket Center (7407), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001. For additional comment submission methods and detailed instructions, go to Unit I.C. of the **SUPPLEMENTARY INFORMATION**.

Submit your notification for "interested party" status separately from any comments submitted, identified "Attention: PFOA ECA Notification" by mail to Brigitte Farren, Chemical Control Division (7405M), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001. To protect personal information from disclosure to the public, please submit these notifications separately from your comments and do not use any online electronic commenting system to submit this notification.

The public meeting to initiate negotiations on ECAs for PFOA and telomers will be held at the Environmental Protection Agency, EPA East Bldg., Rm. 1153, 1201 Constitution Ave., NW., Washington, DC.

FOR FURTHER INFORMATION CONTACT: For general information contact: Barbara Cunningham, Director, Environmental Assistance Division (7408M), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (202) 554-1404; e-mail address: TSCA-Hotline@epa.gov.

For technical information contact: Mary Dominiak, Chemical Control Division (7405M), Office of Pollution Prevention and Toxics, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (202) 564-8104; e-mail address: dominiak.mary@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

This action is directed to the public in general, and may be of particular interest to manufacturers, importers, processors, exporters, distributors, and users of PFOA, fluoropolymers, fluoroelastomers, and telomer chemicals. Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions

regarding the applicability of this action to a particular entity, consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Copies of this Document and Other Related Information?

1. **Docket.** EPA has established an official public docket for this action under docket identification (ID) number OPPT-2003-0012. The official public docket consists of the documents specifically referenced in this action, any public comments received, and other information related to this action. Although a part of the official docket, the public docket does not include Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. The official public docket is the collection of materials that is available for public viewing at the EPA Docket Center, Rm. B102-Reading Room, EPA West, 1301 Constitution Ave., NW., Washington, DC. Additional information concerning the topics discussed in this notice can be found in Administrative Record (AR)-226: PFOS, PFOA, Telomers, and Related Chemicals, which was established by the Agency in 2000 to receive information on various fluorinated chemicals, including PFOA. These materials are also available in the EPA Docket Center. The EPA Docket Center is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The EPA Docket Center Reading Room telephone number is (202) 566-1744 and the telephone number for the OPPT Docket, which is located in EPA Docket Center, is (202) 566-0280.

2. **Electronic access.** You may access this **Federal Register** document electronically through the EPA Internet under the "**Federal Register**" listings at <http://www.epa.gov/fedrgstr/>.

An electronic version of the public docket is available through EPA's electronic public docket and comment system, EPA Dockets. You may use EPA Dockets at <http://www.epa.gov/edocket/> to submit or view public comments, access the index listing of the contents of the official public docket, and to access those documents in the public docket that are available electronically. Although not all docket materials may be available electronically, you may still access any of the publicly available docket materials through the docket facility identified in Unit I.B.1. Once in the system, select "search," then key in the appropriate docket ID number.

Certain types of information will not be placed in the EPA Dockets. Information claimed as CBI and other

information whose disclosure is restricted by statute, which is not included in the official public docket, will not be available for public viewing in EPA's electronic public docket. EPA's policy is that copyrighted material will not be placed in EPA's electronic public docket but will be available only in printed, paper form in the official public docket. To the extent feasible, publicly available docket materials will be made available in EPA's electronic public docket. When a document is selected from the index list in EPA Dockets, the system will identify whether the document is available for viewing in EPA's electronic public docket. Although not all docket materials may be available electronically, you may still access any of the publicly available docket materials through the docket facility identified in Unit I.B.1. EPA intends to work towards providing electronic access to all of the publicly available docket materials through EPA's electronic public docket.

For public commenters, it is important to note that EPA's policy is that public comments, whether submitted electronically or in paper, will be made available for public viewing in EPA's electronic public docket as EPA receives them and without change, unless the comment contains copyrighted material, CBI, or other information whose disclosure is restricted by statute. When EPA identifies a comment containing copyrighted material, EPA will provide a reference to that material in the version of the comment that is placed in EPA's electronic public docket. The entire printed comment, including the copyrighted material, will be available in the public docket.

Public comments submitted on computer disks that are mailed or delivered to the docket will be transferred to EPA's electronic public docket. Public comments that are mailed or delivered to the docket will be scanned and placed in EPA's electronic public docket. Where practical, physical objects will be photographed, and the photograph will be placed in EPA's electronic public docket along with a brief description written by the docket staff.

C. How and To Whom Do I Submit Comments?

You may submit comments electronically, by mail, or through hand delivery/courier. (Please note, however, that to protect personal information from disclosure to the public, you should not follow the instructions in this section to submit your notification for "interested party" status. Such

notification should be submitted separately from any comments on this document using the specific instructions provided under ADDRESSES. Do not use any online electronic commenting system to submit this notification.) To ensure proper receipt by EPA, identify the appropriate docket ID number in the subject line on the first page of your comment. Please ensure that your comments are submitted within the specified comment period. Comments received after the close of the comment period will be marked "late." EPA is not required to consider these late comments. If you wish to submit CBI or information that is otherwise protected by statute, please follow the instructions in Unit I.D. Do not use EPA Dockets or e-mail to submit CBI or information protected by statute.

1. *Electronically.* If you submit an electronic comment as prescribed in this unit, EPA recommends that you include your name, mailing address, and an e-mail address or other contact information in the body of your comment. Also include this contact information on the outside of any disk or CD ROM you submit, and in any cover letter accompanying the disk or CD ROM. This ensures that you can be identified as the submitter of the comment and allows EPA to contact you in case EPA cannot read your comment due to technical difficulties or needs further information on the substance of your comment. EPA's policy is that EPA will not edit your comment, and any identifying or contact information provided in the body of a comment will be included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment.

i. *EPA Dockets.* Your use of EPA's electronic public docket to submit comments to EPA electronically is EPA's preferred method for receiving comments. Go directly to EPA Dockets at <http://www.epa.gov/edocket/>, and follow the online instructions for submitting comments. Once in the system, select "search," and then key in docket ID number OPPT-2003-0012. The system is an "anonymous access" system, which means EPA will not know your identity, e-mail address, or other contact information unless you provide it in the body of your comment.

ii. *E-mail.* Comments may be sent by e-mail to oppt.ncic@epa.gov, Attention: Docket ID Number OPPT-2003-0012. In contrast to EPA's electronic public docket, EPA's e-mail system is not an

"anonymous access" system. If you send an e-mail comment directly to the docket without going through EPA's electronic public docket, EPA's e-mail system automatically captures your e-mail address. E-mail addresses that are automatically captured by EPA's e-mail system are included as part of the comment that is placed in the official public docket, and made available in EPA's electronic public docket.

iii. *Disk or CD ROM.* You may submit comments on a disk or CD ROM that you mail to the mailing address identified in Unit I.C.2. These electronic submissions will be accepted in WordPerfect or ASCII file format. Avoid the use of special characters and any form of encryption.

2. *By mail.* Send your comments to: Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.

3. *By hand delivery or courier.* Deliver your comments to: OPPT Document Control Office (DCO) in EPA East Bldg., Rm. 6428, 1201 Constitution Ave., NW., Washington, DC. Attention: Docket ID Number OPPT-2003-0012. The DCO is open from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the DCO is (202) 564-8930.

D. How Should I Submit CBI To the Agency?

Do not submit information that you consider to be CBI electronically through EPA's electronic public docket or by e-mail. You may claim information that you submit to EPA as CBI by marking any part or all of that information as CBI (if you submit CBI on disk or CD ROM, mark the outside of the disk or CD ROM as CBI and then identify electronically within the disk or CD ROM the specific information that is CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket and EPA's electronic public docket. If you submit the copy that does not contain CBI on disk or CD ROM, mark the outside of the disk or CD ROM clearly that it does not contain CBI. Information not marked as CBI will be included in the public docket and EPA's electronic public docket without prior notice. If you have any questions about CBI or the procedures for claiming CBI,

please consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

E. What Should I Consider as I Prepare My Comments for EPA?

We invite you to provide your views on the various options we propose, new approaches we have not considered, the potential impacts of the various options (including possible unintended consequences), and any data or information that you would like the Agency to consider during the development of the final action. You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.
2. Describe any assumptions that you used.
3. Provide copies of any technical information and/or data you used that support your views.
4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.
5. Provide specific examples to illustrate your concerns.
6. Offer alternative ways to improve the notice or collection activity.
7. Make sure to submit your comments by the deadline in this notice.
8. To ensure proper receipt by EPA, be sure to identify the docket ID number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

II. What Action is the Agency Taking?

EPA has prepared a preliminary risk assessment (Ref. 1) on perfluorooctanoic acid (PFOA) (Octanoic acid, pentadecafluoro-; Chemical Abstracts Service Registry Number (CAS No.) 335-67-1) and its salts, predominantly ammonium perfluorooctanoate (APFO) (Octanoic acid, pentadecafluoro-, ammonium salt (CAS No. 3825-26-1)). This preliminary assessment indicates potential nationwide human exposure to low levels of PFOA. Based on certain animal studies, there could be a potential risk of developmental and other adverse effects associated with these exposures in humans. However, this assessment also reflects substantial uncertainty about the interpretation of the risk. EPA has identified areas where additional information could be very helpful in allowing the Agency to develop a more accurate assessment of the potential risks posed by PFOA and the other compounds addressed in this notice, and to identify what voluntary or regulatory mitigation or other actions, if any, would be appropriate. EPA is

making this preliminary assessment public in order to identify the Agency's concerns, to indicate areas where additional information or investigation would be useful, and to request the submission of data addressing these issues.

EPA is also soliciting the identification of parties who would be interested in monitoring or participating in negotiations for the development of one or more ECAs under section 4 of TSCA on PFOA and on fluorinated telomers (hereafter "telomers") which may metabolize or degrade to PFOA. The intent of the ECAs would be to develop additional information, particularly environmental fate and transport information, to enhance understanding of the sources of PFOA in the environment and the pathways by which human exposure to PFOA is occurring.

III. Background

In 1999, EPA began an investigation after receiving data on perfluorooctyl sulfonate (PFOS) indicating that PFOS was persistent, unexpectedly toxic, and bioaccumulative. These data also showed that PFOS had been found in very low concentrations in the blood of the general population and in wildlife around the world. 3M Company (3M), the sole manufacturer of PFOS in the United States and the principal manufacturer worldwide, announced in May 2000 that it was discontinuing its perfluorooctanyl chemistries, including PFOS. EPA followed the voluntary 3M phaseout with regulatory action under TSCA section 5 to limit any future manufacture or importation of PFOS before EPA has had an opportunity to review activities and risks associated with the proposed manufacture or importation (Ref. 2).

In June 2000, EPA indicated that it was expanding its investigation of PFOS to encompass other fluorochemicals, including PFOA, in order to determine whether these other fluorochemicals might present concerns similar to those found with PFOS. EPA was concerned in part because 3M had also found PFOA in human blood during the studies on PFOS (Ref. 3).

In September 2002, the Director of OPPT initiated a priority review on PFOA because the developmental toxicity data, the carcinogenicity data, and the blood monitoring data presented in an interim revised hazard assessment raised the possibility that PFOA might meet the criteria for consideration under TSCA section 4(f) (Refs. 4 and 5). When the priority review commenced, EPA anticipated completing the review within a few

months. However, as explained in this notice, there remain substantial uncertainties associated with the preliminary risk assessment. EPA believes these uncertainties may be reduced through acquisition of the information described in this notice. EPA is therefore continuing the priority review in order to acquire this information and better inform the Agency's decisionmaking.

A. PFOA Sources and Uses

PFOA and its salts are fully fluorinated organic compounds that can be produced synthetically and formed through the degradation or metabolism of certain other manmade fluorochemical products. PFOA is a synthetic chemical and is not naturally occurring. Consequently, all PFOA in the environment is attributable to human activity.

PFOA is used primarily to produce its salts, which are used as essential processing aids in the production of fluoropolymers and fluoroelastomers. Although they are made using PFOA, finished fluoropolymer and fluoroelastomer products are not expected to contain PFOA. In recent years, less than 600 metric tons per year of PFOA and its salts have been manufactured or imported in the United States (Ref. 6). The major fluoropolymers manufactured using PFOA salts are polytetrafluoroethylene (PTFE) and polyvinylidene fluoride (PVDF). PTFE has hundreds of uses in many industrial and consumer products, including soil, stain, grease, and water resistant coatings on textiles and carpet; uses in the automotive, mechanical, aerospace, chemical, electrical, medical, and building/construction industries; personal care products; and non-stick coatings on cookware. PVDF is used primarily in three major industrial sectors: Electrical/electronics, building/construction, and chemical processing.

PFOA can be commercially manufactured by two major alternative processes: The Simons Electro-Chemical Fluorination (ECF) process, and a telomerization process. Releases from manufacturing processes are one source of PFOA in the environment. Historically, most U.S. production was by 3M using the ECF process. 3M discontinued its manufacture of PFOA between 2000 and 2002, and other domestic producers are using the telomerization process exclusively.

In the ECF process, an electric current is passed through a solution of anhydrous hydrogen fluoride and an organic feedstock of octanoic acid or a derivative. The ECF process replaces the

carbon-hydrogen bonds on molecules of the organic feedstock with carbon-fluorine bonds. Perfluorination occurs when all the carbon-hydrogen bonds are replaced with carbon-fluorine ones. The ECF process yields between 30–45% straight chain (normal) perfluorooctanonyl fluoride (PFOF), along with a variable mixture of byproducts and impurities. The output of the ECF process consists of a complex combination of chemical substances with varying molecular weights, including higher and lower straight-chain homologues; branched-chain perfluoroalkyl fluorides of various chain lengths; straight-chain, branched, and cyclic perfluoroalkanes and ethers; and other byproducts. After disposal or recovery of some of the byproducts and impurities, the acid fluoride is base hydrolyzed in batch reactors to yield PFOA. The PFOA salts are synthesized by base neutralization of the acid to the salt in a separate reactor.

In the telomerization process, tetrafluoroethylene is reacted with other fluorine-bearing chemicals to yield fluorinated intermediates which are readily converted into PFOA. This process yields predominantly straight-chain acids with an even number of carbon atoms. Distillation can be used to obtain pure components. Commercial products manufactured through the telomerization process, sometimes known as telomers, are generally mixtures of perfluorinated compounds with even carbon numbers, although the process can also produce compounds with odd carbon numbers.

In addition to releases from the deliberate manufacture of PFOA through either the ECF or telomerization processes, and from the use of PFOA and its salts in the manufacture and processing of fluoropolymers and fluoroelastomers, PFOA may have entered the environment through other sources. 3M has indicated that PFOA may have been present as a trace contaminant in some of the fluorochemical products which it discontinued manufacturing between 2000 and 2002 (Ref. 7). Because these products are no longer being manufactured, they will likely not be a significant potential future source of PFOA.

EPA has also received data which indicate that the 8–2 telomer alcohol (1-Decanol, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-heptadecafluoro- (CAS No. 678–39–7)) although not itself made with PFOA, can be metabolized by living organisms or biodegrade under environmental conditions to produce PFOA (Refs. 8 and 9). Other telomer chemicals have

not been tested to determine whether they may also metabolize or degrade to form PFOA. Telomers are used widely in a range of commercial products, including some that are directly released into the environment, such as fire fighting foams, as well as soil, stain, and grease resistant coatings on carpets, textiles, paper, and leather. The extent to which these telomer-containing products might degrade to release PFOA is unknown. However, anecdotal evidence of the atmospheric presence of telomer alcohols in a multi-city North American survey suggests that telomers may be one source of environmental PFOA (Ref. 10). Additional fate information is necessary to determine whether and the extent to which telomer product degradation may be a source of PFOA.

EPA is not currently aware of any other potential sources of PFOA in the environment. EPA specifically requests comment on this issue, and the submission of any data identifying or characterizing PFOA sources. EPA is especially interested in the thermal stability and oxidative degradation products of materials containing PFOA or telomer chemicals which are incinerated.

B. Hazard and Exposure

EPA has conducted a detailed review of all available hazard and exposure information on PFOA. This review is available in the Agency's *Revised Draft Hazard Assessment on PFOA and Its Salts* (Ref. 11). This draft hazard assessment has not been formally peer reviewed, but has been reviewed internally by the EPA Office of Research and Development (ORD).

PFOA is persistent in the environment. It does not hydrolyze, photolyze, or biodegrade under environmental conditions. Based on recent human biomonitoring data provided by industry, which found PFOA in the blood of workers and the general population in all geographic regions of the United States, exposure to PFOA is potentially nationwide, although the routes of exposure for the general population are unknown.

Several epidemiological studies on the effects of PFOA in humans have been conducted on workers. An association with PFOA exposure and prostate cancer was reported in one study; however, this result was not observed in an update to the study in which the exposure categories were modified. A non-statistically significant increase in the levels of the hormone estradiol in workers with high serum PFOA levels (>30 parts per million (ppm)) was also reported, but none of

the other hormone levels analyzed indicated any adverse effects.

APFO is the most widely used salt of PFOA, and most animal toxicity studies have been conducted with APFO. An extensive array of animal toxicity studies have been conducted in rodents and monkeys. These studies have shown that APFO exposure can result in a variety of toxic effects in animals including liver toxicity, developmental toxicity, and immunotoxicity. In addition, rodent bioassays have shown that chronic APFO exposure is associated with a variety of tumor types. The mechanisms of APFO tumorigenesis are not clearly understood. At this time, EPA is evaluating the scientific evidence and has not reached any conclusions on the potential significance to humans of the rodent cancer data.

There are marked gender differences in the elimination of PFOA in rats. In addition, there are substantial differences in the half-life of PFOA in rats, monkeys, and humans. The gender and species differences are not completely understood and therefore the extent of potential risks to humans is uncertain.

C. Preliminary Risk Assessment

Because TSCA section 4(f) is focused narrowly on the specific toxicity endpoints of cancer, birth defects, and gene mutation, the preliminary risk assessment prepared as part of this priority review focused on the potential risks for developmental toxicity in humans. EPA did not include cancer risk in this preliminary assessment due to questions concerning the potential significance to humans of the rodent cancer data. Because data indicate that PFOA is not mutagenic, concern for gene mutation was not an issue for this preliminary assessment.

