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3M Specialty Materials

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AR 226 - 0976

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December 19, 2000

For Your Information Docket [Docket AR-226]  
Document Processing Center (7407)  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
401 M Street SW  
Washington, D.C. 20460

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Re: Information on Perfluorooctane  
Sulfonates and Related Compounds

Dear Sir or Madam:

This continues 3M's voluntary submissions of data on perfluorooctane sulfonates and related compounds, as part of our ongoing dialog with EPA regarding fluorochemistry.

Contents of this Submission

Initial Assessment Report

We are providing a copy of 3M's draft Initial Assessment Report on Perfluorooctane Sulfonic Acid and Its Salts, dated October 2, 2000 with this submission. This draft document was provided to members of the OECD Existing Chemicals Task Force for their review prior to a technical meeting held at EPA on October 26-27, 2000. The document is still a draft, subject to modification as new data become available. However, we are providing a copy so that this comprehensive document and accompanying robust summaries will be available to the public in EPA's docket along with all of the raw data we have provided in our series of submissions.

The enclosed draft report follows the format outlined in the Screening Information Data Set (SIDS) Manual of the OECD, even though perfluorooctane sulfonic acid (PFOS) is not considered a high production volume chemical, and even though the data set on PFOS is substantially more robust than that covered in most initial assessment reports.



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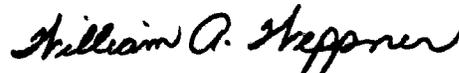
December 22, 2000  
Page 2

This draft report summarizes the information available as of July 20, 2000 and presents and evaluates information on PFOS exposure and biological effects in an initial assessment of potential human health and ecological risk. 3M has previously provided a CD set containing the underlying studies relied upon in this draft report. For some studies, reports are still in preparation. The substantial body of data reviewed in this draft report suggests that human serum levels found in occupational and non-occupational populations are not associated with adverse health effects. Similarly, levels found in the environment and in wildlife are not associated with adverse effects.

As with other CDs submitted by 3M, the enclosed CD includes a copy of the original cover letter and the Initial Assessment Report. These electronic documents are for read-only purposes and are not to be modified. 3M will maintain paper copies, and in the event of any discrepancy, the 3M paper copies will be considered controlling.

We will continue to provide information on a regular basis as it becomes available. I will be retiring from 3M effective February 1, 2001. You may feel free to contact me until then, or after that, please contact my successor Michael Santoro (651-733-6374) with any questions.

Very truly yours,



William A. Weppner, Ph.D.  
Director of Environmental, Health  
Safety and Regulatory Affairs  
Specialty Materials Markets  
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3M Center  
St. Paul, MN 55144  
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cc: Dr. Charles Auer  
Dr. Oscar Hernandez  
(without enclosures)

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#16

AR 226 - 0977

**ORIGINAL**

3M Specialty Materials

3M Center  
St. Paul, MN 55144-1000  
651 733 1100

October 9, 2000



Dr. Oscar Hernandez  
US EPA/OPPT/CCD (7405)  
401 M Street, S.W.  
Room E615B  
Washington, D.C. 20460-0001

Dear Oscar:

Enclosed are twenty (20) copies of a document entitled "Draft Initial Assessment Report: Perfluorooctane Sulfonic Acid and its Salts" prepared by 3M on CD. It is 3M's understanding that you will distribute the CD's to the members of the OECD Existing Chemicals Task Force for their review prior to the technical meeting scheduled for October 26-27 in Washington.

The enclosed draft report follows the format outlined in the Screening Information Data Set (SIDS) Manual of the OECD, even though perfluorooctane sulfonic acid (PFOS) is not considered a high production volume chemical, and even though the data set on PFOS is substantially more robust than that covered in most initial assessment reports.

This draft report summarizes the information available as of July 20, 2000 and presents and evaluates information on PFOS exposure and biological effects in an initial assessment of potential human health and ecological risk. 3M has previously provided a CD set containing the underlying studies relied upon in this draft report. For some studies, reports are still in preparation. The substantial body of data reviewed in this draft report suggests that human serum levels found in occupational and non-occupational populations are not associated with adverse health effects. Similarly, levels found in the environment and in wildlife are not associated with adverse effects.

While the information in this report represents our current knowledge, additional information is currently under development and will aid in improving this initial assessment of risk of PFOS. Areas under study include ecological exposure and effects assessment, human exposure (through sera measurement), chronic studies in laboratory animals and additional tissue measurements of PFOS from previous studies.

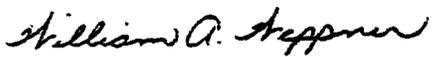
To ensure the most accurate analytical results possible, work is presently being conducted to completely characterize samples used in testing and analysis over the last few years. Based on the results of further purity analysis, the values in the reports upon which this document is based will be revised. Therefore, the numbers in the document will also be modified in future revisions.

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Dr. Oscar Hernandez  
US EPA/OPPT/CCD (7405)  
Page 2

Please contact me directly at 651/733-6374 if you have any questions regarding this report.

