



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

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National Institute of Environmental Health Sciences  
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*Rec'd 8/15/03 SAM*

Dear Dr. Masten:

On behalf of the U.S. EPA Office of Pollution Prevention and Toxics (OPPT), I am submitting a nomination for consideration by the National Toxicology Program (NTP) to conduct studies on a series of perfluorinated chemicals.

OPPT has been assessing perfluorinated compounds since 1999. This interest was prompted by reports submitted to the agency describing the toxic properties and widespread presence in the environment, including in human populations, of some of these chemicals. Initial efforts focused on perfluorooctane sulfonate (PFOS), and the assessment of ecological and human health hazards was recently published under the auspices of the Organization for Economic Cooperation and Development (OECD, 2002). In general, PFOS is persistent and does not biodegrade in the environment. It bioaccumulates in fish, and the half-life in humans is estimated to be on the order of years. Biomonitoring studies have shown that PFOS is present in humans and wildlife around the world. The toxicity profile of PFOS is consistent in mice, rats and monkeys, and includes liver toxicity, hypolipidemia, liver tumors, and developmental toxicity. In all species and life stages, there is a very steep dose-response curve for mortality which appears to be related to the cumulative internal dose. The U.S. EPA Office of Research and Development has been investigating the mode of action of the neonatal mortality associated with prenatal exposure to PFOS for several years.

Subsequent efforts have focused on perfluorooctanoic acid (PFOA). The ecological and human health hazards of PFOA have been summarized (OPPT, 2002), and a preliminary risk assessment of the developmental effects has been released (OPPT, 2003). PFOA is also persistent and does not biodegrade. In contrast to PFOS, PFOA does not bioaccumulate in fish. However, it also has a half-life of years in humans, and domestic biomonitoring studies have shown that it is present in the general population, as well as in wildlife. The toxicity of PFOA has been studied in rats, mice and monkeys, and includes liver toxicity, immunotoxicity, cancer (liver, pancreatic, and leydig cell tumors), and developmental toxicity. The uncertainty in the quantitation of potential human risks is compounded by a substantial gender difference in the elimination rate of PFOA in rats. Since the release of the hazard assessment and the preliminary risk assessment, industry has conducted detailed pharmacokinetic studies in adult rats and monkeys. In addition, studies to elucidate the ontogeny of the gender difference in elimination are currently underway.

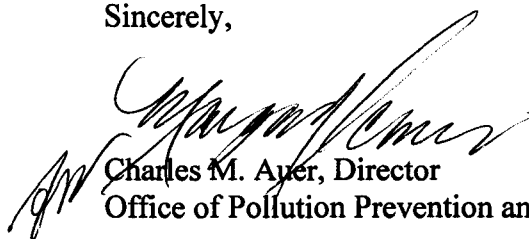
Biomonitoring studies have shown that PFOS, PFOA and several other perfluorinated compounds are present in the serum of the general domestic population. To further understand the distribution of exposure across the country, the U.S. EPA recently nominated several perfluorinated chemicals to CDC for inclusion in the next NHANES survey. A decision by CDC is expected sometime soon. Unfortunately, the sources and pathways of exposure are unknown. This is problematic for any exposure reduction activities in this multi-billion dollar industry. To address this large area of uncertainty, OPPT is currently negotiating Enforceable Consent Agreements (ECAs) with industry groups (FR Notice, April, 2003). This particular ECA process focuses on PFOA and the C10 telomer which may degrade to PFOA, and will, if successful, provide some information on environmental fate, exposure pathways, and some environmental biomonitoring data.