The preliminary risk assessment used a margin of exposure (MOE) approach (Ref. 1). For many risk assessments, the MOE is calculated as the ratio of the administered dose from the animal toxicology study to the estimated human exposure level. The human exposure is estimated from a variety of potential exposure scenarios, each of which requires a variety of assumptions.

A more accurate estimate of the MOE can be derived if measures of internal dose are available for humans and the animal model. In this preliminary risk assessment, serum levels of PFOA, which are a measure of internal dose, were available for some administered dose levels in the rat 2-generation reproductive toxicology study and from human biomonitoring studies. Thus, internal dose was used for the

calculation of MOEs in this assessment. The actual values of the MOEs derived must be viewed with caution, however, due to the differences in kinetics between humans and rodents. The range of MOEs in the preliminary assessment encompasses some values that would indicate potential concern and other values that would indicate a low level of concern. Due to the uncertainties in the assessment, and the possibility that the additional information discussed in this notice might reduce those uncertainties, the Agency has not attempted further interpretation of these MOEs at this time. The interpretation of the significance of the MOEs for ascertaining potential levels of concern will necessitate a better understanding of the appropriate dose metric in rats, and the relationship of the dose metric to the human serum levels.

As this priority review of PFOA progresses, EPA will continue to develop the characterization of hazard and potential risk associated with exposure to PFOA. Because the scientific interpretation issues in this case are particularly complex, given the unusual properties and behavior of PFOA and the absence of data on exposure pathways and levels, EPA anticipates that a more comprehensive risk analysis will be taken to the Agency's Science Advisory Board for review and comment in fall 2003. The preliminary risk assessment described in this notice has not been formally peer reviewed, but has gone through internal review by multiple EPA offices, including ORD, the Office of Science Coordination and Policy (OSCP), the Office of Pesticide Programs (OPP), and the Office of Policy, Economics, and Innovation (OPEI). The preliminary risk assessment has also been the subject of an external letter peer review.

D. Uncertainties and Data Needs

Although EPA has concerns with respect to the potential nationwide presence of PFOA in blood and with the potential for developmental and other effects suggested by animal studies, there are significant uncertainties in the Agency's quantitative assessment of the risks of PFOA. In addition, the uncertainties discussed in this unit with respect to the identification of the pathway or pathways that result in human exposure to PFOA (air, water, food, etc.), and the uncertainties associated with how PFOA gets into those pathways (including the products or processes that are responsible for the presence of PFOA in the environment) make it difficult to determine what, if any, particular risk mitigation measures would be appropriate. The Agency

believes that the additional information identified in this notice would better inform this priority review and Agency decisionmaking with respect to PFOA.

The sources of PFOA in the environment, as described in Unit II.A., are not fully defined or understood. Historically, direct PFOA releases during the manufacture of PFOA and its use in the manufacture and processing of fluoropolymers and fluoroelastomers have been quantified at some sites. Industry has identified and implemented voluntary control technologies to reduce releases, as well as to improve PFOA recovery for recycling or destruction, as described in Unit II.E. The effectiveness of these programs could be assessed, possibly through the ECA process described in Unit V., by monitoring PFOA levels at the respective facilities and determining if the release reduction and waste management programs are reducing the PFOA levels in the media surrounding the affected facilities. PFOA exposures and releases to the environment may also come from the distribution of PFOA in aqueous dispersions of fluoropolymers used by processors to apply coatings to metals and textiles, a topic which industry is also attempting to resolve.

In addition, the question of the potential contribution to PFOA levels from telomer manufacture and from telomer product degradation remains. The universe of specific telomer chemicals that may ultimately degrade or metabolize to PFOA has not been fully defined. Preliminary data suggest that only higher perfluorinated homologues (chemicals with carbon chain lengths of eight and higher) would be converted into PFOA via normal environmental pathways. The 8-2 telomer alcohol has been shown to biodegrade and metabolize to form PFOA, but other telomer chemicals, including telomer iodides and telomer-derived polymers, have not yet been tested. Determining possible telomer product sources of PFOA may be particularly difficult because these fluorochemicals are typically used in products in very low concentrations, indicating that any individual source contribution by specific products could be very small, widely distributed, and difficult to detect. For example, products contaminated with volatile, unreacted telomer alcohol residuals could potentially release those residuals into the environment where they could be subject to biodegradation.

The exposure routes leading to the presence of PFOA in human blood are not known. The nationwide presence of PFOA in human blood, contrasted with

the limited geographic locations of fluorochemical plants making or using the chemical, suggests that there must be additional sources of PFOA in the environment, and exposures beyond those attributable to direct releases from industrial facilities. But whether these exposures are due to PFOA in the air, the water, on dusts or sediments, in dietary sources, or through some combination of routes is currently unknown. Data evaluating the environmental presence of PFOA in water are very limited and site-specific. Data on the presence of PFOA in air or soil are not currently available. Data on the presence of PFOA in wildlife suggest that animals are not as likely as humans to have PFOA in their blood, and that PFOA is not found as widely in animals as PFOS. Whether these differences may be due to different exposure pathways or to differences in how the chemicals are processed or retained by animals and humans is unknown. The technical difficulties of detecting and accurately measuring the chemical in all these various media, particularly in the low concentrations that EPA would anticipate, are considerable.

The preliminary risk assessment on potential developmental toxicity was based on a comparison of serum levels in the 2-generation rat reproductive study with those found in the human population. However, there are considerable species differences in the kinetics of PFOA. Interpretation of the significance of the MOEs for ascertaining potential levels of concern will necessitate a better understanding of the appropriate dose metric in rats, and the relationship of the dose metric to the human serum levels.

Finally, there are some uncertainties regarding the use of the human biomonitoring data. Although the available data include a range of populations with various demographics in many States and all geographic areas of the country, there may be some populations that are not represented. Because it is unknown how the human exposures are occurring, proximity to a manufacturing facility may or may not be a factor in exposure. However, populations living near these facilities were not sampled. Therefore, it is possible that PFOA serum levels may be underestimated for certain portions of the U.S. population. The children's sample was derived from blood collected in 1994/1995; therefore, it may not reflect the current status of PFOA in children's blood.

Voluntary activities by industry are underway as described in Unit II.E. to help address some of these uncertainties

and data gaps. For example, pharmacokinetics studies examining the biological processing of PFOA in rats are expected to be completed in the summer and fall of 2003. These studies may help to reduce the uncertainty in the estimation of risk to humans. In addition, EPA has submitted a nomination to the Centers for Disease Control and Prevention (CDC) to include PFOS, PFOA, and certain related fluorochemicals in the next National Health and Nutrition Examination Survey (NHANES). This would provide a national baseline of PFOA exposure, both to indicate whether current data are representative of the U.S. population and to offer a gauge with which to measure the effectiveness of actions to reduce exposures.

EPA will continue to develop and clarify issues relating to hazard, exposure, and risk as the priority review continues and the Agency receives additional information that allows further resolution of the uncertainties identified in this unit.

Additional data beyond EPA's current activities and the voluntary efforts undertaken by the industry may be necessary to resolve the existing uncertainties and fill remaining data gaps, including gaps not yet identified. EPA requests comment on these issues, and particularly requests that comments include the submission of any additional data that may help to fill these gaps. Certain specific information requests are identified in Unit IV.

E. Ongoing Voluntary Activities

In 2000, EPA opened a non-regulatory public docket file, Administrative Record AR-226, for information on PFOS, PFOA, telomers, and related fluorinated chemicals, and began to express its concerns to the global fluorochemical industry (Ref. 3). In response, the industry began providing information to the Agency, all of which has been placed into AR-226. Two industry groups, the Fluoropolymer Manufacturing Group (FMG) and the Telomer Research Program (TRP), formed and began pursuing voluntary collective actions to address issues associated with PFOA and the telomers. 3M continued its ongoing research efforts despite having discontinued the manufacture of both PFOS and PFOA. Much of the information reflected in the EPA's revised draft hazard assessment and preliminary risk assessment on PFOA was provided through these voluntary activities on the part of industry.

In March 2003, EPA received letters from 3M, FMG, and TRP documenting their ongoing voluntary programs and

outlining their plans for continuing research and product stewardship activities (Refs. 7, 12, and 13). These letters have been placed in the public docket for this notice and can be accessed as described in Unit I.B.2. The letters contain substantial additional information concerning the specifics of the voluntary industry actions beyond what is presented in this notice.

In its letter, 3M indicated that it would not resume the manufacture of PFOA for commercial sale; that it would continue its medical monitoring efforts for workers and provide biannual reports to EPA and update its epidemiological study reports to EPA every 5 years; and that it will continue monitoring groundwater, surface water, and other environmental media and provide a summary report to EPA within 2 years. 3M also stated that it would work with other members of industry to conduct additional validation of PFOA analytical methods and sampling protocols and to participate in human health and environmental fate and effects studies of PFOA. 3M also indicated that the facilities and employees of its subsidiary, Dyneon LLC, would continue to be part of the 3M monitoring program.

The members of the FMG—Asahi Glass Fluoropolymers USA, Inc.; Daikin America, Inc.; E.I. duPont de Nemours & Company; and Dyneon LLC—indicated that they and their parent companies represent most of the known use of APFO for the production of fluoropolymers both in the United States and worldwide. Their letter includes commitments to reduce emissions of APFO from fluoropolymer and APFO manufacturing facilities on a global, individual company-wide basis by a minimum of 50% by 2006; to conduct studies on both finished polymers and finished products from these polymers to determine if any exposure to the general population can be related to the fluoropolymer industry; to conduct studies on emissions from fluoropolymer processing facilities to determine the level of current emissions; and to develop additional toxicological data on APFO. The companies noted that they are participating in activities through the Association of Plastics Manufacturers in Europe (APME) to conduct pharmacokinetics studies in rats and develop a pharmacokinetic model, and would share those data with EPA as they are developed, beginning in spring 2003. The companies indicated that they would continue to follow principles of product stewardship similar to those described in the

Responsible Care® programs of the American Chemistry Council and the Synthetic Organic Chemical Manufacturers Association in their efforts to support toxicological research, control occupational exposures in their own facilities, monitor employee health, assist customers in protecting their employees, and meet the general commitment to reduce emissions to the environment. The companies stated that they will continue to use appropriate criteria, including such standards as the interim air and water screening levels and water quality guidelines recently adopted in West Virginia, to evaluate operations and emissions (Refs. 14 and 15). The letter includes a schedule for the completion of various studies already underway.

The members of the TRP—AGA Chemicals (Asahi Glass); Clariant GmbH; Daikin America, Inc.; and E.I. duPont de Nemours & Company—indicated that they comprise the major telomer producers, and that they are evaluating telomer products sold in the United States to determine whether they contribute to significant human or environmental exposure to PFOA. They noted that their evaluation has six key components: Analysis of products and articles; analysis of "aged" products and "in use" articles; characterization of potential release of PFOA from telomer-based product manufacture; characterization of potential release of PFOA from telomer-treated article manufacture; analysis of possible biodegradation of telomer-based polymeric products; and evaluation of the ultimate fate and disposal routes for telomer-treated articles in the United States. The letter includes lists and schedules for these various evaluation components, as well as for the submission of additional information to the Agency.

EPA appreciates the industry response to the Agency's concerns regarding PFOA and the telomers, and looks forward to continued cooperation on assessment and management activities. EPA invites the participation of additional interested persons in these efforts. EPA considers that the timely submission of the information which industry has already committed to provide will be essential to developing a better and more complete understanding of the potential risks of PFOA. However, in light of the concerns identified to date, the Agency will continue its ongoing expeditious review.

While the voluntary industry activities as described in the letters will provide substantial additional information, EPA considers it likely that

issues will remain even after these activities are complete, and that the results of some of these programs may well identify additional questions that will need to be answered. EPA requests comment on these issues.

IV. Specific Requests for Comments, Data, and Information

EPA specifically requests comments, data, and information on the following topics.

A. Use and Production Volume Information

What are the specific chemical identities (by Ninth Collective Index name and CAS No., if available) of the telomer chemicals, including polymers derived from these telomers, and of the fluoropolymers and fluoroelastomers made with PFOA or related chemicals, currently in commerce? In what volumes and at what locations are these chemicals manufactured or imported? How and in what volumes are these chemicals used? What are the benefits of these chemicals and products in their specific uses, and what alternatives to these chemicals may be available for specific uses?

B. Exposure Information

How are products containing the chemicals identified in Unit IV.A. used? How are these products disposed of? What environmental releases occur at manufacturing and processing facilities where these chemicals are used? What data are available on worker exposures to these chemicals? What data are available on exposures to the general population? What data are available on measured levels of these chemicals in humans and the environment, in all environmental media? What data are available on the biodegradation of these chemicals, on releases of these chemicals from consumer and industrial products, and on their breakdown during product biodegradation, incineration, and other disposal practices?

C. Monitoring and Related Information

EPA specifically requests that any persons who have in their possession existing human or environmental monitoring data indicating or assessing the presence of PFOA and related fluorochemicals in humans, in wildlife, or in any environmental media, including studies conducted in other countries, provide those data to the Agency in response to the publication of this notice to enhance the understanding of PFOA presence in the environment and of the pathways leading to exposures. EPA includes in

this request any existing data not otherwise provided to EPA concerning the toxicity, pharmacokinetics, and half-life of PFOA in organisms.

D. Additional Data

Are there other pieces of information not addressed in Unit IV. A., B., and C., that would help EPA more accurately assess the risks of these chemicals and determine appropriate further action, if warranted?

V. Enforceable Consent Agreement Development

EPA is interested in developing one or more ECAs under TSCA section 4 and 40 CFR part 790 for PFOA and telomers that focus on identifying environmental fate and transport information, as well as other relevant information to enhance understanding of the sources of PFOA in the environment and the pathways by which human exposure to PFOA is occurring. The objective of the ECA process is to conclude one or more ECAs that will set in place an industry-sponsored testing program that will address a number of EPA's current data needs for PFOA and telomers. EPA expects that industry will meet the voluntary testing commitments made in their letters of intent, as discussed in Unit III.E. Therefore, EPA anticipates that the ECA process will focus generally on testing issues beyond or supplemental to those contained in the industry letters of intent.

A. Solicitation of Interested Parties

EPA is soliciting interested parties to monitor or participate in negotiations on ECAs for PFOA and telomers. As discussed in Unit III.E., 3M; AGA Chemicals; Asahi Glass Fluoropolymers USA, Inc.; Clariant GmbH; Daikin America, Inc.; Dyneon LLC; and E.I. duPont de Nemours & Company, have been pursuing voluntary collective actions to address issues associated with PFOA and telomers and have been keeping EPA informed of these activities. Any person who desires treatment as an "interested party" during the development of the ECAs must respond in writing to this notice on or before May 16, 2003 following the instructions in Unit I., and must specifically request that they be given "interested party" status. These interested parties will not incur any obligations by being so designated. Negotiations will be conducted in one or more meetings, all of which will be open to the public. EPA will contact all interested parties who have expressed a desire to participate in or monitor the ECA negotiations and advise them of all meeting dates. EPA will also notify the

public of such meeting dates in the electronic public docket for this action. The negotiation time schedule for PFOA and telomers will be established at the first negotiation meeting. It is EPA's current intent to move quickly to attempt to finalize any ECAs, if possible. If an ECA is not established in principle within a reasonable time-frame, negotiations will be terminated, and any unmet data needs may be pursued via a test rule promulgated under TSCA section 4. If the data generated from the ECA do not meet the Agency's needs, EPA reserves the right to proceed with rulemaking to obtain the needed data. EPA also reserves the right to announce and convene subsequent ECA negotiations for additional data, if the testing from voluntary activities, the initial ECA, or from a test rule identify additional data gaps which must be filled.

B. ECA Process and Public Participation in Negotiations

EPA will provide the public with an opportunity to comment on and participate in the development of any ECAs on PFOA and telomers to ensure that the views of interested parties are taken into account during the ECA process. This process is described generally in this unit, and is more fully addressed in 40 CFR part 790.

Individuals and groups who respond to this notice by May 16, 2003 and request treatment as interested parties will have the status of interested parties. All negotiating meetings for the development of this ECA will be open to the public and minutes of each meeting will be prepared by EPA and placed in the official public docket for this action. The Agency will advise interested parties and the public of meeting dates and make available meeting minutes, testing proposals, background documents, and other relevant materials exchanged at or prepared for negotiating meetings. Where tentative agreement is reached on an acceptable testing program, a draft ECA will be made available for comment by interested parties and, if necessary, EPA will hold a public meeting to discuss any comments that have been received and determine whether revisions to the ECA are appropriate. EPA will not reimburse costs incurred by non-EPA participants in this ECA negotiation process.

Enforceable consent agreements will only be concluded where an agreement can be obtained, which is satisfactory to the Agency, manufacturers or processors who are potential test sponsors, and other interested parties, concerning the need for and scope of testing. In the

absence of an ECA, EPA reserves the right to proceed with rulemaking.

More specifically, EPA will not enter into an ECA if either the Agency and affected manufacturers or processors cannot reach an agreement on the provisions of the ECA, or the draft ECA is considered inadequate by other interested parties who have submitted timely objections to the draft ECA. However, EPA may reject these objections if the Agency concludes that:

1. They are not made in good faith;
2. They are untimely;
3. They are not related to the

adequacy of the proposed testing program or other features of the ECA that may affect EPA's ability to fulfill the goals and purposes of TSCA; or

4. They are not accompanied by a specific explanation of the grounds on which the draft ECA is considered objectionable.

EPA will prepare an explanation of the basis for each ECA. That document will summarize the agreement (including the needed data development), explain the objectives of the data collection/development activity, and outline the chemicals' use and exposure characteristics. That document, which will also announce the availability of the final ECA, will be published in the **Federal Register**. Upon the successful completion of an ECA, export notification under TSCA section 12(b) would be required for all signatories to the ECA who export or intend to export the chemicals subject to the ECA. A separate action would be published in the **Federal Register** following the announcement of the ECA to apply the export notification requirement to others by adding the ECA chemicals to the list of chemicals subject to testing consent orders at 40 CFR 799.5000.

VI. References

These references have been placed in the official docket that was established under docket ID number OPPT-2003-0012 for this action as indicated in Unit I.B.2. Reference documents identified with an Administrative Record number (AR226-XXXX) are available in the public version of the official docket maintained in the OPPT Docket. Copies of these documents may be obtained as described in Unit I.B.2.