Best regards,



William A. Weppner, Ph.D.  
Director  
Environmental, Health, Safety & Regulatory Affairs  
Specialty Material Markets Group  
3M Center, Bldg. 236-1B-10  
St. Paul, MN 55144

on 1d

~~PP~~ PP

**ORIGINAL**

AR226-0978

**DRAFT INITIAL ASSESSMENT REPORT**

**PERFLUOROCTANE SULFONIC ACID**

**AND ITS SALTS**

**October 2, 2000**

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**Prepared by**

**3M**

**in consultation with**

**Jack Moore, DVM, DABT, Hollyhouse, Inc.**

**Joseph Rodricks, PhD, DABT and Duncan Tunbull, DPhil, DABT, The Life Sciences  
Consultancy**

**Bill Warren-Hicks, PhD and colleagues, The Cadmus Group, Inc.**

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## **EXECUTIVE SUMMARY**

### **Introduction**

Perfluorooctane sulfonic acid and its salts (PFOS) are fully fluorinated organic molecules produced synthetically by electrochemical fluorination or from the degradation of other fluorochemical products produced by electrochemical fluorination. As a fully fluorinated organic molecule, PFOS is very stable and resists further degradation. Substantial information related to human and environmental exposures to PFOS has been developed providing evidence of widespread distribution in humans and the environment. PFOS at very low levels has been identified in serum and tissue samples from both occupationally and non-occupationally exposed human populations, in various species of wildlife, and in surface waters and other environmental media. An extensive database has been developed and continues to be developed on the possible biological effects of these exposures. The information available as of July, 2000, together with an assessment of human and environmental risks, is contained in this report. The report follows the methods and procedures outlined in the Screening Information Data Set (SIDS) Manual of the Organization for Economic and Cooperative Development Investigation of High Production Volume Chemicals.

Based on the currently available information presented in this report, the observed levels of PFOS from a wide variety of samples have not been associated with identifiable adverse effects on human health, wildlife, or the environment. Additional data currently under development from ongoing studies will be used in the future to refine this initial assessment.

The primary manufacturer of PFOS and its precursor molecules (3M Company) announced on May 16, 2000 that it will voluntarily cease manufacturing perfluorooctanyl-based products. The company is cooperating with the U.S. Environmental Protection Agency and its customers in implementing a phase-out plan calling for most manufacturing to cease by the end of 2000 and a remaining manufacturing to cease by the end of 2002.

### **Environmental Exposure and Effects**

Releases of PFOS and its precursor molecules can occur during their manufacture, during both commercial and end use application, and after product use. Analyses of manufacturing waste streams and those associated with commercial and end use applications indicates that most of the waste generated is in the form of solid waste which is either incinerated or disposed of in landfills. Smaller amounts are released in waste water or to air. Environmental fate and transport and subsequent exposure to PFOS are still the subjects of several on-going studies.

The exposure potential of PFOS in the environment is being determined by a number of monitoring efforts. A multi-city study designed to obtain information about the dispersion of fluorochemicals in the environment, uptake into foods, and their presence in surface water is currently underway. Another study involves a global biosphere monitoring program aimed at understanding the presence of PFOS in mammals, fish and birds. Finally, an additional study involves gathering samples of groundwater, surface water, sediments and fish and bird species from the vicinity of a manufacturing facility. Monitoring data collected through July, 2000, are presented in this report.

Numerous acute and chronic toxicity studies involving freshwater and marine organisms have been conducted, and the data from these studies provide a substantial basis for characterizing potential risks to aquatic animals. Effects on the particular species of terrestrial wildlife and birds in which PFOS has been found have not been studied, but considerable data on surrogate mammalian species have been generated. In situations where specific species effects data are not available, inter-species extrapolation is an accepted practice in ecological risk assessment, with the recognition that there are some uncertainties associated with such extrapolation.

**Initial Assessment of Ecological Risk**

This initial assessment report applies a well-accepted methodology, wherein levels of environmental and wildlife concentrations are compared with toxicity thresholds that are derived from the various studies. Under this approach to risk assessment, the currently available data indicate that the observed levels of PFOS from a wide variety of environmental samples have not been associated with identifiable adverse effects to wildlife and the environment. Calculated ratios indicate a wide margin of safety, but it should be recognized that uncertainty exists in this analysis. Use of serum and liver data as a measure of internal dose reduces some of the uncertainty in this extrapolation. A number of additional environmental studies are underway or planned to refine this initial assessment.

**Human Exposures**

In the 1960's and 1970's, organic fluorine was identified in human serum at levels less than 0.10 ppm. In the 1990's, as a result of improved analytical techniques, routine measurements of specific organofluorine chemicals became feasible. This allowed for the measurement of PFOS in serum from humans with occupational and non-occupational exposures. Occupationally exposed fluorochemical production workers have measured serum PFOS levels that average 2.0 ppm with highest levels at approximately 10 ppm. In a limited number of non-occupational samples, serum PFOS levels have ranged between 0.01 - 0.10 ppm. Research is ongoing to better characterize the distribution of serum PFOS in non-occupational populations.