To date, extensive toxicity information is only available for PFOS and PFOA. Yet, the class of perfluorinated compounds is quite large, and includes straight chain, as well as branched chain compounds. Some of these compounds have already been shown to be present in human serum, and the production of some of these compounds may increase if they prove suitable as replacements for PFOS in the marketplace. Therefore, OPPT is nominating a class study of the perfluorosulfonates and carboxylic acids, as well as the telomer derivatives. The latter are potential precursors of perfluorinated acids. This category would include C4 and higher compounds. Due to the unique kinetic properties of the C8 compounds and the substantial gender differences in elimination of PFOA in rats, it is recommended that pharmacokinetic studies on representative members of the different classes of chemicals be conducted first to help inform decisions about which chemicals to focus on and the appropriate animal model for toxicology studies. Initial efforts would focus on a subset that would include even and odd chain length compounds of defined isomeric composition. The inclusion of appropriate mechanistic endpoints in the kinetic studies such as protein binding, PPAR $\alpha$  activation, etc., would optimize utilization of resources. Such mechanistic information would also better inform decisions on specific compounds that would move forward for toxicology studies or for

evaluation of specific organ systems. In addition, these efforts will benefit from concurrent collaborative research between NTP and the U. S. EPA Office of Research and Development (NHEERL/RTP) laboratories on the mechanisms of toxicity of perfluorinated organic chemicals. This collaboration offers the opportunity to further extend the value of NTP's research investment by sharing information (generated from the NTP effort) that will greatly promote the understanding how these compounds may act and overall increase the effectiveness of the perfluorinated chemicals research program.

Thank you for your consideration of this class study. If you have any questions or need additional information, please contact Oscar Hernandez at 202-564-7641 or Jennifer Seed at 202-564-7634.

Sincerely,



Charles M. Ayer, Director  
Office of Pollution Prevention and Toxics

Attachments: OECD, 2002 - Hazard Assessment of Perfluorooctane Sulfonate (PFOS) and its Salts  
OPPT, 2002 - Draft Hazard Assessment of Perfluorooctanoic Acid (PFOA) and its Salts  
OPPT, 2003 - Preliminary Risk Assessment of the Developmental Toxicity Associated with Perfluorooctanoic Acid and its Salts  
FR notice - Perfluorooctanoic Acid (PFOA), Fluorinated Telomers; Request for Comment, Solicitation of Interested Parties for Enforceable Consent Agreement Development, and Notice of Public Meeting

cc: Oscar Hernandez  
Jennifer Seed  
William Farland  
Margaret Schneider

## **Attachments to EPA/OPPT Nomination of Perfluorinated Compounds**

OECD, 2002. Hazard Assessment of Perfluorooctane Sulfonate (PFOS) and its Salts. Available at <http://www.oecd.org/dataoecd/23/18/2382880.pdf>

OPPT, 2002. Revised Draft Hazard Assessment of Perfluorooctanoic Acid (PFOA) and its Salts. Available at [http://cascade.epa.gov/RightSite/getcontent/Tempfile.pdf?DMW\\_OBJECTID=090007d4801572b2&DMW\\_FORMAT=pdf](http://cascade.epa.gov/RightSite/getcontent/Tempfile.pdf?DMW_OBJECTID=090007d4801572b2&DMW_FORMAT=pdf)

OPPT, 2003. Preliminary Risk Assessment of the Developmental Toxicity Associated with Perfluorooctanoic Acid and its Salts. Available at <http://www.epa.gov/opptintr/pfoa/pfoara.pdf>

EPA, 2003. Federal Register Notice: Perfluorooctanoic Acid (PFOA), Fluorinated Telomers; Request for Comment, Solicitation of Interested Parties for Enforceable Consent Agreement Development, and Notice of Public Meeting. Available at <http://www.epa.gov/opptintr/pfoa/pfoafr.pdf>