1. USEPA. Preliminary Risk Assessment of the Developmental Toxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) and its Salts. OPPT, Risk Assessment Division. Washington, DC. April 10, 2003.

2. **Federal Register**. (65 FR 62319, October 18, 2000) (FRL-6745-5); (67 FR 11008; March 11, 2002) (FRL-6823-6);

(67 FR 11014, March 11, 2002) (FRL-6823-7); (67 FR 72854, December 9, 2002) (FRL-7279-1).

3. (AR226-0639) PFOS Presentation to CMA. Auer, Charles M., USEPA. Washington, DC. June 19, 2000.

4. (AR226-1127) Revision of PFOA Hazard Assessment and Next Steps. Memorandum from Charles M. Auer to Oscar Hernandez, Mary Ellen Weber, and Ward Penberthy. USEPA. Washington, DC. September 27, 2002.

5. Section 4(f) of TSCA (15 U.S.C. 2603 (4)).

6. (AR226-0620) Sulfonated Perfluorochemicals in the Environment: Sources, Dispersion, Fate, and Effects. 3M. St. Paul, MN. March 1, 2000.

7. Environmental, Health And Safety Measures Relating to Perfluorooctanoic Acid and Its Salts (PFOA). Letter from Dr. Larry Wendling, 3M, to Stephen L. Johnson, USEPA. 3M. St. Paul, MN. March 13, 2003.

8. Characterization of Fluorinated Metabolites by a Gas Chromatographic-Helium Microwave Plasma Detector; The Biotransformation of 1H, 1H, 2H, 2H-Perfluorodecanol to Perfluorooctanoate. Hagen, Donald F.; Belisle, John; Johnson, James D.; and Venkateswarlu, P. *Analytical Biochemistry*. 118, 336-343 (1981).

9. (AR226-1149). Revision 1, Biodegradation Screen Study for Telomer-Type Alcohols. Lange, Cleston C. Pace Analytical Services, Minneapolis, MN. November 6, 2002.

10. Mabury, Scott. Annual Report of Activities for Telomer Research Program Grant to University of Toronto. University of Toronto, Toronto, Canada. September 2002.

11. (AR226-1136) Revised Draft Hazard Assessment of Perfluorooctanoic Acid and Its Salts. USEPA, OPPT, Risk Assessment Division. Washington, DC. November 4, 2002.

12. Voluntary Actions to Evaluate and Control Emissions of Ammonium Perfluorooctanoate (APFO). Letter from Charles D. Allen, Asahi Glass Fluoropolymers USA, Inc.; Takahiko Sakanoue, Daikin America, Inc.; James E. Gregory, Dyneon LLC.; and Richard J. Angiullo, E.I. duPont de Nemours & Company, to Stephen L. Johnson, USEPA. March 14, 2003.

13. Letter of Intent for the Telomer Research Program from H. Okuno, AGA Chemicals, Inc.; Hans Ludwig Panke and Reinhard Jung, Clariant GmbH; Takahiko Sakanoue, Daikin America, Inc.; and Stephen H. Korzeniowski, E.I. duPont de Nemours & Company, to Stephen L. Johnson, USEPA. March 14, 2003.

14. Order on Consent between E.I. duPont de Nemours & Company and

USEPA, Region III and Region V. Philadelphia, PA. March 12, 2002.

15. West Virginia Department of Environmental Protection. Final Ammonium Perfluorooctanoate (C8) Assessment of Toxicity Team (CATT) Report. Charleston, WV. August 2002.

List of Subjects

Environmental protection, Chemicals, Hazardous substances.

Dated: April 14, 2003.

Stephen L. Johnson,

Assistant Administrator for Prevention, Pesticides and Toxic Substances.

[FR Doc. 03-9418 Filed 4-14-03; 1:26 pm]

BILLING CODE 6560-50-S

ENVIRONMENTAL PROTECTION AGENCY

[OPP-2003-0078; FRL-7299-2]

Kansas State Plan for Certification of Applicators of Restricted Use Pesticides; Notice of Availability

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of intent.

SUMMARY: The State of Kansas has submitted to EPA programmatic amendments to its State Plan for Certification and Training of Applicators of Restricted Use Pesticides. The proposed amendment establishes new requirements for the recertification of pesticide applicators. Notice is hereby given of the intention of the Regional Administrator, Region VII, to approve the revised Plan for the Certification of Applicators of Restricted Use Pesticides. EPA is soliciting comments on the proposed amendments.

DATES: Comments, identified by docket ID number OPP-2003-0078, must be received on or before May 16, 2003.

ADDRESSES: Comments may be submitted electronically, by mail, or through hand delivery/courier. Follow the detailed instructions as provided in Unit I. of the **SUPPLEMENTARY INFORMATION**.

FOR FURTHER INFORMATION CONTACT: John T. Tice, Water, Wetlands and Pesticides Division, WWPD-PEST, 100 Centennial Mall N., Room 289, Lincoln, NE 68508; telephone number: (402) 437-5080; e-mail address: Tice.john@epa.gov.

SUPPLEMENTARY INFORMATION:

ATTACHMENT 2

FAST TRACK ARTICLE

Community Exposure to Perfluorooctanoate: Relationships Between Serum Concentrations and Exposure Sources

Edward Anthony Emmett, MD, MS

Frances Susan Shofer, PhD

Hong Zhang, MD, MPH

David Freeman, MS

Chintan Desai, BSc

Leslie Michael Shaw, PhD

Objective: The objective of this study was to determine serum (perfluorooctanoate [PFOA]) in residents near a fluoropolymer production facility: the contributions from air, water, and occupational exposures, personal and dietary habits, and relationships to age and gender. **Methods:** The authors conducted questionnaire and serum PFOA measurements in a stratified random sample and volunteers residing in locations with the same residential water supply but with higher and lower potential air PFOA exposure. **Results:** Serum (PFOA) greatly exceeded general population medians. Occupational exposure from production processes using PFOA and residential water had additive effects; no other occupations contributed. Serum (PFOA) depended on the source of residential drinking water, and not potential air exposure. For public water users, the best-fit model included age, tap water drinks per day, servings of home-grown fruit and vegetables, and carbon filter use. **Conclusions:** Residential water source was the primary determinant of serum (PFOA). (*J Occup Environ Med.* 2006;48:759-770)

Fluoropolymers are used in a variety of industrial and consumer products, including non-stick cookware, water-proof, breathable textiles, consumer house wares, electronics, aerospace, and other applications. Perfluorooctanoate (PFOA, CF_3 , $[\text{CF}_2]_6 \text{COO}^-$, CAS No. 3825-26-1) also occurs as a contaminant in other fluorochemicals and telomer products. Telomers are highly fluorinated compounds used in protective coatings for carpets, paper, construction materials, and apparel, and in insecticide formulations and high performance surfactant products.

PFOA has commercial use primarily as ammonium perfluorooctanoate, an essential surface-active agent in the production of various fluoropolymers, including tetrafluoroethylene. PFOA is a contaminant in other fluorochemicals and telomer products.¹ According to manufacturers, it is typically not present in finished consumer articles. Ammonium perfluorooctanoate is fully dissociated into the anion form, perfluorooctanoate, in environmental media and biologic fluids.

Organofluorine compounds behave very differently to the more widely studied organochlorines and organobromines and have unusual partitioning properties.² Perfluorofatty and perfluorosulfonic acids, particularly PFOA and perfluorooctane sulfonate (PFOS), are now found ubiquitously in marine animals inhabiting widely spread geographic biospheres³ and in human serum from widely disparate groups.⁴⁻⁷ PFOA and PFOS persist in the environment and resist biologic, environmental, and pho-

From the University of Pennsylvania (Dr Emmett, Dr Shofer, Mr Desai, Dr Shaw), School of Medicine, Philadelphia, Pennsylvania; Grand Central Family Medicine (Dr Zhang), Parkersburg, West Virginia; and the Decatur Community Association (Mr Freeman), Cutler, Ohio.

This study was supported by grant ES12591 from the Environmental Justice Program of the U.S. National Institute for Environmental Health Sciences (NIEHS), National Institutes of Health, and by P30 Core Center grant ES 013508 from the NIEHS.

Address correspondence to: Edward A. Emmett, MD, Occupational Medicine, Silverstein Pavilion, Ground Floor, 3400 Spruce St., Philadelphia, PA 19104-4284; E-mail: emmetted@mail.med.upenn.edu.

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tochemical degradation (3M, 2001). They have no known natural sources.⁸

In the general U.S. population, median serum PFOA values are around 4 to 5 ng/mL; occasional values are above 20 ng/mL^{4,5,9} with no significant gender differences. Analyses of blood samples from residents near Washington County, Maryland, found a twofold increase in serum PFOA levels between 1974 and 1989.⁶ Kannan et al⁷ have reported differences in blood serum PFOA levels among populations from different countries.

PFOA toxicology has recently been reviewed.¹ PFOA is well absorbed by rats after both oral and inhalation exposure. Fecal excretion in male rats is increased by feeding cholestyramine resin, suggesting enterohepatic circulation.¹⁰ Dermal penetration is significant in rats but is low to negligible in humans.¹¹ In rats, PFOA is a peroxisome proliferator activated receptor (PPAR) agonist causing liver toxicity^{12,13} with hepatomegaly and hepatic necrosis, and biochemical effects characteristic of PPAR agonists.¹⁴ PFOA promotes liver carcinogenesis in rats,¹⁵ and causes Leydig-cell testicular tumors and acinar cell pancreatic tumors^{16,17} through nongenotoxic mechanisms^{18,19} with questionable human relevance. The human half-life of PFOA was between 4 and 5 years for retirees with previous heavy occupational exposure,²⁰ much longer than in laboratory animals.

Control of human exposure to PFOA has been limited by the lack of information on sources and pathways. As the U.S. Environmental Protection Agency (EPA) states, "At present, there aren't any steps that EPA recommends that consumers take to reduce exposure to PFOA because the sources of PFOA in the environment and the pathways by which people are exposed are unknown. The limited geographic locations of fluorochemical plants making or using the chemical suggest that there may be additional sources of PFOA in the environment

and exposures beyond those attributable to direct releases from industrial facilities. But whether human exposures are due to PFOA in the air, the water, on dusts or sediments in dietary sources or through some combination of routes is currently unknown."²¹

PFOA has been used in the manufacturing of fluoropolymers at a facility in Washington, West Virginia, since 1951. Potential airborne PFOA exposure was modeled using information on releases from the plant, meteorologic conditions, and topography. The wind rose map, which shows the frequency and strength of winds from different directions, for the plant indicates the primary wind direction, toward the north/northeast, would carry airborne emissions into neighboring Ohio. PFOA was also released to the Ohio River, adjacent to the plant, as well as disposed in landfills and surface impoundments in the vicinity. According to the facility, total PFOA emissions from the facility have been reduced from 87,000 lbs (31,000 air, 56,000 water) and 80,000 lbs (31,000 air, 49,000 water) in 1999 and 2000, respectively, to 11,000 lbs (6000 air, 5000 water) and 1700 lbs (200 air, 1500 water) in 2003 and 2004, respectively.

PFOA has been detected in public and private drinking water supplies near the facility. The highest levels reported in public water supplies in the United States to date have been in the Little Hocking water system, in operation since 1968, which draws water from wells across the Ohio river from the facility. The average PFOA in Little Hocking system distribution water for 2002–2005 has been 3.55 ng/mL (range, 1.5–7.2 ng/mL).

The objectives of the present study were to measure serum PFOA levels in a stratified random sample of the population served by the Little Hocking water service to determine: how the serum PFOA levels compared with levels measured in other populations; the relative contributions of air and water exposure to serum PFOA levels; and to determine the effects, if any, of demographic variables, occupational

exposures, personal habits, use of water filters, and dietary factors such as the ingestion of locally harvested game and fish and of homegrown vegetables.

Materials and Methods

Eligibility Criteria

Eligibility criteria for participation in the study were:

- Residence in the area serviced by the Little Hocking Water Association for at least the past 2 years as of July 2004;
- Ages 2 or older (changed to ages 4 or older after the study began to minimize participant discomfort); and
- Not known to have a bleeding disorder (to diminish any risk from phlebotomy).

Selection of Households for Sampling Frame

Two populations of residents were identified for participation in the stratified random sampling. One population represented those whose residence was potentially exposed to PFOA in both air and water, and the other whose residence was potentially exposed to PFOA in water but had very minimal potential for exposure in air. The sampling randomly selected households from each of these strata.

To identify areas where there was higher exposure to PFOA in the air, we used an air dispersion model that estimated the air concentration for PFOA emanating from the PFOA source plant. Inputs into the air dispersion model included the amounts of air emissions for the plant, wind velocities, and topographic contours. The air concentrations had been modeled for years 2002 and 2003 on an annual basis; the model produced very similar results for each of these years. To identify areas in the Little Hocking water service distribution area, a map of the water distribution system was obtained for the Little Hocking water service. The potential air and water exposure group comprised all those who had resided for

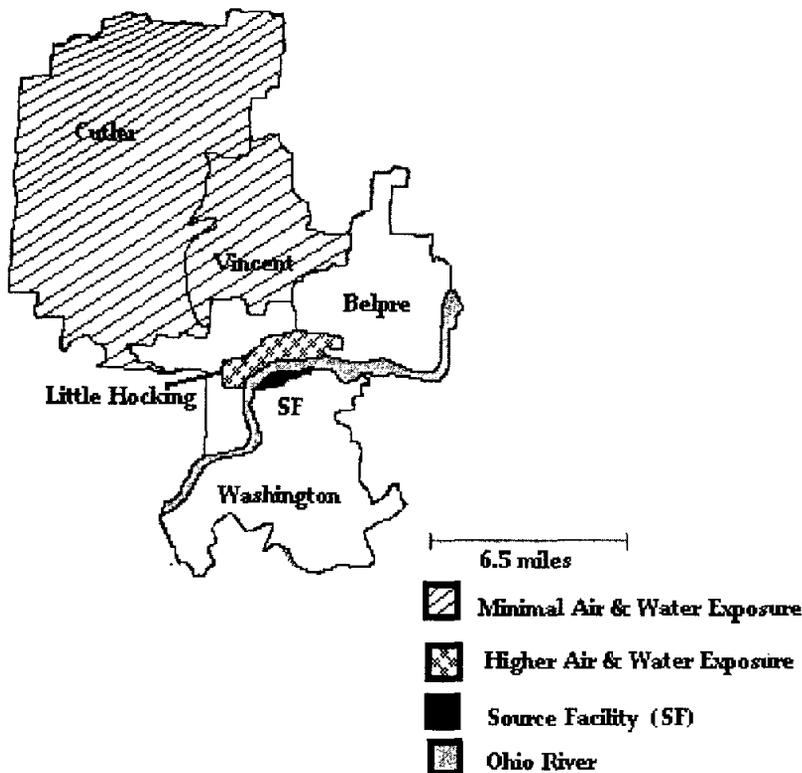


Fig. 1. Map showing the locations of the studied communities and the source facility. Subjects for the minimal air exposure group were selected from the area shown in yellow; subjects for the higher air exposure group from the area are shown in red. Residents in both of these areas obtained their water from the same public residential water supply. The location of the source facility is shown in black. The residents lived in Ohio; the source facility is located in West Virginia. The state boundary, the Ohio River, is shown in blue.

at least 2 years in the water distribution system area of the Little Hocking water service and also within the contour line representing $0.2 \mu\text{g}/\text{m}^3$ PFOA in the air as a yearly average for 2002. These households were all located in portions of zip codes 45714 (Belpre) and 45742 (Little Hocking).

The potential water exposure group comprised residents who had resided for at least 2 years in the water distribution system area of the Little Hocking water service but in an area where air exposure to PFOA from the facility was negligible. The selected study area was zip codes 45724 (Cutler) and 45784 (Vincent). These areas were all at least several miles outside the lowest air concentration contours derived from the air dispersion model. Figure 1 shows the location of the residence areas for both the potential air and water ex-

posure and the potential water-only exposure zones.

To identify households and residents in the zip codes of interest, demographic and other information were purchased from *www.infousa*, a proprietary database of detailed information on U.S. consumer households compiled from thousands of public sources. The items used to select invitees were names of head of household, street address, city, state, zip code, and length of residence.

Selection of Stratified Random Sample. For the area identified as having both air and water exposure, 95 households in the *www.infousa* database met the requirements; all were invited to take part in the study. These included households with measured PFOA levels in potable well water measured by the Ohio Department of Environmental Protection and households using Little Hocking Water As-

sociation water. For the area identified as having only water exposure to PFOA, a stratified random sampling of households was performed, resulting in the selection of 342 households. All members of selected households who met the study eligibility criteria were invited to participate.

Invitations to Participate. Invitation letters were sent from the University of Pennsylvania to each selected household. If no response was received, a second mailing was sent. If there was still no response after approximately 10 days, a telephone call was made to the household by staff of the Decatur Community Association. No participant chose an option for anonymous participation. On the weekend before the mailing of the invitation letter, a flyer was placed in the area weekend newspaper to announce that invitation letters were forthcoming. The principal local newspaper, the *Marietta Times*, independently wrote an editorial encouraging those selected to consider participation.

Community Volunteer Group. Because of great community interest, a lottery was conducted to select an additional sample of invitees from households that volunteered to participate in the study in response to a newsletter notice. Those households that met study criteria, including residing in one of the areas used for stratified random sampling, were included in the lottery.

Administration of Questionnaires

Administration of questionnaires and collection of blood samples were performed between July 2004 and February 2005 in nearby Parkersburg, West Virginia. The questionnaires were developed and revised after review by the members of the Community Advisory Committee and an expert panel from the U.S. EPA. The Community Advisory Committee, convened by the Decatur Community Association, comprised representatives of the townships in the Little Hocking Water Association Service District, representatives from the Ohio and U.S. EPA, the Warren School District, and

the County Health Commissioner. Before finalization, the questionnaires were pilot tested on a representative group of 20 individuals from similar southeastern Ohio or western West Virginia communities, who did not live in the Little Hocking Water Association District.

Trained interviewers administered all questionnaires. Only one person from each household supplied household information. The household questionnaire elicited information to ensure that participants met the eligibility criteria, demographic information on eligible participants, household contact information, sources of residential drinking water (private well, water district, cisterns, bottled water, hauled water, and so on), use of a home water filter, and water source and estimated use for cooking, canning, and reconstituting canned soups and frozen juices.