**Health Effects**

The database includes several sub-chronic studies in rodents and non-human primates, multigeneration reproduction/developmental studies, an extensive array of genotoxicity tests, toxicokinetic work and chronic studies. In addition, several epidemiological investigations in exposed workers are available. The studies are of good quality and acceptable for use in hazard evaluation.

Several investigations involving fluorochemical production workers show no evidence of excess mortality or specific clinical signs attributable to PFOS exposure. 3M has conducted medical surveillance of perfluorochemical production workers for over 20 years. A battery of clinical tests (including lipids, hematological parameters, enzymes and 11 different hormone assays) showed no association with PFOS levels; these findings were based on serum levels in workers up to 6 ppm. A mortality study showed no excess mortality for any cause of death, including cancer. All of this information suggests that workers are not at risk at the serum levels reported.

It is reasonable to assume these workers have the highest level of human exposure to PFOS. Since the production workforce studied is largely male, these studies do not adequately represent women. It is noted that male and female monkeys responded similarly in sub-chronic dosing studies with respect to the nature of adverse effects observed.

Results from several repeat dose toxicological studies consistently demonstrate that the liver is the primary target organ. Manifestations of liver tissue response to high doses of PFOS include enlargement of the liver and apparent alterations in metabolic processes. Liver enlargement and reduction in serum cholesterol are early responses to PFOS. These effects occur in rats as well as monkeys.

Also at high doses PFOS adversely affects survival of rat pups in the neonatal period of life as a result of maternal exposure during fetal development. Reduced weight gain, abortions and resorptions are seen in developmental studies at the higher doses tested. There were no effects on developmental milestones, including post-natal neurological development, or on fertility and estrous cycling in offspring in multi-generation studies.

Multiple genotoxicity assays covering a variety of endpoints demonstrate that PFOS does not present a hazard from interaction with genetic material. The results of a two-year cancer study in rats will be available in the next several months.

PFOS is well-absorbed orally and very slowly eliminated from the body. The mean serum elimination half-life for PFOS is approximately 300 days in humans, based on a continuing study of retired fluorochemical workers. PFOS is not metabolized in any of the multiple species studied, although it can be formed metabolically from other fluorochemicals containing the perfluorooctanesulfonyl moiety. Unlike many chemicals of environmental consequence, PFOS does not preferentially distribute to fatty tissue, preferring instead to associate with proteins in blood and liver. It has been found to cross the placenta and there is evidence for distribution in milk. Due to the good oral absorption, poor elimination and extensive protein binding, PFOS concentrations in liver and serum are proportional to cumulative exposure. Therefore, serum PFOS concentrations can be used as an integrated measure of exposure over time, regardless of source.

Several investigations have been conducted or are in progress to better understand the mechanism(s) through which PFOS exerts its toxicity. While not completely understood at this time, the mechanism(s) of toxicity is thought to include changes in metabolic processes associated with fat metabolism.

### **Initial Assessment of Human Risk**

Retrospective cohort mortality assessments of fluorochemical production workers have not revealed excess mortality in any category of disease. PFOS levels up to 6 ppm in production workers have not been associated with abnormalities in clinical testing (chemistries included lipids, hematologic parameters and 11 different hormone values). Considering the study information available to date, and given the distinctly higher PFOS levels in animals necessary to produce toxicity (cholesterol lowering and liver abnormalities), it is unlikely that workers would have these abnormalities at the levels to which they have been exposed. Current knowledge

indicates that general population sera levels are approximately two orders of magnitude lower than production workers at the higher end of the range in these studies.

Although there is some species variation in the levels at which PFOS induces toxicity, the toxic effects are consistent. Furthermore, the fact that the same measure of exposure (serum values for PFOS) is used to extrapolate across species reduces the uncertainty in understanding exposure and ultimately human risk. The information available to date on toxicity associated with PFOS serum levels indicates that PFOS levels in the general population are approximately two to three orders of magnitude lower than serum levels in animal studies that are associated with no adverse health effects.

### Conclusion

This report summarizes the information that is available as of July 20, 2000. There is a substantial body of data relating human and environmental exposures to PFOS and the possible biological effects of these exposures. This information suggests that human serum PFOS levels found in occupational and non-occupational populations are not associated with adverse effects. Similarly, levels found in the environment and in wildlife are not associated with adverse effects. Additional research now underway will be used to refine this initial assessment.

## **INTRODUCTION**

### **Background**

The human health and ecological risk assessment process for PFOS contained in this report follows the methods and procedures outlined in the Screening Information Data Set (SIDS) Manual of the Organization for Economic Cooperation and Development (OECD) Programme On the Co-Operative Investigation of High Production Volume Chemicals (OECD, 1997). In particular, this report follows the provisional guidance for the outline of the SIDS Initial Assessment Report, which is discussed in Chapter 4 of the manual. The environmental portion of the SIDS Initial Assessment Report is effectively a Tier I Screening-Level Risk Assessment as envisioned by U.S. EPA. This format was followed recognizing that this initial assessment report is to be part of the OECD Existing Chemicals Program.