## **Proposal for Perfluorinated Compounds Class Study**

### **Introduction**

EPA proposes a class study that would comprise a series of chain lengths ranging from C6 to C12 of fluoroalkyl sulfonates, fluorocarboxylic acids, and fluorotelomeric alcohols. The chain lengths selected are based on existing knowledge of the uses, exposures and toxicology of these compounds. The fluoroalkyl sulfonates (C6 - C12) and their derivatives were predominantly intermediates for the polymeric products used as water, oil, and stain treatments for carpet, paper, and textiles. A few product lines were developed to use the surfactant properties including metal working fluids, fire fighting foams, and photographic additives. The C6 and C8 product lines were the dominant materials manufactured. Some higher homologs as well as other residual organic fluorides have no commercial use but are components of the formulated final products. Ultimately the sulfonates may be the degradation chemicals from the corresponding polymeric products. The fluorocarboxylic acids have chemical properties that make them useful as additives and surfactants, the chief use being as a processing aid for the polymerization of fluoropolymers (polytetrafluoroethylene, polyvinylidene fluoride). The fluorocarboxylic acids or their simple derivatives have also been used as additives in fire fighting foams, electronic circuit and photographic film manufacturing. The C6 and C8 are the predominant commercial products, although others, including the C9, are also commercially used. The 8:2 and 10:2 fluorotelomeric alcohols (perfluoroalkyl ethanols) are the building blocks (and the anticipated abiotic degradation products) for most of the polymeric products used as carpet, paper and textile coatings to impart water, oil, and soil repellency. The alcohols have no substantial market apart from chemical intermediates.

Toxicology studies of the C4 fluoroalkyl sulfonate (PFBS), the C8 fluoroalkyl sulfonate (PFOS) and the C8 fluorocarboxylic acid (PFOA) indicate that chain length is an important factor in toxicity, perhaps partially due to pharmacokinetic factors; toxicity and persistence appears to increase with increasing chain length. Human biomonitoring studies have shown that the C6 perfluorosulfonate, PFOS and PFOA are present in the serum of the general US population, and that the levels of the C6 perfluorosulfonate are quite high in children. Other chain lengths have not yet been monitored in the general population. Environmental monitoring studies have demonstrated the presence of the entire series of perfluorinated compounds, as well as some higher homologs. Current hazard and risk assessments have addressed individual chemicals. If there is a common mode of action for these chemicals the latter efforts are likely to underestimate potential hazard and risk to exposed populations.

### **Rationale for Specific Studies**

A summary of the recommended chemicals and studies is provided in Table 1. The recommended sequence is to begin with the lower chain lengths followed by the higher homologs. The rationale for these studies is provided below.

**Table 1. Summary of Proposed Studies<sup>1,2</sup>**

Chemical	Pre-chronic range finding	Pharmacokinetics	Modified one-generation reproductive toxicity study	2-year bioassay with in utero exposure
C6 sulfonate	XXX	XXX	XXX	
C9 sulfonate	XX	XX	XX	
C10 sulfonate	XX	XX	XX	
C12 sulfonate	X	X	X	
C6 carboxylic acid	XXX	XXX	XXX	
C8 carboxylic acid				XXX
C9 carboxylic acid	XX	XX	XX	
C10 carboxylic acid	XX	XX	XX	
C12 carboxylic acid	X	X	X	
Telomer alcohol 8+2	XXX	XXX	XXX	
Telomer alcohol 10+2	X	X	X	

- 1- The number of X's denotes the recommended sequence - XXX denotes the highest priority.
- 2- Selection of appropriate animal model to be determined during study design but it is anticipated that studies in both sexes of rats and mice will not be necessary for each "cell" in table.

Extensive pharmacokinetic information is available for PFOS and PFOA and more limited information is available for PFBS. The existing information for PFOS and PFOA suggest the following issues may be critical determinants of pharmacokinetics and blood dosimetry for other members of the class:

- These compounds are well absorbed.
- The carboxylic acids and sulfonates are cleared by urinary and biliary elimination in rodents with no evidence of metabolism, while the telomer alcohols are metabolized apparently to carboxylic acid derivatives. Extensive enterohepatic recirculation has been demonstrated for both PFOA and PFOS.
- Species and sex differences in clearance are most dramatic for PFOA (female rat (hrs)>>male rat (days)>mouse>monkey (weeks)>human (years)). PFOS demonstrates higher blood levels in female rats than males following repeated exposures and the clearance during week 105 was faster than older intravenous and oral studies would predict. PFBS is rapidly eliminated in several hours in rats. The mechanism(s) for species and sex variation in clearance is ill-defined but may in part be related to differential expression of renal transport proteins.
- Serum protein binding (generally albumin) is extensive resulting in high concentrations in serum. Liver has very high concentrations as well, followed by kidney. Other tissues have generally low concentrations (and the fluorination make this a non-lipophilic compound), but account for a significant fraction of the mass in the body.