All adults 18 years and older were administered the adult questionnaire that elicited demographic information, diet (including consumption of vegetables or fruit grown in your garden, meat or game grown locally, and fish caught locally), health conditions (liver, thyroid, bleeding disorders), current medications, current occupational or school if a full-time student, employment (including at a facility using PFOA, visiting or processing waste from that facility, work as a firefighter, in carpet cleaning or retreating carpets or rugs, or in professional carpet installation), and smoking and alcohol habits.

All children were administered a questionnaire that was similar to the adult questionnaire except that the questions about occupation and about smoking and alcohol habits were omitted.

Collection and Assay of PFOA Acid in Serum

Specimen Collection. Twenty milliliters of blood were drawn into red-topped Vacutainer tube for PFOA analysis, immediately centrifuged, and the resulting serum was transferred to polypropylene aliquot tubes, labeled, and shipped on dry ice to the analysis

laboratory (Exygen Research) where it was stored at -80°C pending analysis.

Standards and Chemicals. The standard for perfluorooctanoic acid (99.2%) was obtained from Oakwood Products, Inc. (West Columbia, SC) and characterized by DuPont (Newark, DE). Analysis by ^{19}F NMR confirmed that the PFOA standard contained 98.7% straight chain PFOA and 0.53% branched PFOA isomers. The internal standard, [1,2- ^{13}C]-PFOA ($\text{C}_6\text{F}_{13}\text{CF}_2^{13}\text{CO}_2\text{H}$, ^{13}C -PFOA) (96.4%) was provided by DuPont.

Chemicals and reagents used in the sample preparation procedure or in the mobile phase were of reagent grade and were obtained from VWR Scientific (Bridgeport, NJ) and Sigma-Aldrich (St. Louis, MO). Solvents used for the mobile phase (acetonitrile, water) were of HPLC grade and were obtained from EM Science (Gibbstown, NJ). The control human serum was purchased from Lampire Biological Laboratories, Inc. (Pipersville, PA) and stored frozen at -20°C . This fluid was used for the preparation of laboratory quality control samples with spiked-in PFOA.

Chromatographic and Mass Spectrometric Conditions. PFOA was analyzed through HPLC/tandem mass spectrometry by a slight modification of the method of Flaherty et al.²²

Standards, Sample Preparation, and Calibration. Controls and study subject samples were added to 300 μL of acetonitrile. The samples were thoroughly mixed by vortexing, centrifuged, and 5 μL of the cell- and protein-free supernatant used for analysis by the HPLC tandem mass spectrometer system. A seven-point calibration curve was analyzed throughout the analytical sequence for the fluorocompounds. The calibrators included normal human serum spiked with 0.5, 1, 5, 10, 20, 50, and 100 ng/mL of PFOA. The instrument response versus the calibrator concentration was plotted for each point. Linear regression with $1/\times$ weighting was used to determine the slope, y-intercept, and coefficient of determination (r^2). Calibration curves were deemed acceptable

if $r^2 \geq 0.985$. This is the external standardization method used for the determination of PFOA in the set of 408 samples described in this study. For samples with PFOA concentrations >100 ng/mL, the sample was diluted in 50:50 methanol/water and rerun. In addition, the analysis of PFOA was done using ^{13}C -perfluorooctanoic acid as an internal standard for a randomly selected set of 35 of the samples to certify that the external standardization method used provided equivalent PFOA concentration values. For these analyses, the internal standard was mixed in acetonitrile at a concentration of 1 ng/mL. As described previously for the externally standardized assay for sample preparation: to 100 μL of standards, controls and study subject samples was added to 300 mL of acetonitrile containing the internal standard and the cell- and protein-free supernatants prepared as described previously. On comparison of the externally standardized with the internally standardized sets of results on the 35 selected samples, linear regression analysis showed excellent agreement between the two calibration procedures: $Y(\text{IS}) = 1.073 \pm 0.0229 * X(\text{ext std}) - 0.385 \pm 0.468$; $r^2 = 0.985$; $S_{y-x} = 1.54$.

Matrix Spike Samples and Duplicate Sample Assays. One matrix spike for every 20 samples was prepared by adding a known concentration of the PFOA to the study subject serum sample for the purpose of assessment of the method's accuracy throughout the set of study subject serum samples. The mean PFOA recovery for these spiked samples was 95% with a standard deviation (SD) of 16.2%. In addition, one sample of every 10 was extracted and analyzed in duplicate to provide an assessment of the method's precision throughout the set of samples. The average between assay %CV for PFOA duplicates was 5.7%. The lower limit of quantification of this method is 0.5 ng/mL. Validation of this LLOQ was conducted with replicate spiked samples of human serum with PFOA spiked into the samples at

0.5 ng/mL, the concentration of the lowest calibrator for this assay. The mean recovery \pm SD was $101 \pm 2.7\%$.

Serum (PFOA) Philadelphia Volunteer Group. To help ensure that published general population serum PFOA levels were suitable for comparison purposes under the circumstances of the study, we identified a comparison group of 30 volunteers from the Philadelphia area. The Philadelphia volunteers, staff, and students at the Hospital of the University of Pennsylvania were paid \$20 each to participate. Their mean age was 34.3 years (range, 20–56 years); there were nine men and 21 women. None identified previous or current occupational exposure to PFOA. Blood from these individuals was drawn, handled spun, stored, shipped, and analyzed for PFOA in an identical manner to the blood obtained during the study. The mean serum PFOA levels for the Philadelphia comparison group was 6 ng/mL (interquartile range, 5–10 ng/mL), consistent with published values for the U.S. population.^{4–6}

PFOA Water Sampling and Comparison to Serum Levels

The concentration of PFOA in finished water in the Little Hocking water system has been measured approximately quarterly from January 22, 2002, to March 18, 2005, by the Ohio EPA. Fourteen measurements were available for this period; results before November 29, 2004, had been reported as ammonium perfluorooctanate (APFO) and as PFOA from that date. PFOA concentration in private residential well water was publicly available for nine individuals for whom private well water was their only reported source of residential drinking water. In one instance, six samples had been taken at regular intervals from 2002 through 2005. For this well, the values obtained were averaged to obtain a mean level over the period. For the remaining wells, only one sample had been analyzed from a single point in time. The aver-

age PFOA concentration in Little Hocking system distribution water from January 2002 until May 2005 was 3.55 ng/mL (range, 1.5–7.2 ng/mL). For private wells used by study participants, PFOA concentrations ranged from not detectable (<0.010 ng/mL) to 14.0 ng/mL.

Statistical Analysis

To determine if serum PFOA levels differed by dietary or personal habits, water source, water use, occupational exposure, and so on, preliminary data analyses included the *t* test for binary predictors or the analysis of variance for greater than two exposure categories. Adjustment for multiple comparisons were made using Tukey-Kramer. To check the assumptions of the statistical approach used, various analyses were rerun with the exact test using Monte Carlo. Results were similar to that of the F test. Subsequent higher-order analyses included analysis of covariance adjusting for age. Final multivariate analysis to assess the independent contribution of multiple variables was a generalized estimating equation (GEE) to adjust for household cluster. Only variables associated with serum PFOA levels on univariate analysis with a probability <0.10 were included. To determine model of best fit, both forced entry and backward elimination were used. All analyses were performed using SAS statistical software (version 9.1; SAS Institute, Cary, NC). A *P* < 0.05 was considered statistically significant. Serum PFOA levels serum (PFOA) are presented as mean, median, and interquartile range (IQR).

To examine the effect of demographic variables (age, gender, duration lived at current residence), we excluded the 18 participants who reported substantial occupational exposure (defined subsequently) to PFOA. To examine the effects of number of glasses of drinking water per day, use of a residential water filter, and of dietary exposures, we included only those residents whose sole source of residential drinking water was Little

Hocking water system water. Only individuals who designated a single source of residential drinking water and who did not have substantial occupational exposure to PFOA were included in these analyses.

Human Subjects Approval

The study was approved by the Institutional Review Board of the University of Pennsylvania. The study was voluntary and informed consent was obtained for all participants before any study. Minors under the ages of 17 were encouraged to give informed assent whenever feasible. A certificate of confidentiality was obtained from the National Institutes of Health to ensure maximum protection of personal information and results.

A partnership among the University of Pennsylvania School of Medicine, The Decatur Community Association, a local community association in the Little Hocking water service area, and Grand Central Family Medicine in Parkersburg, West Virginia, a local healthcare provider, conducted the study through a grant from the Environmental Justice Program of NIEHS. The community was involved at all stages of the study. A local healthcare provider informed each participant of his or her personal PFOA results together with any necessary explanation.

Results

Response and Participation Rate

Stratified Random Sample. Three hundred forty-three individuals from 169 households participated in the phlebotomy and questionnaire administration. One subject withdrew from the study, six subjects could not donate sufficient blood, one subject did not complete the questionnaire, and 11 subjects did not meet eligibility criteria because their household water service was received from a water system other than the Little Hocking Water Association. Accordingly, data were available for analysis from 324 subjects from 161 households selected through the stratified random selection process.

TABLE 1
Household Participation Rates for Randomly Selected Households
by Community

	Households Invited to Participate	No. Agreeing to Participate	No. Completing Data Acquisition	Participation Rate
Little Hocking	78	45	38	48.7
Belpre	17	8	7	41.2
Cutler	101	45	30	29.7
Vincent	241	115	86	35.7
Total	437	213	161	36.8

The participation rate by location of household mailing address is given in Table 1.

Response and Participation—Community Volunteer Group. One hundred percent of the 37 households selected by lottery participated in the phlebotomy. However, two individuals from two households did not complete the questionnaire and were excluded from further analysis. Thus, data from 54 individuals from 35 households were included in the final analysis. The racial and ethnic composition of both participants and volunteers was predominantly white non-Hispanic (97% [$N = 367$]), reflecting the composition of Washington County, Ohio.

Role of Occupational Exposure

We established criteria for substantial occupational exposure to PFOA of at least 1 year's work in a production area within a facility in which PFOA was used in the production process with the last such occupational exposure within the previous 10 years. Seventeen individuals from the stratified random sample and one from the local volunteer sample met this definition for substantial occupational exposure. All had received their occupational exposure to PFOA in the same fluoropolymer manufacturing facility located in Washington, West Virginia, across the Ohio River from the study area. An additional 48 individuals reported past or current potential occupational exposure to PFOA as follows (individuals can be represented more than once): 18 individuals had worked in a fluoropolymer manufacturing fa-

cility in a nonproduction area at the fluoropolymer production facility in a production area for less than 1 year total and/or more than 10 years ago or in a job for another employer that required visits to the fluoropolymer production facility so did not meet the criteria for substantial occupational exposure; eight individuals had worked in a job involving waste disposal or waste processing from the fluoropolymer manufacturing facility; 29 individuals had worked as firefighters (volunteer, military, as a company employee or paid); and 13 individuals had worked in carpet cleaning, retreating carpets or rugs, or in professional carpet installation. Compared with the no-exposure group, none of these occupational exposure groups had statistically significant elevated serum PFOA levels ($P > 0.05$) (Table 2). Among those with potential occupational exposure, the highest median values were observed for firefighters. However, these values remained well below the concentrations of the substantial occupational exposure group. Because none of these groups had significantly elevated serum PFOA levels, they were aggregated into one group (potential exposure) for statistical analysis purposes.

When comparing substantial, potential, and no occupational exposure groups, the substantial occupational exposure group had a significantly higher median serum PFOA levels of 775 ng/mL than the potential exposure (388 ng/mL) and no occupational exposure groups (329 ng/mL) ($P = 0.0002$ and $P < 0.0001$, respectively, Table 2).

As a result of this finding, the substantial occupational exposure group was removed from further analysis of PFOA exposure in the community. Because the serum PFOA levels for the potential exposure group were not different from the rest of the community, they were included in subsequent analyses of community exposures and treated for purposes of analysis as residents without substantial occupational exposure.

Role of Community Air Exposure: Serum (PFOA) by Community of Residence

The median serum PFOA level in the combined two areas with highest potential air exposure (Little Hocking and Belpre) was 326 ng/mL compared with 368 ng/mL in the two combined areas with a potentially minimal contribution from PFOA through air pollution (Cutler and Vincent) (Table 3). This difference was not statistically significant ($P = 0.32$).

Additionally, the inclusion of local volunteers made no appreciable difference to the results (Table 3). Because of the similarity of serum PFOA levels in each community regardless of air pollution or the inclusion of volunteers, all communities and samples were combined in the subsequent analyses to examine the effects of water exposure on PFOA.

Role of Exposure in Water: Serum PFOA and Primary Source of Residential Drinking Water

With regard to water exposure, the highest median serum PFOA level (374 ng/mL) was found for the group who used only Little Hocking system water as their residential drinking water source (Table 4). The lowest was found in those who currently used only bottled and/or cistern and/or spring water as the source of their residential drinking water. The serum PFOA levels in those who used bottled, spring, or cistern water was significantly lower than those in both the Little Hocking water system only and the

TABLE 2
Serum (PFOA; ng/mL) by Occupational Exposure Group

Occupational Exposure	N	Median	Mean	Interquartile Range
No occupational exposure	312	329	423	175-537
Potential occupational exposures*	48	388	406	168-623
Firefighter: voluntary, military, company employee, or paid	29	447	453	236-709
Nonproduction area of fluoropolymer facility, in production area not meeting criteria for substantial occupational exposure, or requiring visits to facility	18	381	386	125-430
Carpet cleaning, retreating carpets or rugs, or in professional carpet installation	13	302	408	191-631
Facility processing or disposing fluoropolymer production waste	8	253	578	115-918
Substantial occupational exposure (production area within a facility in which PFOA was used in the production process >1 yr and last exposure having occurred within previous 10 yrs)	18	775	824	422-999

*Some individuals had more than one potential occupational exposure, therefore, N for the potential occupational exposure subgroups does not total to 48.
PFOA indicates perfluorooctanoate.

TABLE 3
Serum (perfluorooctanoate; ng/mL) by Community Area for Randomly Selected Participants and for All Participants*

	Randomly Selected Participants				All Participants (local volunteers and randomly selected)			
	N	Mean	Median	IQR	N	Mean	Median	IQR
Community areas with higher expected contribution from air								
Belpre	14	321	298	83-533	30	307	244	103-445
Little Hocking	74	478	327	187-572	92	458	311	175-567
Total	88	453	326	176-568	122	421	298	155-556
Community areas with minimal expected contribution from air								
Cutler	59	361	316	169-477	70	380	314	185-477
Vincent	160	439	370	190-570	168	438	370	188-577
Total	219	418	368	182-555	238	421	361	186-555

*Eighteen subjects with substantial occupational exposure were excluded from analysis.
IQR indicates interquartile range.

TABLE 4
Serum (PFOA; ng/mL) by Primary Residential Source of Drinking Water, All Participants (randomly selected and local volunteers)*†

Drinking Water Source	N	Median	Mean	Interquartile Range	Range
Little Hocking system water only	291	374	448	221-576	7-1950
Little Hocking system plus bottled or spring	26	320	358	206-370	72-1280
Bottled and/or cistern and/or spring only‡	10	71	154	49-217	12-527
Well water and well and other	26	79	296	28-155	8-4520

*Subjects with substantial occupational exposure to PFOA were excluded from these analyses.

†Seven subjects did not indicate residential source of drinking water.

‡Significantly different from Little Hocking water only ($P = 0.003$) and Little Hocking system plus bottled or spring water ($P = 0.05$).

PFOA indicates perfluorooctanoate.

mixed Little Hocking plus another water source groups ($P = 0.0004$ and $P = 0.007$, respectively). The serum PFOA levels for those who used Little Hocking water system water only and the mixed Little Hocking and another water source were not statistically significantly different ($P = 0.17$).

The mean serum PFOA levels in those who used any well water as their sole residential drinking water source was variable; this group included some of the lowest and some of the highest PFOA serum concentrations.

Relationship Between PFOA in Primary Residential Water Supply and Serum PFOA in Residents. Fig-

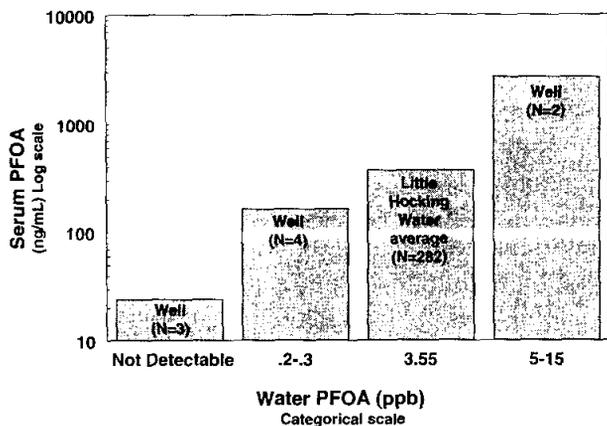


Fig. 2. Relationship of perfluorooctanoate (PFOA) concentration in water source (Little Hocking and private wells) to serum PFOA levels. The numbers in parentheses indicate the number of samples. Although the number of observations from persons using only residential well water source is small, there is a marked and statistically significant relationship between the PFOA levels in serum and the PFOA concentration in the residential drinking water source. Only subjects 6 years of age or older using a single residential drinking water source were included in the analysis.

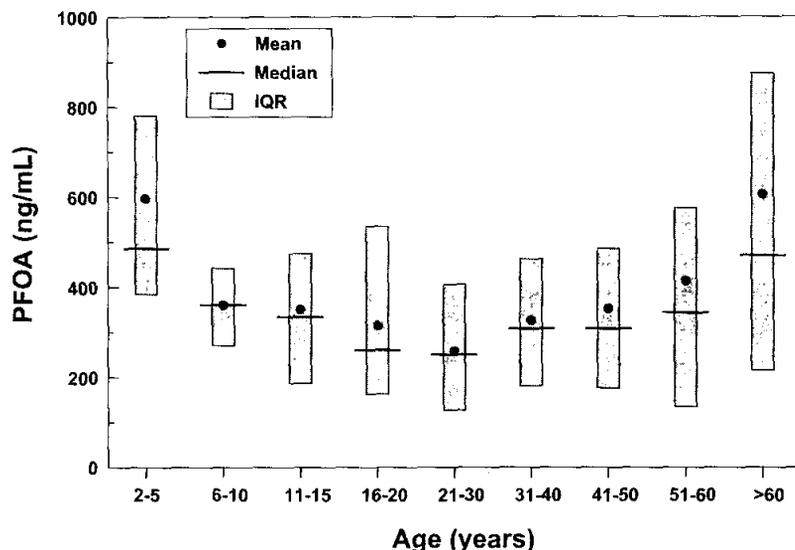


Fig. 3. Distribution of serum perfluorooctanoate (PFOA) levels (in ng/mL) by age. Residents >60 years had significantly higher serum PFOA levels compared with all other age groups except children aged 2-5 years.

ure 2 presents a graphic relationship between PFOA concentrations in drinking water and serum PFOA levels. Three individuals drank from wells where the PFOA was not detectable; their average serum PFOA level was 20.8 ng/mL (range, 13.6-31.4 ng/mL). Six individuals used a private well with measurable PFOA in water as their only source of residential drinking water. Although the numbers of individuals for whom the PFOA concentration in well water is

known is small, there is an apparent strong relationship between the level of the serum PFOA levels and the PFOA concentration of the drinking water source.