Overall, the assessment presents, evaluates, explains, and combines information on PFOS exposure and effects into an initial assessment of potential risk. Based on current information, the observed levels of PFOS in a wide variety of samples are not associated with identifiable adverse effects in humans, wildlife, or the environment. The information in this report is based on a substantial body of data and represents our current knowledge. Additional information is currently under development and will aid in improving this initial assessment of risk of PFOS to human health and the environment.

Section 1 of this report provides the PFOS CAS number, molecular formula, and composition; describes its physicochemical properties; and discusses the behavior implications of these characteristics, such as anticipated sources, sinks, and bioaccumulation. Section 2 presents general information on ecological and human exposures to PFOS, including its uses and function, production volume and expected exposure pathways. Ecological exposure, effects on aquatic and terrestrial ecosystems, and other ecological effects are described in Section 3. Human health exposures, potential hazards, and risks are evaluated in Section 4. Section 5 presents the conclusions and recommendations of this assessment, and the literature and data sources upon which this document is based are listed in Section 6. Summary Reports for the compound's physicochemical properties are included in Appendix I. Appendix II presents Summary Reports for aquatic toxicological studies. Reports summarizing the environmental exposure studies are included in Appendix III. Appendix IV lists planned environmental studies on PFOS. Appendix V contains summary reports of mammalian toxicology studies.

### **Overview of PFOS**

The fluorochemicals discussed in this document are produced by an electrochemical process that exchanges all of the hydrogen atoms of an organic feedstock with fluorine atoms from hydrogen fluoride. The highest volume perfluorochemical produced in this way is perfluorooctane sulfonyl fluoride (POSF). Over eight million pounds of this compound will be produced in 2000. Using this perfluoroorganic molecule as a basic building block, unique chemistries can be created by further reactions with functionalized hydrocarbon molecules. These compounds repel water and oil, reduce surface tension, catalyze oligomerization and polymerization, and maintain their properties under extreme conditions. Depending upon the specific functional derivatization

or the degree of polymerization, such POSF-based compounds may degrade or metabolize to PFOS. PFOS is the stable and persistent end-product that has the potential to bioaccumulate.

In the environment, PFOS is resistant to chemical and biological changes and does not degrade under any observed conditions except for combustion. PFOS or precursors enter the environment through factory discharges, as manufacturing residuals in products or as products themselves. Mechanisms by which PFOS can be transported through the environment include transport in surface water, adsorption onto particles present in air, surface water and sediments, and uptake by aquatic, avian or terrestrial organisms.

The ability to detect and quantify PFOS and its precursor compounds at very low levels in the environment has been limited until recently, when reliable and sensitive methods for extracting, separating, and identifying and quantifying them in tissues and environmental samples became available. For this reason, knowledge of the environmental fate of this class of chemicals has been enhanced. Research is underway to assess PFOS accumulation in the environment, atypical partitioning behavior, and significant surface activity. Uncertainties about the applicability of existing fate-and-transport models and gaps in physicochemical and environmental data also complicate the characterization of the environmental fate of PFOS. More information is being gathered to better understand environmental fate. This includes efforts to help characterize releases from product manufacture and use, including developing fate-and-transport models and designing methods to sample various habitats and species of interest.

PFOS has been found at low levels in samples of human serum from several sources and locations. It is persistent and widespread in human populations. The mechanisms and pathways leading to its presence in human blood are not well characterized, but it is likely there are multiple sources of the compound. Some may arise from environmental exposure to PFOS or precursor molecules, or from residual levels of precursors to PFOS in commercial products. 3M production workers have the highest known blood levels of PFOS. Epidemiological and medical surveillance studies of these workers have not associated adverse health effects with this exposure. An extensive toxicological database on PFOS and specific precursor molecules continues to be developed. While much work in this area is still in progress, the available information indicates that current levels of PFOS are not associated with identifiable adverse effects to human health.

The analytical values represented in this report result from various methodologies and represent the most accurate information available as of July, 2000. For this data, final reports have been issued or are in preparation. To ensure the most accurate analytical results possible, work is presently being conducted to completely characterize samples used in testing and analysis over the last few years. Based on the results of further purity analysis, the values in the reports upon which this document is based will be revised. Therefore, the numbers in this document would also be modified in future revisions.

## 1.9 IDENTITY

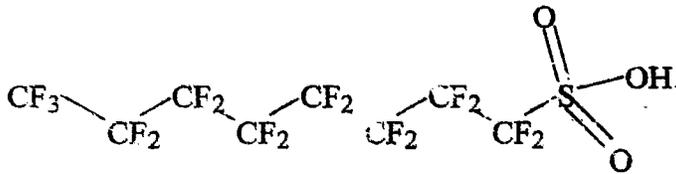
**Chemical Name:** Perfluorooctane Sulfonic Acid

**CAS Number:** Various, including: 1763-23-1 (acid)  
 29081-55-9 (ammonium salt)  
 70225-14-8 (DEA salt)  
 2795-39-3 (potassium salt)  
 29457-72-5 (lithium salt)

The perfluorooctane sulfonate anion (PFOS) has no specific CAS number. The above-listed acid and salts are all considered perfluorooctane sulfonates.