Blood concentrations of perfluorinated hydrocarbon compounds play a critical role in the interpretation of animal toxicity data with respect to differences among members of this class and cross-species comparisons with measured levels in human blood. As a broader range of

compounds in this class are addressed, EPA considers it essential to develop adequate data to support risk assessment activities based upon blood concentrations. This reflects, in part, the increasing ability to measure these compounds in human blood (e.g. NHANES), as well as the difficulty in reconstructing the exposures leading to these blood levels. In addition, it reflects the observations with PFOA indicating dramatic differences in urinary elimination in male and female rats, while early indications are that mice clear the compound much more slowly; humans are apparently even slower still. Thus, default methods using exposure doses and  $BW^{0.75}$  scaling (or  $UFa=10$ ) currently appear particularly uninformative and inappropriate for this class of compounds making the focus on blood dosimetry critical.

Blood dosimetry is a valuable surrogate for target organ dosimetry because the target organs for the perfluorinated compounds are only partially identified, particularly for developmental effects in contrast to adult liver and kidney toxicity and because it is measurable in humans. It is generally measured as plasma levels. Data required to support analyses based upon blood dosimetry (and potentially target organ dosimetry) are of two overall kinds. First, measurements of blood and tissue levels in animals in the various repeated exposure toxicity studies (or satellite groups, particularly for mice) provide direct data on the exposures in the toxicity studies, at a minimum at terminal sacrifice. Such data should be routinely a part of all study designs for this class of chemicals. Second, pharmacokinetic studies provide time course data following controlled exposures. Pharmacokinetic issues related to different species, repeated dosing, and life stages in the relevant toxicity studies will need to be addressed. The combination of these two kinds of data provide the information needed to construct classical or physiologically-based pharmacokinetic models for use in interspecies extrapolation for data interpretation and risk assessment.

There is extensive toxicology information available on PFBS, PFOS and PFOA. Studies of PFOS and PFOA have shown that the developing organism is a primary target. A two-generation reproductive toxicity study of PFOS in rats, and several subsequent studies in rats and mice, have shown a very high incidence of mortality in the F1 offspring in the first few days following birth. A two-generation reproductive toxicity study of PFOA in rats has demonstrated mortality in the F1 offspring in the first few days following weaning, as well as a delay in sexual maturation. Preliminary studies of PFOA in mice have shown a mortality pattern very similar to that observed following exposure to PFOS in that mortality occurs in the first few days after birth. In contrast, these effects were not noted in a two-generation reproductive toxicity study of PFBS in rats or a limited one-generation toxicity study of C6 perfluorosulfonate in rats. To date, there is no information on developmental effects following exposure to chain lengths greater than C8.

Given that the postnatal developmental outcomes are a key feature of PFOS and PFOA, it is crucial that we understand the impact of chain length on developmental endpoints. The two-generation reproductive toxicity studies of PFOS and PFOA have shown that there are no unique effects in the F2 generation. Therefore, we are proposing a modified one-generation toxicity study which would include following the F1 generation up to a minimum of 70 days and assessing the endpoints that are typically assessed in the two-generation reproductive toxicity study, including full histopathology assessments. Assessments of developmental neurotoxicity and immunotoxicity should also be considered for inclusion in the one-generation toxicity

studies. In addition, serum and tissue levels of the administered chemical need to be determined at appropriate timepoints as described above.