The median serum/drinking PFOA water ratio residents using only the Little Hocking water system was 105 (371/3.55) with an interquartile range between 62 (221/3.55) and 162 (576/3.55). For the six individuals who used a private well with measured PFOA as their only source of resi-

dential drinking water, the serum/drinking water PFOA ratios ranged from 142 to 855.

Serum PFOA Levels and Gender, Age, Years of Residence, Smoking, and Alcohol

Serum PFOA level was not significantly different by gender for participants without substantial occupational exposure ($P = 0.32$). The median PFOA for females was 320 ng/mL (IQR, 161-509), and for males, it was 345 (IQR, 190-576).

Serum PFOA concentrations were highest in those aged more than 60, followed by those aged from 2-5 and those aged 51-60 (Fig. 3). Participants >60 years were significantly more likely to have higher serum PFOA levels compared with participants in all other age groups except children 2 to 5 years old ($0.0006 < P < 0.02$).

With regard to residence, only participants over 18 years were examined. Years lived at current residence was grouped into 2-5 years, 6-10 years, 11-15 years, and >15 years. Age was also found to be correlated with years of residence ($r = 0.6$). Therefore, age was controlled for in the analysis for which no statistically significant association between years lived at current residence and serum PFOA levels was found ($P = 0.7$).

The influence of alcohol consumption (consumption of beer wine or liquor in the last 30 days) and smoking (current cigarette smoker) were evaluated in all adult participants ages 18 and over who did not have substantial occupational exposure. No significant association was found between serum PFOA levels and smoking ($P = 0.28$) or serum PFOA levels and alcohol consumption ($P = 0.46$).

Little Hocking Water System Users: Water Use Variables Affecting Serum PFOA Concentrations

The effect of drinking tap water, eating local fruits and vegetables, meat

TABLE 5

Serum (perfluorooctanoate; ng/mL), Number of Tap Water Drinks per Day, Consumption of Local Meat and Game, Fish, Vegetables, and Fruits, and Use of Carbon Water Filter*

Factor	N	Mean†	Median	Interquartile Range	pr > t
Tap water drinks/d					
0	20	374	301	233-423	<0.0001
1-2	40	324	265	176-438	
3-4	66	413	370	206-550	
5-8	90	450	373	242-373	
>8	55	565	486	294-486	
Local meat					
0	157	389	329	179-498	0.018
1-20	49	488	451	246-690	
>20	77	516	424	295-595	
Local fish					
No	273	448	374	221-571	0.8958
Yes	18	458	398	290-681	
Fruit and vegetables from your garden					
0	133	356	295	174-485	<0.0001
1-20	75	458	420	264-661	
>20	77	571	469	308-802	
Carbon water filter‡					
Yes	64	360	318	170-482	0.0005
No	209	493	421	258-631	

*Little Hocking water source only.

†Means adjusted for age unless otherwise indicated.

‡Not adjusted for age.

pr indicates probability.

t indicates t-value.

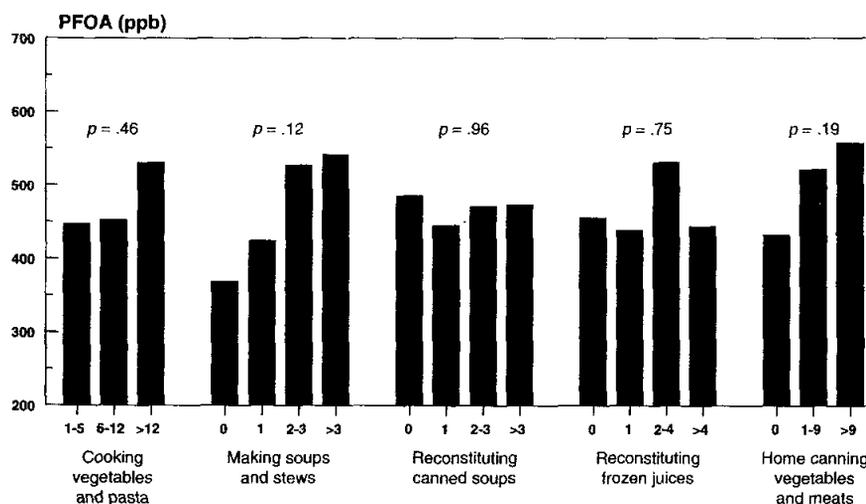


Fig. 4. Distribution of serum perfluorooctanoate (PFOA) levels (in ng/mL) within household* for cooking tap water use† (amounts are servings per week). *PFOA levels represents average household value. †Households using Little Hocking water system only.

or fish, or having a carbon water filter on serum PFOA concentrations in Little Hocking Water System Users is shown in Table 5. With increasing tap water drinks per day (at home or at work), PFOA levels increased ($P =$

0.004). Particularly, participants who drank eight or more cups of tap water per day (at home or at work) had significantly higher serum PFOA levels compared with other drinking categories ($0.002 < P < 0.004$).

A secondary analysis has been performed examining air exposure and local vegetable/fruit intake. There was no effect of air exposure on PFOA ($P = 0.16$) or the interaction between air exposure and local vegetable/fruit intake ($P = 0.73$). As a result of the lack of association between these two variables, air exposure was not included in the GEE model. Similarly, there was a statistically significant increase ($P = 0.0002$) in the mean serum (PFOA) associated with increasing numbers of weekly servings of fruits and vegetables from a local garden. Additionally, there was an increase in serum PFOA with servings of meat or game grown or harvested locally ($P = 0.005$). No association was found between local fish consumption and serum PFOA concentrations.

With regard to water filtration systems, residents using only Little Hocking water system water as their residential drinking water source were divided into two groups: those using a home water filter system based on carbon ($N = 64$), and those who had no home water filtration system or used a system not known to remove PFOA or used a system whose type and composition could not be verified ($N = 209$). Residents using carbon water filters had significantly lower median serum PFOA levels (318 ng/mL) compared with residents using Little Hocking System water who did not use carbon water filtration (421 ng/mL) ($P = 0.008$).

Serum PFOA Levels and Household Cooking Use of Tap Water

There was no relationship between serum (PFOA) and the use of tap water in cooking for those households using only Little Hocking water system water (Fig. 4). When cooking vegetables and pasta, making soups and stews, reconstituting canned soups, reconstituting frozen fruit juices, and home canning of vegetables and meats were examined, no statistically significant relationship with serum PFOA levels

TABLE 6
Results of Application of General Estimating Equations

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	pr > Z
Intercept	110.54	58.10	-3.34	224.42	1.9	0.0571
Vegetable and fruit from your garden servings/wk	62.31	20.96	21.23	103.39	2.97	0.0029
Tap water drinks/d	5.93	2.02	1.97	9.88	2.94	0.0033
Age (yrs)	3.53	1.03	1.50	5.55	3.42	0.0006
No carbon filter use	104.92	35.86	34.65	175.20	2.93	0.0034

Note: This analysis includes only participants from households using Little Hocking water system only. Participants with substantial occupational exposure were excluded.

pr indicates probability.

Z indicates Z-value.

was found. However, a linear trend of increasing serum PFOA levels was observed with increasing use of water for making soups and stews and for home canning of vegetables and meats.

Little Hocking Water System Users: Multivariate Analysis Adjusting for Household Clustering

The model of best-fit included age, tap water drinks per day, fruit and vegetable servings per week from your garden, and use of a carbon filter (Table 6). Eating meat and game grown or harvested locally was not found to be associated with serum PFOA levels in the multivariate analysis.

Discussion

We found that median serum PFOA levels in randomly selected residents of the Little Hocking water service district ranged from 298 to 370 ng/mL, on the order of 60 to 75 times the median levels of approximately 5 ng/mL previously described for general U.S. populations.⁴⁻⁶ The majority of serum PFOA levels in these residents exceeded the maximums reported in previous community studies in other geographic locations. For example, the range of serum PFOA levels for 645 U.S. adult blood donors was from 1.9 ng/mL to 52.3 ng/mL⁴; for 238 elderly volunteers in Seattle, it was 1.4 ng/mL to 16.7 ng/mL⁵; and for 598

children from across the United States, it was from 1.9 ng/mL to 56.1 ng/mL.⁹ The serum PFOA levels for the 30 comparison subjects for the Philadelphia area in our study all fell within previously reported normal population ranges.

Our random sampling of residents in the water district included a number of individuals who worked in the production area of a fluoropolymer manufacturing facility located across the Ohio River in Washington, West Virginia. This facility is believed to be the primary source of PFOA pollution in the area. A recent study of workers at this plant found the median serum PFOA level of 490 ng/mL for 259 workers currently working in production areas where PFOA was used.²³ We found a median serum PFOA level of 774 ng/mL for the 18 workers who had worked in the production area at the facility, lived in the Little Hocking water service area, and participated in our study. The median serum PFOA level for these 18 individuals was 284 ng/mL higher than the median reported for all production workers at the facility, suggesting a combination of residential water and occupational contributions to the PFOA body burden. Because all but one of the production workers we studied were selected through stratified random sampling, we consider it unlikely that selection bias could explain this elevation. Workers from nonproduction areas of the facility included in

our sampling did not have significantly increased serum PFOA levels compared with other residents. The serum PFOA levels in nonoccupationally exposed community residents in the Little Hocking water service district approached and frequently surpassed those measured in production workers exposed to PFOA at the source fluoropolymer manufacturing plant. These results illustrate that body burdens of pollutants sustained through community environmental exposures are not necessarily less than those sustained through occupational exposure.

We were able to explore other potential occupational exposure contributions to the serum PFOA levels. In addition to use in the manufacture of fluoropolymers, it has been suspected that PFOA may also be a breakdown product of fluorinated telomers. PFOA is used as a surfactant or surface treatment chemical in many products, including firefighting foams; personal care and cleaning products; oil, stain, grease, and water repellent coatings on carpet; textile leather; and paper.²¹ PFOA has had limited use as a fire suppressant. A study of PFOA in consumer products identified extractable PFOA in carpet care solution-treated carpeting.²⁴ Because PFOA and related fluorinated compounds are currently unregulated, there is relatively little available information on the extent of their use. Based on a qualitative assessment of potential occupational exposure to PFOA in the southeastern Ohio area, we explored occupational exposure in firefighting, carpet cleaning, and carpet installation in addition to potential exposure in the disposal or incineration of PFOA and/or waste from the fluoropolymer manufacturing facility. We did not observe a significant increase in median serum PFOA concentration in any of these occupational groups. It remains possible that in a population with less exposure to PFOA from ambient contamination, identifiable contributions to the body burden might be found from one or more of these occupational exposures.

Several observations support the conclusion that the major source of the

PFOA in Little Hocking water district residents was drinking water. Serum PFOA levels were similar whether residents lived in the area proximate to the plant where the air plume would have been concentrated or in an area that had the same water service but was located up to 20 miles from the plant and where air pollution with PFOA was estimated to be minimal. Serum PFOA levels were considerably lower in those residents who were currently using only bottled, spring, or cistern water as their drinking water source. Where the primary drinking water source was well water, serum PFOA levels varied in proportion with well water PFOA levels.

The median serum/drinking water PFOA ratio of 105 we observed in Little Hocking water users likely reflects both high PFOA absorption after oral ingestion and a long half-life of PFOA in human blood. In rats, the oral bioavailability of PFOA is approximately 100%.²⁵ The serum half-life varies widely by species and sex: several hours for female rats, approximately 7 to 10 days for male rats,²⁵ and 20.9 days for male and 32.6 days for female cynomolgus monkeys.²⁶ The half-life in humans appears to be much longer. In the one set of data that is available, a study of nine retirees from a fluoropolymer production facility, the mean serum PFOA half-life was found to be 4.4 years.²⁰ However, we did not find a relationship between serum PFOA levels and length of residence in the Little Hocking water district among study participants, all of whom had lived in the area for at least 2 years. If the half-life in the general community is in the order of 4 to 5 years, we would have expected to find a significant relationship with duration of residence. Our results thus lead us to question whether the serum PFOA half-life in the general community is as long as that published for the small retired worker group.²⁰ We expect to have more data on this subject from a follow-up study.

In residents who drank only Little Hocking system water, the model of

best-fit for serum PFOA levels included age, tap water drinks per day, fruit and vegetable servings per week from a local garden, and use of a carbon water filter. The finding that PFOA concentrations were higher in children aged 5 and below and in the elderly aged over 60 is disturbing, because these may represent groups particularly vulnerable to adverse health consequences.^{27,28} The reason for the higher serum PFOA levels in those aged 60 and above is not entirely clear; multivariate analysis shows the increased consumption of drinking water in this group does not fully explain the observed increase. Both the elderly and those aged 5 and below may spend more time at home with exclusive use of residential water than working or school-aged residents. Infants and young children may have proportionately greater exposure to water-borne pollutants because they drink more water per kilogram of body weight than do adults.²⁸ The levels in the very young may also represent additional exposures as PFOA has been shown to cross the placenta and to be present in breast milk (at approximately one tenth of the serum concentration) in Sprague Dawley rats,²⁹ although comparable studies in humans are lacking. We are performing further studies to elucidate PFOA exposures in maternal milk and infant formula. A higher serum PFOA level for young children was previously observed by Olsen et al⁹ who measured PFOA in the serum of 598 children aged 2 to 12 who participated in a nationwide U.S. study of group A streptococcal infections, 645 adult blood donors from six U.S. blood bank donation sites, and 238 elderly subjects in Seattle participating in a study of cognitive function. The geometric mean serum PFOA levels (4.6 ng/mL, 4.2 ng/mL, and 4.9 ng/mL, respectively) were similar in all groups. However, in the children, there was a statistically significant negative association with age with the highest mean serum PFOA levels noted at age 4 and the

lowest at age 12. Our failure to find gender differences is consistent with previous observations in the U.S. general population.

The association with the number of servings of fruits and vegetables from the home garden was unexpected. Possible explanations include the use of PFOA containing water for cooking, canning, and washing fruits and vegetables, PFOA in the raw fruits and vegetables, and different dietary and drinking habits in those who consume more home-grown fruits and vegetables. We consider it unlikely that PFOA is elevated in raw fruits and vegetables from the garden because as a result of the natural rainfall characteristics, it is unusual to water gardens and fruit trees extensively with residential water in this district. Also, the association between serum PFOA and servings of fruits and vegetables was not reduced by adjusting for residence in the areas with known higher airborne and soil levels of PFOA. We are undertaking further studies to better understand the observed association.

Individuals using carbon-type water filters for residential drinking water had a reduction of approximately 25% in median serum PFOA levels compared with those not using a filter. This reduction was much less than we have seen for those who drank only bottled, spring, or cistern water. Because of limited effectiveness, potential reliability problems associated with the need to maintain the filter system, and potential health problems associated with the use of home filtration systems, we do not recommend reliance on home filters to remove PFOA. New water filtration products to remove PFOA are currently being pilot-tested with prospects of wider use in the near future.

The high serum PFOA levels in our study as a result of the relatively high exposure in drinking water may have limited our ability to detect relatively small increases associated with contributions from ambient air pollution. Thus, we cannot exclude

the possibility that exposure to PFOA in air could lead to a detectable contribution to the PFOA body burden in other populations with minimal water exposure.

Our finding that the major source of serum PFOA was residential drinking water has helped empower those in the community who may choose to lower their PFOA exposure with a view to lowering their body burden. As a result of our preliminary findings that the levels of PFOA were abnormally high in residents of the Little Hocking water district and that the major nonoccupational PFOA source was residential drinking water, the option of free bottled drinking water has been made available through the Little Hocking Water Association to those with this water service. More than half of the residents are already taking advantage of this offer. In addition, a new water filtration system designed to remove PFOA is now planned. We would anticipate that these actions should result in reduced serum PFOA levels. We plan to monitor changes in serum PFOA levels in the study group over the next 18 months to determine the extent of any serum PFOA reductions.

Identification of water as the major route of community exposure to PFOA in this population should encourage efforts to define exposure sources in other populations and should provide a basis for personal and regulatory efforts to reduce human exposure to a pollutant, which is of concern because of remarkable persistence in both the environment and in humans.

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ATTACHMENT 3

Non-ECA PFOA Information Forum

Begins Immediately Following Plenary

- ***Welcome and Introduction:***
 - Charles M. Auer, Director, US EPA Office of Pollution Prevention and Toxics

- ***Updates on EPA's Non-ECA PFOA-Related Research and Information Activities***
 - Telomer Biodegradation Research Under DuPont Supplemental Environmental Project With EPA
 - EPA Office of Research and Development Telomer Biodegradation and Other Research
 - EPA's Nomination to the Centers for Disease Control and Prevention for Human Biomonitoring
 - EPA's Nomination to the National Toxicology Program of a Class Study on Perfluorinated Sulfonic and Carboxylic Acids
 - PFOA Risk Assessment Process
 - PFOA Stewardship Program
 - EPA Activities on Related Chemicals
 - International Activities

- ***Updates on Non-ECA PFOA-Related Research and Information Activities By Others***
 - State of Minnesota: Brief Update on Perfluorochemical Activities
James Kelly, Minnesota Department of Health

 - Environment Canada: PFCAs and Their Precursors, Proposed Action Plan for Assessment and Management
Joseé Portugais, Environment Canada

 - AGC Chemicals, Asahi Glass Co., Ltd.
Dr. Seiji Shin-ya

 - DuPont: 2010/2015 PFOA Stewardship Program
Susan Stalnecker

 - Fluoropolymer Manufacturers Group
Don Duncan, FMG

**Perfluorooctanoic Acid (PFOA) Enforceable Consent Agreement (ECA)
Process Ninth Plenary Session and
Non-ECA PFOA Information Forum
Tentative Agenda**

**June 8, 2006
9:00 AM to 4:00 PM**

**EPA East Building, Room 1153
1201 Constitution Avenue, NW
Washington, DC 20460**

Ninth PFOA ECA Plenary Session

- ***Welcome and Introductions***
 - Charles M. Auer, Director, US EPA Office of Pollution Prevention and Toxics

- ***Agenda Amendments***

- ***Update on Incineration ECAs***

- ***Fluoropolymer Technical Workgroup Report to Plenary***
 - Discussion
 - Directives from Plenary to Workgroup

- ***Public Comment Period***
 - Please sign up at the registration desk if you are not a registered Interested Party and wish to speak at the meeting. Individual public comments are limited to five minutes each. Registered Interested Parties can participate in all discussions throughout the meeting.