**Molecular formula:**  $C_8H_{17}F_{17}O_3S$

**Structural formula:**



**Synonyms:** 1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptafluoro-; 1,1,2,2,3,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptafluoro-1-octanesulfonic acid; 1-Octanesulfonic acid, heptafluoro-; 1-Perfluorooctanesulfonic acid; Heptafluoro-1-octanesulfonic acid; Perfluoro-n-octanesulfonic acid; Perfluorooctanesulfonic acid; Perfluorooctylsulfonic acid

**Table 1-1. Physical and Chemical Properties (See Appendix I for Robust Summaries)**

Parameter	Report Date	Results
Melting Point	2/24/99	> 00 °C
Vapor Pressure	5/05/99	$3.31 \times 10^{-4}$ P @ 20 °C
n-Octanol/Water Partition Coefficient	2/11/00	Not measurable
Air-Water Partition Coefficient	3/19/00	0 ( $< 2 \times 10^{-6}$ )
Solubility in Pure Water	5/03/99	0.05 mg/L

## **1.1 Discussion**

PFOS appears to be stable in the environment. This compound is not biodegradable and does not undergo hydrolysis or photolysis. Based on an analysis of bond strength the compound is destroyed by combustion at high temperatures. The very low vapor pressure and immeasurable air/water coefficient indicate that volatility of the compound is insignificant.

PFOS has a solubility of about 519 mg/L in pure water. Solubility decreases significantly in seawater to about 25 mg/L. These data suggest that any PFOS discharged to a water source would tend to remain in that medium, unless it is adsorbed onto particulate matter or assimilated by organisms. If PFOS does bind to particulate matter the material would ultimately end up in the sediment. Further study is underway to determine the presence of PFOS in sediments from various locations and the binding potential of PFOS to sediments.

PFOS is not anticipated to be present in the atmosphere because of its extremely low volatility. In fact, obtaining an air/water partition coefficient reading for PFOS has not been possible because the partitioning has been too small to measure. Therefore, atmospheric dispersion of PFOS is considered unlikely.

Because of the compound's surface active properties and the test protocol itself, determining the n-octanol/water partitioning coefficient has not been possible. The difficulty in measuring this coefficient is caused by the formation of a third layer between the water and the n-octanol. Because the octanol/water coefficient is used extensively in models to predict bioconcentration and transport mechanisms, a different test method will be used to determine the coefficient. An actual bioconcentration study will also be performed.

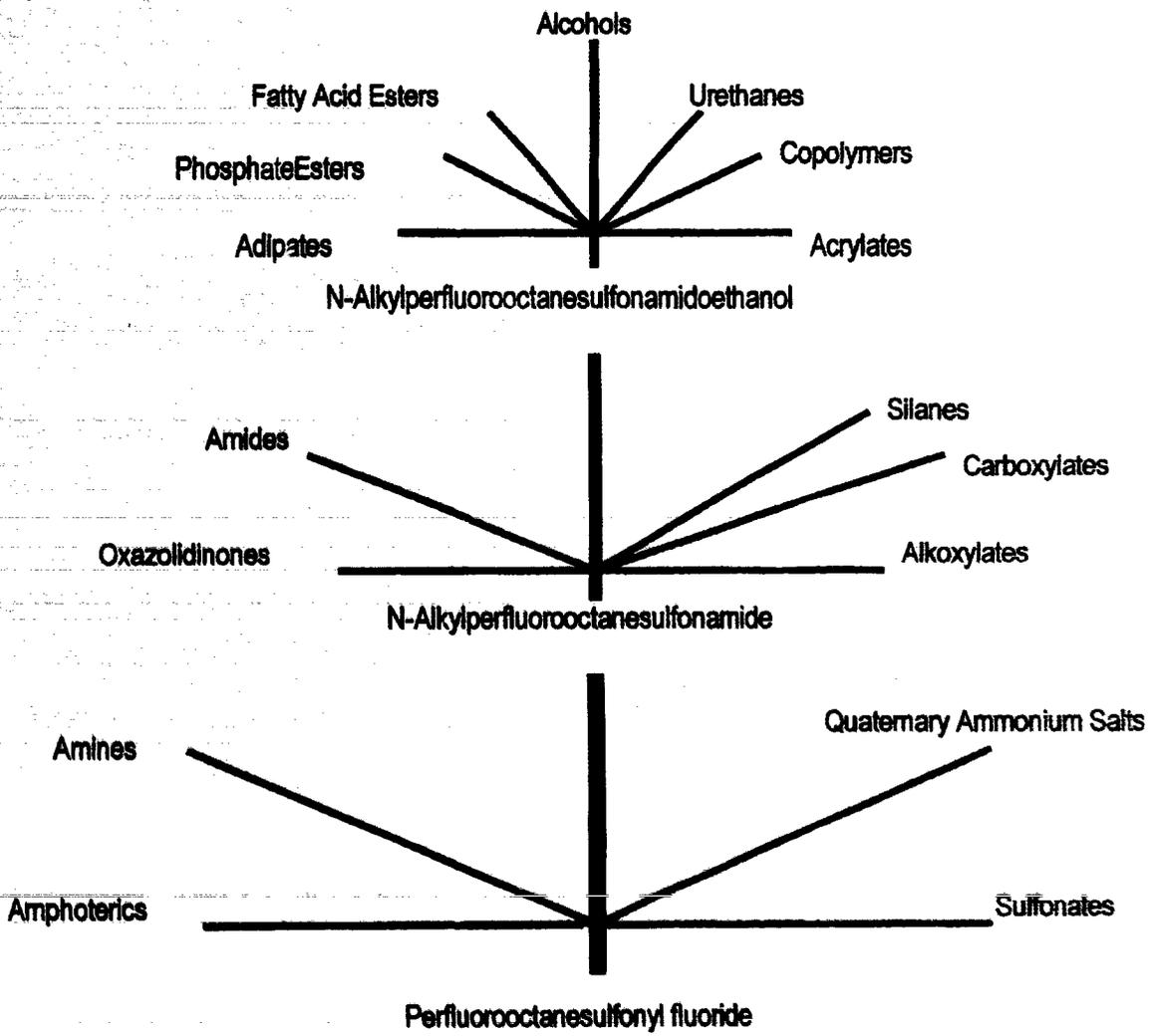
Even with this information, classic models (which are based on log P, or  $K_{ow}$  for predicting bioconcentration) may not be appropriate. Studies performed on laboratory rats show PFOS does not bioconcentrate in the lipid fraction but tends to bind to certain proteins. These findings may negate the utility of the conventional models, which are based on measures of affinity for lipids.