In addition, several of the compounds in the proposed series are peroxisome proliferators, and PFOS and PFOA have been shown to be carcinogenic in rats. Chronic studies of PFOA in rats have shown the presence of hepatocellular, Leydig cell and pancreatic acinar cell tumors. PFOA is a demonstrated PPAR- $\alpha$  agonist and this has been hypothesized to be the mode of action for the hepatocellular adenomas. Chronic exposure of PFOS in rats is also associated with hepatocellular adenomas. PFOS is also a peroxisome proliferator, but studies have not been conducted to firmly establish the role of PPAR- $\alpha$  agonism in the induction of the liver adenomas. Chronic exposure studies of PFBS have not yet been conducted. Although preliminary studies indicate that PFBS is a weak peroxisome proliferator at comparatively high doses, only very limited liver toxicity has been noted in a two-generation reproductive toxicity study, and no liver toxicity was noted in 28-day and 90-day studies at comparable doses. Limited studies of the C9 and C10 perfluorocarboxylic acids indicate that both compounds are peroxisome proliferators. Thus, it is likely that liver adenomas may be expected following chronic exposures to many of the compounds in the proposed series. However, several scientific groups have concluded that PPAR- $\alpha$  agonist induced liver tumors in adult rodents are of questionable relevance to humans. Others have questioned whether chronic exposure to peroxisome proliferators would result in a different outcome if exposures were initiated prenatally rather than in adulthood. To resolve this issue, we are proposing a 2-year bioassay that commences with *in utero* exposure of PFOA. We are not proposing chronic studies of the other compounds at this time.

The EPA is also interested in pursuing opportunities to share tissues from animals in selected toxicity studies. This would facilitate follow-up on mechanistic and other endpoints, which are the subject of ongoing studies within EPA laboratories with selected members of this class.

Finally, there are several ongoing efforts to utilize “omics” to help better define the target organ effects and potential common modes of action for this class of compounds. Use of “omics” will improve our predictive ability for this class of compounds. Where appropriate, adjunct comparative “omics” and mechanistic studies should be considered for the compounds in Table 1. These studies should also include the C4 and C8 sulfonates, and others as appropriate.



**Table 2. Chemical identification for perfluorinated compounds for EPA class study nomination**CASRN links to EPA Substance Registry System record (<http://www.epa.gov/srs>)

Chemical shorthand name	CASRN	Chemical name (acronym)	Systematic chemical name (9CI)
C4 sulfonate	<a href="#">375-73-5</a>	Perfluorobutanesulfonic acid (PFBS)	1-Butanesulfonic acid, 1,1,2,2,3,3,4,4,4-nonafluoro-
C6 sulfonate	<a href="#">355-46-4</a>	Perfluorohexanesulfonic acid (PFHxS)	1-Hexanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluoro-,
C8 sulfonate	<a href="#">1763-23-1</a>	Perfluorooctanesulfonic acid (PFOS)	1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-
C9 sulfonate	474511-07-4*	Perfluorononanesulfonic acid (PFNS)	1-Nonanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-nonadecafluoro-
C10 sulfonate	<a href="#">335-77-3</a>	Perfluorodecanesulfonic acid (PFDS)	1-Decanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heneicosafuoro-
C12 sulfonate	79780-39-5*	Perfluorododecanesulfonic acid (PFDoS)	1-Dodecanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-pentacosafuoro-
C6 carboxylic acid	<a href="#">307-24-4</a>	Perfluorohexanoic acid (PFHxA)	Hexanoic acid, undecafluoro-
C8 carboxylic acid	<a href="#">335-67-1</a>	Perfluorooctanoic acid (PFOA)	Octanoic acid, pentadecafluoro-
C9 carboxylic acid	<a href="#">375-95-1</a>	Perfluorononanoic acid (PFNA)	Nonanoic acid, heptadecafluoro-
C10 carboxylic acid	<a href="#">335-76-2</a>	Perfluorodecanoic acid (PFDA)	Decanoic acid, nonadecafluoro-
C12 carboxylic acid	<a href="#">307-55-1</a>	Perfluorododecanoic acid (PFDoA)	Dodecanoic acid, tricosafuoro-
Telomer alcohol 8+2	<a href="#">678-39-7</a>	1,1,2,2-Tetrahydroperfluoro-1-decanol	1-Decanol, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro
Telomer alcohol 10+2	<a href="#">865-86-1</a>	1,1,2,2-Tetrahydroperfluoro-1-dodecanol	1-Dodecanol, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heneicosafuoro-

\*From CAS Registry record; not in EPA SRS, ChemFinder; PFDoS in ChemIDplus (on EINECS)