- ***Next Steps***

- ***Adjourn***

ATTACHMENT 4

Determinants of Fetal Exposure to Polyfluoroalkyl Compounds in Baltimore, Maryland

BENJAMIN J. APELBERG,[†]
 LYNN R. GOLDMAN,^{*,‡}
 ANTONIA M. CALAFAT,[§]
 JULIE B. HERBSTMAN,^{†,⊥}
 ZSUZSANNA KUKLENYIK,[§]
 JOCHEN HEIDLER,[‡] LARRY L. NEEDHAM,[§]
 ROLF U. HALDEN,[‡] AND
 FRANK R. WITTER^{||}

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205, Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341, and Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Polyfluoroalkyl compounds (PFCs), such as perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), are ubiquitous, man-made chemicals. Human data suggest that *in utero* exposures to these chemicals occur and some evidence of developmental toxicity in animals exists. To assess the distribution and determinants of fetal exposure to PFCs, we analyzed cord serum samples from 299 singleton newborns delivered between 2004 and 2005 in Baltimore, MD for 10 PFCs by employing on-line solid-phase extraction coupled with reversed-phase high-performance liquid chromatography–tandem mass spectrometry. PFOS and PFOA were detected in 99 and 100% of umbilical cord sera, with geometric mean concentrations of 4.9 and 1.6 ng/mL, respectively. PFOS and PFOA concentrations were highly correlated (Pearson's $r = 0.64$ after natural log transformation, $p < 0.01$). Eight other PFCs were detected less frequently and at lower concentrations than PFOS and PFOA. Geometric mean concentrations of PFOS for Asians (6.0 ng/mL) and Blacks (5.1 ng/mL) were higher than those for Whites (4.2 ng/mL), while PFOA levels were more evenly distributed by race. Other maternal demographic and socioeconomic characteristics, including age, education, marital status, and living in the city limits were not significantly associated with cord concentrations. Our findings suggest that *in utero* exposure to PFOS and PFOA is ubiquitous in a population of babies born in Baltimore, MD.

* Corresponding author phone: (410) 614-9301; e-mail: lgoldman@jhsph.edu.

[†] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health.

[‡] Department of Environmental Health Sciences, Johns Hopkins Bloomberg School of Public Health.

[§] Centers for Disease Control and Prevention.

^{||} Johns Hopkins University School of Medicine.

[⊥] Current affiliation: Columbia Mailman School of Public Health, New York, NY 10032.

Introduction

Polyfluoroalkyl compounds (PFCs) comprise a class of man-made, fluorinated organic compounds that have been used in a variety of consumer and industrial applications for more than 50 years. These applications include protective coatings for food-contact packaging, textile, carpets, and leather, processing aids in the production of fluoropolymers, commercial and industrial surfactants, and insecticides (1, 2). Only recently have reports documented widespread exposure in wildlife and humans (3–6). In 2000, the major manufacturer of perfluorooctane sulfonate (PFOS) announced a voluntary phase-out of this product (7). Early in 2006 the major manufacturer of perfluorooctanoate (PFOA) reported having achieved a voluntary reduction in PFOA emissions by the end of 2005 as well as a commitment for a total reduction in emissions of 98% by 2007 (8).

PFOS has been identified as a hepatic peroxisome proliferator that targets the liver and disrupts lipid metabolism in some animal species (9). Toxicity studies in animals have shown marked reductions in serum cholesterol and/or triglycerides (10–12) and endocrine (10, 12–15), developmental, and reproductive effects (12, 14–16). PFOS has been found to be tumorigenic and carcinogenic in rats (17). PFOA is also hepatotoxic (18), a peroxisome proliferator (19), and disrupts lipid metabolism in some species (11). PFOA has been shown to be tumorigenic in rats (18, 20), and some suspect that it may be a human carcinogen (21). In rats and mice, PFOA has shown the potential for developmental toxicity (22–24). However, it should be noted that serum concentrations associated with toxicity in animal studies are orders of magnitude higher than those reported in humans, even those exposed occupationally.

PFCs are highly stable in the environment and the half-life in humans has been estimated at 5.4 years for PFOS and 3.8 years for PFOA (25). Many PFCs are surfactants; rather than accumulating in lipids like traditional persistent organic pollutants, they are bound to proteins in the liver, serum, and other tissues (26–28). PFOS and PFOA have been detected consistently in human biomonitoring studies in the United States (5, 29–31) and many other countries (3), while other PFCs are not consistently found.

Despite the growing body of evidence suggesting widespread human exposure, little is known about the presence of PFCs *in utero*. A study of 15 maternal–fetal pairs in Japan confirmed that PFOS could cross the placental barrier in humans, albeit incompletely (32). Other small studies in Germany and Northern Canada documented detectable levels of PFOS and PFOA in cord blood samples (33, 34). The aims of the current study were to characterize the distribution of serum concentrations of PFCs and to identify demographic and socioeconomic factors associated with *in utero* exposure to these chemicals among a population of babies born in Baltimore, MD from November 2004 through March 2005.

Materials and Methods

Subjects. We conducted a cross-sectional study (the Baltimore THREE Study) of newborn deliveries at the Johns Hopkins Hospital in Baltimore, MD. This study received approval from the Johns Hopkins Medicine Institutional Review Board and was determined to be exempt from the Health Insurance Portability and Accountability Act. The study required the collection only of specimens that otherwise would have been discarded and information from medical records that were available to hospital personnel. Thus, there was no requirement for informed consent due to the

anonymization of all samples and data. Members of a community advisory committee, who were selected for their specific knowledge and expertise, and their focus on important child health concerns in Maryland, had the opportunity to learn about and comment on this study before it was conducted. Between November 26, 2004 and March 16, 2005 all singleton, live birth deliveries occurring in the Labor and Delivery Suite at the hospital were eligible for participation in the study.

Over the course of the study period, 609 live births occurred at the hospital, of which 597 were singleton births. We obtained cord blood specimens from 341 of these. We conducted a brief survey of hospital personnel to understand the major reasons for missed specimen collection. The most common explanations for missed collection included: complications during delivery, premature birth and/or small size of the infant resulting in small quantity of available cord blood, and logistical factors such as understaffing. The babies who were not included had somewhat lower gestational ages and birth weights. Forty-two of the 341 specimens collected had insufficient volume for laboratory analyses of PFCs and were excluded, leaving a total of 299 in this study. Factors associated with lower blood volumes collected were: preterm birth, low birth weight, being first born, and younger age of mother.

Cord blood samples were collected by hospital personnel immediately following delivery from the umbilical cord vein (35). After delivery, a section of the cord was cleaned with an alcohol wipe and blood was drawn using a sterile 60-mL Becton Dickinson (BD) syringe with an 18-gauge safety needle. A BD Vacutainer Blood Transfer Device was then attached to the syringe and up to five 10 mL glass BD vacutainers were filled. Cord blood specimens were stored in Labor and Delivery refrigerators and, within 3 h, transported to a laboratory at the Johns Hopkins Bloomberg School of Public Health for processing. Blood specimens were centrifuged at 1000g for 15 min. Serum was aliquotted into prescreened 2 mL polypropylene cryovials and stored at -80°C . The prescreened containers were previously shown to be free of PFC contaminants. Frozen specimens were transferred on dry ice to the Centers for Disease Control and Prevention (CDC) for analyses.

Medical Records. Two study investigators concurrently abstracted maternal and infant characteristics from clinical databases maintained by the hospital. A random 10% sample was verified by two other investigators. Additional information was obtained from forms filled out by the nursing staff at the time of delivery. These data were collected to examine factors that may be associated with *in utero* exposure to PFCs, such as maternal birth cohort, social class, and past pregnancies. Age, race, education, marital status, and parity were based on self-report. Insurance type was recoded from the medical record as "Private" or "Public Assistance." Body mass index (BMI) was calculated from reported pre-pregnancy weight and height. Gestational age was based on the "best obstetric estimate" and categorized as term (≥ 37 full weeks) or preterm (< 37 full weeks). Infant sex was abstracted from medical records. Maternal smoking status during pregnancy was defined using the maternal medical record and cord serum cotinine concentrations. Cotinine concentrations of 1–10 ng/mL were categorized as passive smoking exposure and concentrations above 10 ng/mL as active smoking exposure (36). If the clinical record indicated that the mother smoked during pregnancy, she was considered an active smoker regardless of the cotinine concentration in cord blood. The mother's home address was geocoded by Geolytics, Inc. Residence inside the city limits was defined using Federal information processing standards code 24510.

Laboratory Analysis. Cord serum samples were analyzed for 10 PFCs by on-line solid-phase extraction (SPE) coupled with reversed-phase high-performance liquid chromatography (HPLC)–tandem mass spectrometry (MS/MS). The method has been described in detail by Kuklenyik et al. (37). This method, used to measure PFCs in large-scale surveys, including the National Health and Nutrition Examination Survey (NHANES), has excellent recovery, precision, and reliability for the detection of PFCs in human serum (37). Briefly, without protein precipitation, one aliquot of 100 μL of serum was injected into a commercial column switching system allowing for concentration of the analytes on a SPE column. This column was placed automatically in front of an analytical column for chromatographic separation of the analytes. Detection and quantification were done using negative-ion TurboIonSpray ionization, a variant of electrospray ionization, tandem mass spectrometry. The limits of detection (LODs) were in the low ng/mL range for the following PFCs: perfluorooctane sulfonamide (PFOSA), 2-(*N*-ethyl-perfluorooctane sulfonamido) acetate, 2-(*N*-methyl-perfluorooctane sulfonamido) acetate (Me-PFOSA-AcOH), perfluorobutane sulfonate, PFOS, perfluoroheptanoate, PFOA, perfluorodecanoate (PFDeA), perfluoroundecanoate (PFUA), and perfluorododecanoate. Although the analytical method allows for the quantification of perfluorohexane sulfonate (PFHxS) and perfluorononanoate (PFNA), these analytes could not be measured in the cord sera due to the presence of interferent compounds that eluted at the same retention times and shared precursor/product ion transitions of identical mass-to-charge ratios (m/z) with PFHxS and PFNA. Similarly, the precursor/product ion m/z transition normally used for the quantification of PFOS (37) also had an interference. Therefore, PFOS concentrations had to be calculated using another transition, one of the two normally used to confirm the presence of PFOS (37). The nature of these interferences is at present unknown. Analytical standards, quality control (QC), and reagent blank samples were included in each analytical batch along with the unknown samples. QC samples were evaluated according to standard statistical probability rules.

Serum cotinine was measured by the CDC using a method described by Bernert et al. (38). It employs HPLC coupled with atmospheric pressure chemical ionization MS/MS to measure serum cotinine with high accuracy and sensitivity (LOD = 0.015 ng/mL). This method has been used to assess exposure to environmental tobacco smoke in NHANES and other large-scale surveys.

Statistical Analysis. We used descriptive statistics to describe cord serum PFC concentrations. Because PFC concentrations were skewed to the right, analyses utilized natural log-transformed concentrations. We used Pearson's correlation to test for linear co-occurrence of PFCs and linear regression to describe univariate relationships between predictors and PFC concentrations. The possibility of non-linear relationships was explored using restricted cubic spline models.

We used linear regression to estimate the ratio of geometric mean concentrations (and 95% confidence intervals [95% CI]) among categories of maternal characteristics. Under the linear regression model, the expectation (or average) of the natural log PFC concentration is described as follows:

$$E(\ln\text{PFC}) = \beta_0 + \beta_1 x_1 + \epsilon$$

where β_0 is the intercept, ϵ is the normally distributed error term, x_1 is a maternal or infant predictor, and β_1 is the regression coefficient, which is equal to

$$\beta_1 = E(\ln\text{PFC})_{x_1=1} - E(\ln\text{PFC})_{x_1=0}$$

TABLE 1. Perfluorinated Chemicals (PFCs) Measured in Cord Blood Serum and Reported in Units of ng/mL (*n* = 299) from the Baltimore THREE Study, 2004–2005

compound ^a	limit of detection (LOD)	% above LOD	geometric mean ^b (range)
PFOSA	0.05	26	<LOD (ND–0.8)
Et-PFOSA-AcOH	0.2	1	<LOD (ND–0.5)
Me-PFOSA-AcOH	0.2	40	<LOD (ND–1.8)
PFBuS	0.1	3	<LOD (ND–0.2)
PFOS	0.2	99	4.9 (ND–34.8)
PFHpA	0.4	2	<LOD (ND–2.6)
PFOA	0.1–0.2	100	1.6 (0.3–7.1)
PFDeA	0.2	24	<LOD (ND–1.1)
PFUA	0.2	34	<LOD (ND–1.9)
PFDoA	0.2	5	<LOD (ND–1.7)

^a PFOSA = perfluorooctane sulfonamide; Et-PFOSA-AcOH = 2-(*N*-ethyl-perfluorooctane sulfonamido) acetate; Me-PFOSA-AcOH = 2-(*N*-methyl-perfluorooctane sulfonamido) acetate; PFBuS = perfluorobutane sulfonate; PFOS = perfluorooctane sulfonate; PFHpA = perfluoroheptanoate; PFOA = perfluorooctanoate; PFDeA = perfluorodecanoate; PFUA = perfluoroundecanoate; PFDoA = perfluorododecanoate. ^b Non-detects (ND) are computed as the LOD/√2. Geometric mean is listed as <LOD if ≥60% of observations are <LOD.

After exponentiating the coefficient, the equation reduces to

$$e^{\beta_1} = \frac{e^{E(\ln PFC_{x_1=1})}}{e^{E(\ln PFC_{x_1=0})}} = \frac{GM(PFC_{x_1=1})}{GM(PFC_{x_1=0})}$$

The exponentiated coefficient can be interpreted as the ratio of geometric mean concentrations (GM) comparing one stratum of the categorical predictor, *x*₁, to another. The 95% CI on this ratio can be estimated similarly, by exponentiating the confidence intervals of the coefficient.

We used multivariate linear regression to compare geometric mean concentrations, after adjusting for other covariates. For all models, regression diagnostics were conducted to assess fit and the presence of heteroskedasticity. Concentrations below the LOD (<LOD) were imputed as the LOD divided by the square root of two (39). Statistical analyses were performed using STATA version 8.0 (StataCorp, College Station, TX).

Results

Table 1 summarizes the occurrence and concentration of PFCs detected in umbilical cord blood serum. PFOA was

detected in all samples and PFOS was detected in all but two samples, with corresponding geometric means of 1.6 ng/mL for PFOA (range 0.3–7.1 ng/mL) and 4.9 ng/mL for PFOS (range <LOD–34.8 ng/mL). The 95th percentile concentration was 3.4 ng/mL for PFOA and 12.4 ng/mL for PFOS. Four other PFCs were detected in at least 20% of samples (PFOSA, Me-PFOSA-AcOH, PFDeA, PFUA). PFOS and PFOA made up most of the total concentration of the PFCs measured in these specimens. Because of the observed low detection frequency and concentrations of eight of the ten analytes, further analyses of determinants of exposure were conducted only for PFOS and PFOA.

As expected, concentrations of both PFOS and PFOA were right skewed and became more Gaussian after natural log-transformation. Cord concentrations of PFOS and PFOA were highly correlated with one another (Figure 1; Pearson's *r* = 0.64, *p* < 0.01).

In Table 2, the geometric mean PFOS and PFOA concentrations are shown by maternal and infant characteristics, along with the multivariate adjusted ratio of geometric means and 95% CIs. The geometric mean concentrations of PFOS for Asians (6.0 ng/mL) and Blacks (5.1 ng/mL) were higher than those for Whites (4.2 ng/mL), while PFOA levels were more evenly distributed by race. Male babies had lower geometric mean concentrations than female babies for both compounds (PFOS, *p* = 0.07; PFOA, *p* < 0.01). Obese (BMI ≥30 kg/m²) and underweight (BMI <18.5 kg/m²) women had babies with slightly higher geometric mean concentrations compared with normal weight (BMI 18.5–24.9 kg/m²) women, although only statistically significant for PFOA among obese women (*p* = 0.03). Evidence of a nonlinear relationship with BMI was confirmed using restricted cubic spline models (data not shown). Multiparous births had slightly lower PFOS and PFOA cord concentrations than primiparous births, and preterm births (<37 completed weeks of gestation) had lower concentrations than term births, although the difference was statistically significant only for PFOA and parity (*p* = 0.02). There were no other significant predictors of cord concentrations among the remaining covariates, which included age, education, insurance type, marital status, smoking status, and living inside the city limits. When examining covariates as continuous measures, no significant linear trends were observed between PFOS or PFOA and maternal age, gestational age, or cord cotinine concentration (data not shown).