## **2.0 GENERAL INFORMATION ON EXPOSURE**

### **General Information on Exposure**

Perfluorooctane sulfonic acid (PFOS) is a fully fluorinated organic acid produced by electrochemical fluorination. The starting feedstock for the electrochemical fluorination reaction is 1-octane sulfonyl fluoride and the primary product produced is perfluorooctane sulfonyl fluoride (POSF). POSF is a commercialized product to some extent, but it is primarily an important intermediate in the synthesis of higher molecular weight fluorochemical products. PFOS is itself a commercialized product produced from the hydrolysis of POSF. 3M sells approximately 50,000 pounds per year of PFOS in various salt forms. It is used for a variety of surfactant applications (mainly fire-fighting foams and coating additives). Unique chemistries are created by further derivatizing POSF through the sulfonyl fluoride moiety using conventional hydrocarbon reactions. POSF is reacted with methyl or ethyl amine to produce either N-methyl or N-ethyl perfluorooctane sulfonamide. At this stage, these intermediates can be used to make amides, oxazolidinones, silanes, carboxylates and alkoxylates as commercial products. These intermediates can be subsequently reacted with ethylene carbonate to form either N-methyl or N-ethylperfluorooctanesulfonamidethanol. These intermediates can be used to make adipates, phosphate esters, fatty acid esters, urethanes copolymers, and acrylates as commercialized products. See Figure 2.1.

**Figure 2.1 POSF Fluorochemical Reaction Tree**



The secondary reactions producing all of these derivatives are single or sequential batch processes that do not necessarily produce pure products. There may be varying amounts of fluorochemical residuals (unreacted or partially reacted starting materials or intermediates) that are carried forward to the final product. Typically, these residuals are currently present at a concentration of 1% or less in commercialized product. The non-fluorochemical moieties added to the sulfonyl fluoride group of these residuals can be removed through a variety of degradation processes (chemical, environmental, and metabolic). The terminal fluorochemical moiety of such degradation will be PFOS. Higher molecular weight polymeric fluorochemical products tend to be stable and do not degrade to PFOS by these same processes.

Total worldwide POSF production by 3M in 2000 will be 3,000,000 lbs. POSF-derived fluorochemicals (polymers and monomers) are formulated with water or solvent, with the fluorochemical component (or fluorochemical solids) representing a variable percent of the formulation. Total fluorochemical solids include the hydrocarbon reactants combined with the fluorochemical starting material and do not represent the POSF molecule itself. 3M produced fluorochemical solids represent the majority of the total production of sulfonyl based fluorochemicals in the world. The breakdown of 3M fluorochemical production into different product categories include:

**Surface Treatments (High Molecular Weight (MW) polymers or formulated products with low percentages of non-polymeric FC solids)**

Carpet Protector  
 Fabric/Upholstery Protector  
 Apparel and Leather Protector  
 Protective Products for After Markets and Consumer Application

**Paper and Packaging Protectors (Phosphate esters or high MW polymers)**

Food Packaging  
 Paper Products

**Performance Chemicals (Low MW chemical substances)**

Fire Extinguishing Foam Concentrates  
 Mining and Oil Surfactants  
 Electroplating and Etching Bath Surfactants  
 Household Additives  
 Chemical Intermediates  
 Coatings and Coating Additives  
 Carpet Spot Cleaners  
 Insecticides Raw Materials

Potential sources of human or environmental exposure to PFOS include the producer's manufacturing operations and waste streams, the manufacturing operations and waste streams of users of POSF-based fluorochemical products, and the use or degradation of some final commercial products containing POSF-based fluorochemicals.