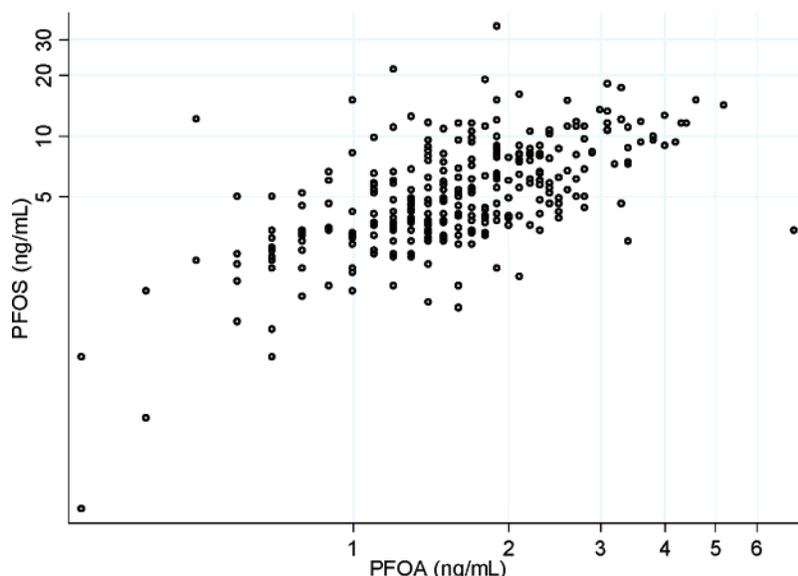


FIGURE 1. Correlation between log perfluorooctane sulfonate (PFOS) and log perfluorooctanoate (PFOA) concentrations in cord blood serum (*n* = 299). Pearson's *r* = 0.64; *p* < 0.01. Baltimore THREE Study, 2004–2005.

TABLE 2. Adjusted Ratios (and 95% Confidence Intervals) of Geometric Mean Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) Concentrations in Cord Blood Serum by Maternal and Infant Characteristics from the Baltimore THREE Study, 2004–2005

characteristic	N	PFOS		PFOA	
		GM ^a [ng/mL]	GM ratio ^b	GM ^a [ng/mL]	GM ratio ^b
maternal age					
<18 years	25	4.9 (4.0–6.2)	1.02 (0.73–1.42)	1.5 (1.2–1.8)	0.98 (0.77–1.24)
18–35 years	250	4.9 (4.5–5.4)	1.00	1.6 (1.5–1.7)	1.00
>35 years	24	5.0 (3.8–6.5)	1.13 (0.84–1.53)	1.5 (1.2–1.9)	1.07 (0.86–1.33)
maternal race					
White	64	4.2 (3.5–5.0)	1.00	1.5 (1.3–1.7)	1.00
Asian	25	6.0 (3.8–9.4)	<i>1.43 (1.02–2.07)</i>	1.5 (1.1–2.1)	1.06 (0.83–1.35)
Black	210	5.1 (4.7–5.5)	1.28 (0.98–1.68)	1.6 (1.5–1.7)	1.12 (0.92–1.36)
maternal education					
<HS diploma	87	4.8 (4.3–5.4)	1.00	1.5 (1.4–1.7)	1.00
HS diploma	97	5.1 (4.6–5.7)	1.05 (0.84–1.32)	1.7 (1.5–1.8)	1.13 (0.96–1.33)
1–4 years college	69	4.9 (4.0–5.9)	1.05 (0.79–1.41)	1.5 (1.4–1.7)	1.15 (0.93–1.42)
5+ years college	42	5.1 (3.8–6.8)	1.05 (0.70–1.57)	1.6 (1.3–1.9)	1.19 (0.89–1.60)
health insurance					
public assistance	98	4.9 (4.3–5.6)	1.00	1.6 (1.5–1.8)	1.00
private	116	5.1 (4.4–5.8)	1.10 (0.86–1.41)	1.5 (1.4–1.7)	0.95 (0.80–1.14)
marital status					
unmarried	198	5.0 (4.6–5.5)	1.00	1.6 (1.5–1.7)	1.00
married	101	4.8 (4.1–5.6)	0.90 (0.67–1.19)	1.5 (1.3–1.7)	0.99 (0.81–1.22)
maternal body mass index (kg/m ²)					
underweight (<18.5)	16	5.9 (3.7–9.2)	1.21 (0.85–1.74)	1.7 (1.3–2.2)	1.13 (0.87–1.46)
normal (18.5–24.9)	135	4.8 (4.3–5.4)	1.00	1.5 (1.3–1.6)	1.00
overweight (25–29.9)	65	4.7 (3.9–5.7)	0.96 (0.78–1.18)	1.6 (1.4–1.8)	1.04 (0.89–1.20)
obese (30+)	72	5.4 (4.8–6.1)	1.11 (0.90–1.37)	1.8 (1.6–1.9)	<i>1.19 (1.02–1.38)</i>
parity					
primiparous	125	5.2 (4.5–5.9)	1.00	1.7 (1.5–1.8)	1.00
multiparous	174	4.8 (4.4–5.2)	0.91 (0.76–1.08)	1.5 (1.4–1.6)	<i>0.86 (0.76–0.98)</i>
maternal smoking					
non/passive	243	5.1 (4.6–5.5)	1.00	1.6 (1.5–1.7)	1.00
active	56	4.5 (3.9–5.1)	0.91 (0.73–1.14)	1.6 (1.4–1.8)	1.09 (0.93–1.27)
infant sex					
female	133	5.3 (4.9–5.8)	1.00	1.8 (1.6–1.9)	1.00
male	166	4.7 (4.2–5.3)	0.86 (0.74–1.01)	1.4 (1.3–1.6)	<i>0.81 (0.73–0.91)</i>
residence within Baltimore city limits at birth					
no	92	4.8 (4.1–5.6)	1.00	1.5 (1.4–1.7)	1.00
yes	207	5.0 (4.6–5.4)	0.94 (0.75–1.17)	1.6 (1.5–1.7)	1.01 (0.86–1.19)
preterm delivery (<37 wk)					
no	260	5.0 (4.7–5.5)	1.00	1.6 (1.5–1.7)	1.00
yes	39	4.3 (3.3–5.7)	0.90 (0.70–1.14)	1.4 (1.2–1.6)	0.88 (0.74–1.05)

^a GM = geometric mean. ^b GM Ratio = ratio of geometric means. Adjusted for all variables listed in the table. The following data were missing: 4 observations for education, 85 for insurance, and 11 for BMI. Missing data were treated as an indicator term in regression models. Italicized GM ratio indicates statistically significant ($p < 0.05$) difference from reference group.

Discussion

This study confirms earlier findings indicating that the developing fetus is exposed to persistent PFCs *in utero* and that PFOS and PFOA are the predominant polyfluoroalkyl compounds detected in cord blood (32–34). Cord concentrations of PFOS and PFOA were strongly correlated, despite arising from different industrial sources, implying that the pathways of human exposure to PFOS and PFOA may be similar. PFOS and PFOA, along with possible precursors (polyfluoroalkyl sulfonamides and fluorotelomer alcohols), have been identified in consumer products, house dust, water, and/or indoor air (40–44), and these are possible pathways of exposure. For example, Me–PFOS–AcOH is a metabolite of *N*-methyl perfluorooctane sulfonamidoethanol, which has been widely used as a stain repellent for carpets. The detection of this compound in 40% of samples may reflect exposure from contact with treated carpets (30). The correlation between PFOS and PFOA in blood may reflect the co-occurrence and uptake of these compounds through secondary pathways, such as food or drinking water intake. PFOS and PFOA have been detected in surface waters, suggesting that drinking water is a possible source (44–46). Environmental contamination of these compounds has been well-

documented in regions as far away as the Arctic (47), raising the possibility of exposures through the food chain. PFOS (and PFOA to a lesser extent) bioconcentrate in fish and biomagnify in aquatic food chains (4, 45, 46, 48), suggesting fish consumption as a possible pathway. In a recent study in Poland, Falandysz et al. found that individuals with high fish consumption had higher concentrations of PFOS (and PFOA to a lesser extent) in their blood relative to other groups (49). Further study is needed to better understand the pathways of exposure to these compounds in our population.

The analytic method used to measure human serum concentrations of PFCs has excellent precision and accuracy at concentrations of PFOS and PFOA in the range of the current study (37). However, in this study, the measurement error for PFOS may be greater, because the ion transition normally monitored for quantification could not be used due to an interferant. Random measurement error generally would bias bivariate associations to the null (50), which may contribute to the lack of observed differences in PFOS concentrations between subgroups.

Geometric mean cord PFOS and PFOA concentrations in this study were within the range of previous reports from Germany and Japan (Figure 2). Inoue et al. reported the

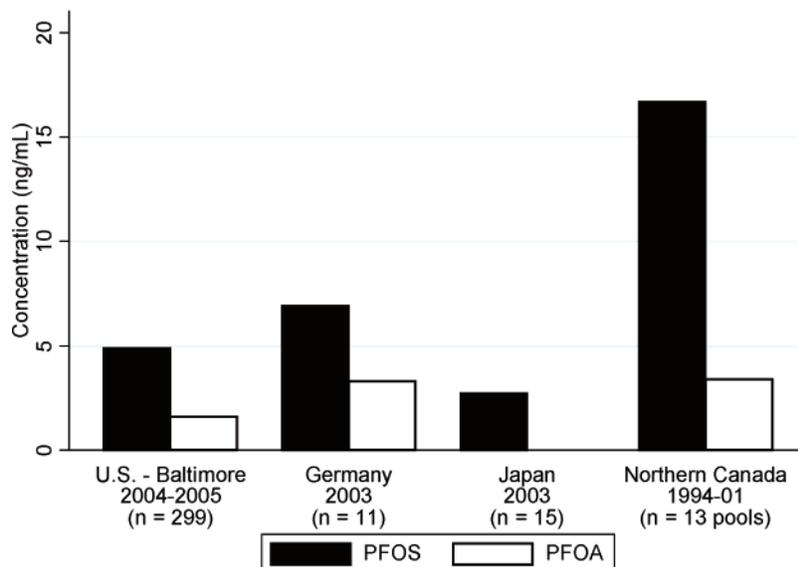


FIGURE 2. Comparison of geometric mean perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations (ng/mL) in cord blood obtained for the Baltimore THREE study (2004–2005) and prior cord blood studies in Germany (34) (plasma), Japan (32) (serum), and Canada (33) (plasma, arithmetic mean).

presence of PFOS in all 15 cord serum samples collected in Japan, at concentrations ranging from 1.6 to 5.3 ng/mL (32). In the same study, PFOA was detected in only 3 maternal samples and no fetal samples (LOQ 0.5 ng/mL). In a recent German study of 11 plasma cord samples, the geometric mean PFOS and PFOA concentrations were 6.9 and 3.3 ng/mL, respectively (34). Finally, in a study of 13 pooled cord plasma samples in northern Canada, collected from 1994 to 2001, only arithmetic mean concentrations were reported. The means for PFOS and PFOA were 16.7 and 3.4 ng/mL, respectively (33), higher than arithmetic means for the present study (PFOS 6.0 ng/mL; PFOA 1.8 ng/mL).

Very few maternal or infant characteristics were predictors of cord PFC concentrations. Consistent with studies of adults, PFOS and PFOA concentrations were relatively constant across maternal age (29–31). None of the socioeconomic measures in our study (e.g., education, insurance, marital status, living in Baltimore City) were associated with PFC concentrations. Even statistically significant differences sometimes reflected minor absolute differences in dose. For example, although male babies had lower concentrations of PFOS and PFOA than females, the absolute difference in geometric means was only 0.6 ng/mL for PFOS and 0.3 ng/mL for PFOA. Overall, our results imply that cord levels are fairly uniformly distributed by maternal age and socioeconomic characteristics.

Asian and Black infants had somewhat higher PFOS concentrations than Whites. This is in contrast to an analysis of pooled serum samples from 2001–2002 NHANES, in which White females had higher levels than Black females (5) and to the 1999–2000 NHANES sample, in which no differences were observed between Blacks and Whites (6). There are several possible reasons for differences in this relationship, including random variation or ethnic differences in exposure patterns between the study populations.

The estimated lower bound of the benchmark dose associated with a 5 or 10% change in response (BMDL₅ or BMDL₁₀) can provide a useful basis for comparison. Luebker et al. estimated a BMDL₅ for PFOS and birth weight in rats of 0.39 mg/kg/day, equivalent to a rat fetal serum concentration of about 34 μg/mL (15). Butenhoff et al. reported BMDL_{10s} for several postnatal developmental endpoints for PFOA in rats, ranging from 22 to 44 mg/kg/day, equivalent to rat fetal serum concentrations from 29 to 59 μg/mL (51).

By contrast, maximum concentrations in our study were 0.035 μg/mL (PFOS) and 0.007 μg/mL (PFOA). Thus, the serum concentrations of these compounds associated with developmental effects in rats are several orders of magnitude higher than what was observed here.

Our findings confirm the presence of *in utero* exposure to PFOS and PFOA, and less so, to other PFCs under study. Our data suggest that exposure is occurring among babies born in the Baltimore area, although the cord serum concentrations are lower than those reported among adults in the United States. Concentrations of PFOS and PFOA were highly correlated, possibly due to common pathways for exposure. Further, *in utero* serum concentrations of PFOS appear to be higher in Asian and Black babies when compared to White babies. What was most surprising was a lack of association between PFOS and PFOA concentrations and maternal age, socioeconomic status, and inner city residence (urban vs suburban exposures). The finding that levels were higher among obese and underweight mothers is interesting but does not have an obvious explanation. Further research to identify sources, transport, fate, and pathways of exposure to PFOS and PFOA to mothers should concentrate on general exposures, such as drinking water and commonly eaten foods. The fact that PFOA (and possibly PFOS) concentrations are slightly decreased with increased parity of mothers implies that maternal–fetal transfer may be reducing maternal stores. However, a recent study has indicated that levels of these compounds in human milk are quite low (52). Thus, direct transfer during pregnancy may result in a reduction in the quantities transferred for subsequent pregnancies. Future studies are needed to examine the extent of maternal–fetal transfer of these compounds.

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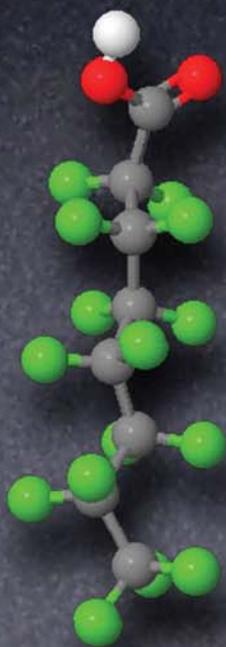
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ATTACHMENT 5



PERFLUOROALKYL ACIDS

What Is the Evidence Telling Us?

It was 2000 when the scientific community first became widely aware that perfluorooctanyl sulfonate (PFOS), then the key ingredient in 3M Company's popular Scotchgard stain repellent, was being found at extremely low levels throughout the environment and the human population. Since that time, environmental scientists and toxicologists have begun paying much more attention to PFOS, its sister compound perfluorooctanoic acid (PFOA; known for its use in DuPont's Teflon products), and other members of the family of perfluoroalkyl acids (PFAAs). As more tests have been conducted, the research has revealed that laboratory animals respond in vastly different ways to PFAAs and related compounds, which can make it difficult to pinpoint the mechanisms underlying the responses. However, toxicologists are making headway in their understanding of these compounds, an important fact in light of new research suggesting that the levels being found in both people and animals may have an impact on their health.

The tremendous variation in the speed with which humans and laboratory animals can eliminate PFOA is one example of why understanding how the compounds are processed in the body poses such a formidable challenge. "You go from hours for the female rat, to days for the male rat, to months for the monkey, to almost four years in humans," explains Jennifer Seed, a branch chief with the EPA Office of Pollution Prevention and Toxics.

"We truly don't understand what are the biological events that drive this difference," says Christopher Lau, a lead research biologist with the EPA National Health and Environmental Effects Research Laboratory (NHEERL). "Are there binding protein differences? Do humans have a different set of transporters that is not the same as in animals?" Lau terms these gaps in understanding "a black hole."

These gaps render the toxicologist's goal of extrapolating from one species to another "a very complex state of affairs," as Seed puts it. For this reason, deciphering the human risk posed by exposure to PFAAs is a major challenge, Lau says. "We need to go to the next level to identify the underlying events that drive the adverse effects," he says.

Anatomy of a PFAA

The compounds used in commercial perfluorinated formulations are sometimes identified by the number of carbon atoms they contain. In general, the longer the carbon chain length, the more the PFAA persists in the body, according to Naomi Kudo, an associate professor of toxicology and applied pharmacology at Josai University in Japan. For example, perfluorobutane sulfonate (PFBS), which has 4 carbons, is eliminated in a little over 1 month in humans, on average, while PFOA and PFOS (so-called C8 compounds with 8 carbons each) are eliminated in 3.8 and 5.4 years, respectively. Perfluorohexane sulfonate (PFHxS), with 6 carbons, is an exception to the rule; it is eliminated in 8.5 years.

3M no longer manufactures PFOS, and the compound is now used only in relatively small quantities for applications for which there is no acceptable substitute, such as in semiconductor manufacturing. All eight of the companies currently using PFOA—Arkema, Asahi, Ciba, Clariant, Daikin, DuPont, 3M/Dyneon, and Solvay Solexis—have agreed to reduce PFOA releases and levels in products by 95% by 2010 and to eliminate their use by 2015.

The new compounds being introduced to replace PFOA and PFOS fall into three general groups: the perfluoroalkyl sulfonates (a group that includes PFOS), the perfluoroalkyl carboxylates (including PFOA), and the fluorotelomer alcohols, which are used to produce perfluorinated surfactants and polymers for products including hair care products, paper products used in direct contact with food, rug cleaners, and lubricants for bicycles, garden tools, and zippers, according to the nonprofit Environmental Working Group. 3M is building its new PFAA products around compounds containing fewer carbons, including PFBS, because of their shorter half-lives in humans, says John Butenhoff, a corporate scientist in toxicology for 3M's Medical Department.

But some of the new replacement compounds may pose problems of their own. More than 20 different such compounds were discussed at a 14–16 February 2007 meeting of the Society of Toxicology (SOT) on the toxicokinetics and mode of action of PFAAs and related chemistries. For example, fluorotelomer alcohols are emerging as the main remaining source of PFOA in the environment. These and other “residual”



Human exposure to PFAAs comes through myriad sources including contaminated drinking water and household products treated with stain or water repellants.



compounds can be transformed into PFOA or PFOS as the result of metabolism or environmental biodegradation. In a presentation at the SOT conference, Butenhoff noted that 1% of the total dose of 8-2 fluorotelomer alcohol given to laboratory rats is metabolized to PFOA. Similarly, other researchers have observed that *N*-ethyl-*N*-(2-hydroxyethyl)perfluorooctanesulfonamide, a constituent of coatings used on paper and cardboard, can be transformed into PFOS in the environment. It also may produce PFOA in the atmosphere.

Other PFAAs being detected in the environment are also receiving more attention. The CDC detected not just PFOS and PFOA but also PFHxS, perfluorononanoic acid, and perfluorooctane sulfonamide in every U.S. human blood sample from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) that was

analyzed for PFAAs, according to Antonia Calafat, a lead research chemist at the CDC's National Center for Environmental Health. In a paper in the 1 April 2007 issue of *Environmental Science & Technology*, CDC researchers also reported finding two compounds used in surfactants and coatings on fabric, paper, and upholstery—2-(*N*-ethyl-perfluorooctane sulfonamido) acetic acid and 2-(*N*-methyl-perfluorooctane sulfonamido) acetic acid—in more than 90% of the samples, she says. Similarly, perfluorobutyrate (a 4-carbon compound) has been detected in surface water and public and private wells. Lau adds that PFOS and PFOA have been found at locales near PFAA production plants and waste disposal facilities.

Polar Bears, Pandas, and People

Although a growing body of research is focused on other PFAAs, PFOA and PFOS have been the subject of the lion's share of study to date. Both compounds are found throughout the environment—from polar bears living in Greenland, to giant pandas in China, to albatrosses on the Midway Atoll in the middle of the Pacific Ocean. The compounds are also widely dispersed in surface waters, according to 3M.

At the SOT meeting in February, researchers from the New Jersey Department of Environmental Protection (NJDEP) reported detecting PFOA in drinking water samples from 78% of 23 treatment plants sampled and PFOS in samples from 57% of the plants. The finding prompted the NJDEP to recommend in February 2007 that the state move toward regulating PFOA in water. Currently New Jersey recommends that the concentration of PFOA in drinking water be less than 0.04 ppb.

This value is significantly lower than the Site-Specific Action Level of 0.5 ppb developed by the U.S. EPA as part of a consent order in 2006 with DuPont for drinking water in Ohio and West Virginia impacted by DuPont's Washington Works facility in West Virginia. (This action level applies only to the DuPont–West Virginia settlement; there is no federal standard for PFOA in drinking water.) The highly publicized C8 Study conducted by Edward Emmett and colleagues the University of Pennsylvania has examined drinking water exposures to PFOA among Ohio and West Virginia residents living near the Washington Works plant. At the



PFAAs are ubiquitous in the environment, found on every continent in the world, in numerous mammal, fish, and bird species.

start of the study, the PFOA concentrations in the blood serum of residents in Little Hocking, Ohio, were up to 89 times higher than the U.S. average, according to a report by Emmett in the August 2006 *Journal of Occupational and Environmental Medicine*. At press time, investigators on the study expected any day to release results of whether use of bottled drinking water had reduced these concentrations.

The NJDEP findings “suggest that PFOA is commonly present in public water systems not known to be specifically contaminated by a point source,” says Gloria Post, a toxicologist with the department. Additionally, Emmett’s *Journal of Occupational and Environmental Medicine* paper indicates that even low concentrations of PFOA in drinking water may significantly contribute to levels found in the general population.

People can also be exposed to PFOA and PFOS due to poor disposal practices. In Germany, industrial waste contaminated with high concentrations of PFAAs was mixed with soil by a recycling company. Although the amended soil was later declared illegal as a “soil improver,” it was nonetheless used by farmers in the Arnsberg

agricultural area in the country’s North Rhine–Westphalia state, according to Martin Kraft of the state’s Ministry of the Environment and Conservation, Agriculture, and Consumer Protection. When Kraft and his colleagues analyzed how PFOA and PFOS had spread through the environment, they found concentrations of the two compounds together reached 148 ppb in surface waters and 0.6 ppb in drinking water, according to a poster he presented at the SOT meeting. The concentrations in edible fish including trout, chub, and eel reached as high as 1.2 ppm, with a median of 133 ppb. In comparison, similar fish from unpolluted waters contained an average of 4 ppb.

PFOA was the predominant compound detected in serum from the area’s people, whose average serum levels of the compound were 6 to 8 times higher than an unexposed region of the country, Kraft says. In a German-language government document published 15 March 2007, Kraft and his colleagues reported that the average serum PFOA concentration in Arnsberg children was 22.1 ppb, in women it was 24.9 ppb, and in men it was 27.4 ppb.

For the U.S. population, CDC researchers analyzed NHANES samples

collected in 1999–2000 to produce the first nationally representative survey of PFAAs, and these data are meant to serve as a baseline, Calafat says. The average concentration of PFOS in the 1,562 serum samples collected from people aged 12 years and older was 30.4 ppb, whereas the average concentration of PFOA was 5.2 ppb. The levels in men were slightly higher, on average, than those in women, and the people with the highest levels of the compounds also were the most educated.

PFOA and PFOS have also been detected in human breast milk and babies’ blood. A Swedish study in the February 2007 issue of *EHP* calculated that the total amount of PFAAs transferred to breastfeeding infants was approximately 200 ng/day.

3M researchers have collected some evidence that the company’s decision to phase out production of materials including PFOS and greatly reduce its use of PFOA by the end of 2002 was already beginning to affect levels of the compounds three years later. In a pilot study published in the May 2007 issue of *Chemosphere*, 3M researchers compared concentrations of PFOA and PFOS in plasma samples taken from 40 American Red Cross donors in the Minneapolis–St. Paul area in 2005 with 100 samples taken five years earlier from the same general population. They found that the average concentrations of both PFOA and PFOS in the donor samples dropped by more than 50% over that five-year period, says Geary Olsen, a staff scientist with 3M’s Corporate Occupational Medicine Department.

The information gleaned from 3M’s pilot study is not directly comparable to the PFAA data from the 1999–2000 NHANES because it is a random sample and not statistically representative of the U.S. population, Olsen acknowledges. However, he points out that a study of concentrations of PFOA and PFOS in American Red Cross donations in six cities in 2000, which was published in the December 2003 issue of *EHP*, produced numbers that were nearly identical to what the CDC has reported for the same time frame. 3M has just completed analyzing the samples from a follow-up study conducted in 2006 that involves samples from the same six cities and expects to submit them for publication later this year. The company hopes these new data will validate the drops in PFAA concentrations seen in the pilot study, Olsen adds.

Health Effects in Animal Studies

In animal studies, toxicologists have seen that high doses of both PFOS and PFOA cause cancer, physical development delays, endocrine disruption, and neonatal mortality. This



Laboratory mice exposed prenatally to PFOS and PFOA develop more slowly and suffer a higher rate of neonatal mortality than nonexposed mice (left). Once PFOA-exposed mice reach adulthood, however, they are more likely to become obese (above).

last effect is arguably the most dramatic result of laboratory animal tests with PFOS and PFOA. “Animals are born, they look quite healthy and pink, and then they die quite rapidly,” Seed says. Other studies show that the compounds can impact growth and development and disrupt the body’s hormone and immune systems.

In older animals, toxicological studies have shown that the compounds cause liver and pancreatic tumors. A number of studies have demonstrated the ability of both PFOS and PFOA to bind to peroxisome proliferator-activated receptors (PPARs), a class of receptors associated with carcinogenesis. In addition to being investigated as a cause of the cancers seen in laboratory animals, PPAR activation is believed to affect fetal growth and immune function.

Much of the research conducted to date has focused on the ability of PFAAs to act as PPAR agonists by triggering a response to a key receptor isoform, PPAR- α . New research is beginning to show that the compounds affect other aspects of the body’s biochemistry, Seed says; in fact, both PFOA and PFOS may have multiple mechanisms of action.

By working with mice genetically engineered not to contain PPAR- α , Barbara Abbott, a research biologist at NHEERL, implicated that isoform in the neonatal mortality caused by PFOA exposure. Because PFOA is a fairly potent PPAR- α agonist (much more so than PFOS), the work suggests that different mechanisms are responsible for the PFOS-induced neonatal mortality seen in animals. “Both PFOS and PFOA cause neonatal mortality, and it is tempting to suggest that they have the same mode of action, but in reality, they may not at all,” points out John Rogers, chief of the Developmental Biology Branch of the NHEERL Reproductive Toxicology Division.

At the SOT meeting, Kudo presented research showing that the way male rats process low doses of PFOA differs from how they process high doses. These studies show that the compound is preferentially taken up by the liver and is more likely to be excreted from the liver into the bile only at higher doses. Kudo’s research may help account for why 3M plant workers exposed to low doses tended to retain the compound in their bodies

for such long periods, while laboratory rats exposed to high doses quickly removed the compound from their bodies, she says. The work may also explain why female rats can rid their bodies of PFOA so much more quickly than males can, according to Butenhoff.

Scientists have also made some progress in understanding how PFOA and PFOS cause neonatal mortality in laboratory mice. Researchers at the EPA have determined that newborn mice treated with these substances that appeared to be unable to breathe were biochemically mature and genetically normal, Rogers said at the SOT meeting. The latest hypothesis is that PFOS may impede the function of the endogenous pulmonary surfactant needed to inflate the lungs, he says.

The Human Health Impact

What does all this mean for human health? To provide a more useful context for comparing human data with the insights derived from animal

studies, researchers working with laboratory animals should be determining the concentrations of PFAAs in the bodies of their test subjects, rather than simply reporting the administered dose, stresses Melvin Andersen, director of the Computational Biology Division of The Hamner Institutes For Health Research.

Although most of the studies showing adverse effects in laboratory animals involved much higher levels of PFOS and PFOA than are actually being seen in humans and other animals, as-yet unpublished research conducted at environmentally relevant concentrations suggests that exposure at such levels may have an effect on humans.

Researchers at The Johns Hopkins University found PFOA in 100% and PFOS in 99% of 297 serum samples collected in 2004 and 2005 from the umbilical cords of children born in Baltimore, according to Lynn Goldman, a pediatrician and epidemiologist at the Bloomberg School of Public Health. Overall, the levels were lower than in adults, but the highest concentration of PFOS detected was 34.8 ppb, says Goldman, who stresses that



Prenatal exposure to PFOS and PFOA has been correlated with changes in body weight and head circumference in human infants. Postnatal exposures, as through breastfeeding, have unknown effects.



these unpublished results need to be confirmed. The source of the PFOA and PFOS in the infants' blood was unclear, though research published online 12 January 2007 in the *International Archives of Occupational and Environmental Health* suggests that transplacental transfer may account for it.

In addition to revealing a statistically significant correlation between infants born with higher levels of PFOS and PFOA and decreased birth weight and head circumference, the Johns Hopkins study unearthed a correlation between the compounds and the scores the babies earned on the ponderal index, which measures fetal body mass and can serve as a rough approximation of nutritional status. "The lower the ponderal index, the higher the [cord serum] PFOS and PFOA [concentrations]," Goldman says. Other studies have suggested that low birth weight may be a risk factor for obesity, diabetes, and cardiovascular diseases later on.

The Johns Hopkins researchers also correlated the babies' PFOA (but not PFOS) concentrations with their total circulating thyroxine levels, Goldman says. Higher concentrations of PFOA and PFOS were linked with longer gestational periods, as well. This raises the question of whether these compounds are transported more readily later in pregnancy, or accumulate with the fetus during pregnancy, says Goldman.

Unlike the CDC study, the Johns Hopkins research did not find any correlation between the socioeconomic status of

the parents and the children's blood PFOA and PFOS concentrations, which Goldman says is "quite remarkable." Because the babies were born into families from a wide socioeconomic range, and because other research points to consumer products as the source of the compounds, Goldman says the new study suggests that if consumer products are the source, "they are the ones everyone in our [study] group is using."

Given the association in Goldman's research of higher levels of PFOS and PFOA with lower ponderal index scores, some researchers wonder if this finding could tie in with new evidence connecting high levels of PFOA in rodent pups to obesity later in life. The research to date shows that the offspring of exposed pregnant mice have a dose-related increase in obesity, Rogers explains. "By the time they're obese," he says, "they have very little remaining PFOA and their liver is back to normal size."

One hypothesis for why this is happening is that PFOA could be acting as a hypolipidemic agent in increasing fatty acid metabolism, according to Rogers. In other words, the PFOA treatment is "essentially asserting an [undernourished] environment *in utero*."

"We know that these compounds affect fatty acid metabolism," Seed says. "Maybe something is happening in the developing organism that is interfering with the program of energy metabolism."

Rogers says this fits with what is known as fetal programming syndrome in human infants, in which children who experience a prenatal environment chronically short of nutrients and are then reared with an abundance of food are more likely to become overweight. "Whatever is happening that mediates its effects on lipid metabolism, whether through PPAR- α or otherwise, could be very important," he says. "We know very little about what's going with the fetus in terms of metabolic programming. The environment, in a very critical period of development, might affect metabolism or shift metabolism for a lifetime."

However, Lau points out that PFOA is but one of a number of environmental contaminants that are being linked to adult obesity. Follow-up research is in order to more carefully pinpoint the events that lead to obesity, perhaps by looking at gene expression or protein markers for adipogenesis earlier in test animals' lifetimes.

More research is needed, agrees Suzanne Fenton, the EPA research biologist who conducted most of the research linking prenatal PFOA exposure in mice with adult obesity. She says the latest data suggest this effect is being seen at dosages below 1 mg of PFOA per kg of body weight (the actual amount of PFOA in the animals' blood was not determined). Her studies also revealed PFAA-induced abnormalities in other mouse tissues, including the ovaries, mammary glands, and spleen.

Immunotoxicity: The Case of Atlantic Dolphins

In light of research suggesting that PFOA and PFOS both cause potent suppression of the adaptive immune system, in 2006 the EPA Science Advisory Board called for immunotoxicity to be the subject of more study. The EPA is currently conducting such studies and has replicated findings showing that PFOA suppresses the primary immune response, says Robert Luebke, a research biologist with the NHEERL Immunotoxicology Branch. The researchers are looking for PPAR- α activity, but there are some indications that something else may be going on, he says. He and his colleagues have noticed that the adrenal glands of treated mice are somewhat enlarged, which fits with reports that corticosteroid levels rise in PFOA-treated animals.

The first research to suggest that the levels of PFAAs being detected in wild animals could be impacting their immune systems involved bottlenose dolphins believed to have “the highest [PFOS levels] ever reported in any wildlife species,” according to Margie Peden-Adams, an assistant professor at the Medical University of South Carolina Department of Pediatrics and Marine Biomedicine and Environmental Science Center. At the SOT meeting, she presented a poster discussing her work with an international team that analyzed

blood samples collected from 89 dolphins living near Charleston, South Carolina, and Indian River Lagoon, Florida. The animals harbored concentrations of PFOA that were approximately twice the levels that the CDC found in U.S. citizens, but their average levels of PFOS were 20 to 40 times higher, according to an analysis published by a team of University of Guelph researchers in the 1 October 2006 edition of *Environmental Science & Technology*.

In conjunction with collaborators at Clemson University and the Mystic Aquarium, Peden-Adams helped develop a suite of assays to test immune function in the bottlenose dolphin. “We did not find overwhelming suppression [associated with PFAAs],” she says. For example, the researchers observed no alterations in T-cell proliferation or NK-cell activity. However, lysozyme activity was suppressed, B-cell proliferation was stimulated, and numbers of various lymphocytes increased. “The immune system is very compensatory, and often when one thing is suppressed, another thing may be increased,” she says.

“It is important to note that any deviation on the continuum of possible immune effects from normal homeostasis is considered an alteration,” Peden-Adams stresses. “Suppressed immune function can lead to increased vulnerability to pathogens, but enhanced immune function can be detrimental as well, leading to

hypersensitivity reactions, allergy, and autoimmune reactions.”

For comparison, Peden-Adams and her colleagues dosed B6C3F1 mice with PFOS at concentrations comparable to those found in the dolphins. “The effects on antibody production seen in the mice are what would be expected based on studies with PFOA and PFDA [perfluorodecanoic acid] and . . . occurred at environmentally relevant exposure levels as compared to control animals,” she says. This new research is noteworthy because no studies to date have determined the immune effects of PFOS, and “no other laboratories we are aware of are assessing [these effects],” Peden-Adams says.

Next Up for PFAA Research

The toxicological research conducted to date with PFAAs shows “profound changes in the biochemistry of [test] animals,” Andersen says. “I believe that enough work has been done to have a hypothesis that most of the responses are coming from some receptor-mediated processes.” Andersen therefore proposes that it makes sense for the research community to move forward with low-dose studies that attempt to look for genetic or genomic changes associated with effects such as immunotoxicity and reproductive toxicity. Rogers agrees, although he points out that such low-dose studies can be very difficult to conduct because the effects are more subtle, and carrying them out can involve the use of hundreds of test animals.

“Doing more human population studies is another approach,” says Goldman, who adds that closer collaboration between toxicologists and epidemiologists would aid such an effort immensely. In animal studies, toxicologists can “look directly at biomarkers and molecular changes in the brain, kidney, and the liver—anywhere they wish—whereas in human studies, we are limited by what is available without creating an excessive burden on research subjects,” she says.

“If we’re going to bring the fields closer together, we need to have human epidemiological research that is focusing more on mechanisms,” Goldman adds. For example, she says that environmental health research would be much more relevant to epidemiologists if toxicologists would work toward identifying biomarkers in human serum that are indicative of risk. “If we’re interested in what the effects are in humans, then one of the things I think we need to do better is to begin thinking about modes of action in people as well as toxicology,” she concludes.

Kellyn S. Betts



Studies of bottlenose dolphins with some of the highest levels of PFOS reported in wild animals indicate that the chemical may affect immune function.

ERRATUM

ERRATUM

In the May Focus article, “Perfluoroalkyl Acids: What Is the Evidence Telling Us?” [Environ Health Perspect 115:A250–A256 (2007)], the caption on page A254 should have read “Once PFOA-exposed mice reach adulthood, however, they are more likely to become obese (above)”; PFOS (perfluorooctanyl sulfonate) exposure *in utero* has not been linked to later obesity in laboratory animals. In addition, the caption on page A255 may be interpreted as implying causality between prenatal exposure to PFOS and PFOA (perfluorooctanoic acid) and altered body weight and head circumference in human infants. This was not *EHP*'s intention. In fact, although an association has been shown, causality has not been established. On the same page, the journal identified as *Archives of Occupational and Environmental Health* is actually *International Archives of Occupational and Environmental Health*.

EHP regrets the errors.