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**The primary manufacturer of PFOS-based chemicals capable of potentially degrading to PFOS (3M) has announced that its production of these materials will be substantially discontinued by the end of 2000. Manufacture and distribution of a few, well-defined products having essential uses will continue for a limited time period thereafter. The company is working with the U.S. EPA and with its customers to implement an orderly transition away from all such perfluorooctanyl chemical products by the end of 2002.**

### **3.0 ENVIRONMENT**

#### **3.1 Environmental Exposure**

This section discusses available information on the presence of perfluorooctane sulfonate (PFOS) in the environment. As part of a larger study, monitoring data have been collected for surface water column samples. Summary reports are presented in Appendix III. A global biosphere monitoring program has resulted in analysis of more than 400 archived serum and liver specimens from a wide range of aquatic and terrestrial species. These data are described in Section 3.1 and are summarized in Tables 3-2, 3-3 and 3-4.

##### **3.1.1 General Discussion**

###### **Exposure Potential**

One potential source of PFOS exposure is the release to the environment of POSF-derived materials in the waste streams generated from the manufacturing process, supply chain operations, and consumer use. Based on extensive engineering calculations and mass balance determinations, estimates of 3M waste stream generation have been derived. 3M has no information on waste streams from other producers and users of these materials.

Generally, the wastes generated from the manufacture and use of POSF derived materials are not in the form of PFOS itself, but rather in the form of high molecular weight polymeric materials, which contain small amounts of residual molecules which may be precursors to PFOS. The degradation of the polymeric substances is very complex and efforts are underway to understand the mechanism and the extent to which they may degrade to PFOS.

From the standpoint of waste type, approximately 90% of the waste generated from all sources is in the form of solid waste, which is either incinerated or disposed of in landfills. The remaining wastes are discharged as wastewater (~9%) or as air emissions (~1%). Several ongoing studies will improve the understanding of the possible mechanisms associated with environmental fate and transport of PFOS. (See Appendix IV.)

The exposure potential from waste generation sources and actual environmental concentrations are being determined through a series of monitoring efforts. For example, a multi-city study was designed to obtain information about the dispersion of fluorochemicals in the environment, uptake into foods, and presence in surface water. The purpose of the study, which has been initiated but not completed, is to improve the understanding of the potential sources of human and ecological exposure. Where possible, samples were taken or will be taken from the surface water column and surface microlayer, sediment, river fish, drinking water, influent and effluent to publicly owned treatment works, sludge, and landfill leachate. Additionally, a "market basket" of several food products will be sampled. The data from this study will provide a more definitive exposure analysis. The surface water column data collected as part of this study were used to create the Initial Assessment for the Environment (Section 3.3.1).

Two other studies are underway to characterize the exposure potential of PFOS. The first study involves a global biosphere monitoring program aimed at understanding the distribution of PFOS in a variety of organisms, such as mammals, fish, and birds. These data provide a direct measure of PFOS exposure to these organisms. In this assessment, this information is combined with the results of ecotoxicological testing and mammalian toxicity testing to understand the potential risk of those exposures, if any. The discussion of the findings from this biosphere program and results of ecological effects studies are presented in Section 3.2.

The second study is being conducted in the vicinity of a manufacturing facility (Decatur, Alabama). Samples of groundwater, surface water, sediments, and fish and bird species have been collected and analyses are in progress. This study will also provide information on PFOS concentrations in progressive levels of the food web and, in conjunction with other information, will be used to develop an analysis of the biomagnification characteristics of this compound.

### **Exposure and Release Management**

3M has already announced that it will voluntarily cease production of POSF chemistry. Even prior to that announcement, several activities to reduce the waste and emissions from 3M manufacturing operations and to improve product quality had been implemented. Product and process understanding have been enhanced, the level of residuals and wastes from the manufacturing operations have been reduced (through improved process controls and installation of treatment equipment), most fluorochemical solid waste materials from 3M manufacturing receive thermal treatment, and the program of product phase-out is underway. All of these steps have had and will continue to have a significant impact on reducing the exposure potential from 3M manufactured fluorochemicals.

#### **3.1.2. Predicted Environmental Concentrations (PEC)**

As the SIDS Manual indicates, the predicted environmental concentration or PEC should be derived based on monitoring data and/or calculation using exposure models. At this time, the development of predictive models is in a very early stage. The physical/chemical properties of PFOS and the overall characteristics of the products and waste streams may hinder the development of predictive models. Typically, the models call for the use of log P or  $K_{ow}$  factors, which are not available for this compound. These factors are required for predicting bioconcentration and, because of the surface active properties of the compound, the factors cannot be determined. In addition, the nature of exposure routes would add considerable complexity to the development of these models. For example, PFOS degradation in the atmosphere or its binding potential in ecological species or compartments such as sediments is not fully understood. Consequently, the analysis presented in Section 3.2, Effects in the Environment, is based on actual monitoring data which are likely to be more reliable than modeling estimates for this compound.

Data are available from the multi-city study and the global biosphere monitoring program. With these data and the extensive ecotoxicological and animal testing results, the predicted environmental concentrations (PECs) and the predicted no effect concentrations (PNECs) of the compound can be thoroughly compared. This information is presented in the following sections.

### **3.1.2.1 Surface Waters**

PFOS concentrations in surface waters were analyzed in samples from six cities (Nishioka and Strauss, 2000). For each city, a list of key 3M supply chain customers was generated, and the locations of the customers were determined. Examining the various locations resulted in the identification of surface water bodies in both the upstream and downstream vicinity of the key 3M customers. The locations were chosen to integrate the potential PFOS exposure due to all POSF-based manufacturing and fluorochemical use by key supply chain sources. In addition, a "quiet water" site was located at each city except for Cleveland, Tennessee. Details on the sites and locations are contained in the study design. A description of the sites for each city is found in Table 3-1.

At each city sampling site, two water samples were analyzed for PFOS concentration. Table 3-1 presents the results of the laboratory analysis. A site average and a maximum value are presented for each city. The reporting limits and method detection limits are indicated in the table. The average and maximum values are used in the risk assessment analyses presented in Section 3.2. The largest concentration of PFOS was found in the quiet surface water in Port St. Lucie 2,930 parts per trillion (ppt) and the second largest at Decatur (114 ppt). The concentrations of PFOS at Cleveland, Tennessee, were all less than the limit of quantification of 25 ppt. Of those cities with average PFOS concentrations greater than the reporting limit, Columbus, Georgia, had the second largest average PFOS concentration of 80.0 ppt while Pensacola, Florida, had the smallest detectable average PFOS concentration of 25.7 ppt.

The analytical findings of the Port St. Lucie quiet water sampling location are not completely understood but are considered to be an anomaly in the multi-city data set. The PFOS levels at this site are considerably higher than other quiet water sites in the study and are not consistent with other findings at Port St. Lucie. The sampling site is a relatively small and stagnant pond about 200 feet by 200 feet. The pond contained considerable manmade debris including plastic, styrofoam and bottles.

### **3.1.2.2 Biota**

The biosphere monitoring program was designed to assess the global distribution of PFOS. Samples of blood, liver, and other tissues were collected from archived specimens of a variety of species from several locations and analyzed for PFOS. Areas of focus included North America (the Great Lakes and coastal marine locations) the Arctic, and Europe. Analyses of these samples indicated that PFOS is present in the livers and sera of animals, especially in piscivorous (fish-eating) animals. Tables 3-2 and 3-3 summarize the results of these analyses. The highest average concentrations of PFOS in biota was found in the blood of bald eagles and the liver of

minks. Average concentrations in other tissues and other species were relatively lower (Table 3-4).

Concentrations of PFOS measured in blood and liver of wildlife appear to be valid measures of environmental exposure. In laboratory toxicity tests with rats and monkeys, PFOS was found to distribute to blood and liver. In a 26-week capsule toxicity study with *Cynomolgus* monkeys, serum PFOS values increased almost linearly at doses up to about 100 ppm, although serum levels did not increase linearly at higher doses (Table 3-5). In 14-week dietary and two-generation reproductive studies in rats, serum and liver concentrations also increased approximately linearly with dose (Table 3-5). In a radiolabel study the majority of the administered dose was found in blood and liver. Thus, primate and rat studies indicate that serum PFOS concentrations resulting from daily exposure over a broad range of PFOS doses are directly proportional to cumulative dose up to serum concentrations of 100 ppm (see section 4.3.1.2).

### **3.2 Effects on the Environment**

#### **3.2.1. Effects on Aquatic Animals from Exposure to Aqueous Concentrations**

Since 1974 numerous acute and chronic toxicity tests using a variety of freshwater and estuarine aquatic organisms have been conducted (Table 3-6). Over this time, protocols for conducting the toxicity tests have changed. For a given type of test and test endpoint, however, the effect of PFOS to aquatic organisms has been demonstrated to be within a relatively small range. Table 3-6 summarizes the aquatic toxicity test results that are currently available. A variety of effect level test endpoints are available including the EC10, EC50 or EL50 or LL50 or LC50, LOEC and EC90. No effect levels (NOEC and NOEL) are also available. Appendix II contains the robust summaries for each of the tests shown in Table 3-6. Ongoing and planned aquatic toxicity test results are presented in Appendix IV.

Examination of Table 3-6 shows that the lowest NOEC found was 0.3 mg/L PFOS, which is calculated from a 47-day chronic test of fathead minnow conducted in 1999. The value represents the PFOS concentration at which no effect was found using a post-hatch survival of eggs as the test endpoint. In keeping with the SIDS approach of using the most sensitive indicator of PFOS effect as the PNEC, this report uses 0.3 mg/L in the risk assessment for aquatic species.

#### **3.2.2 Effects on Terrestrial and Aquatic Birds and Mammals from Bioaccumulation of PFOS**

In situations where specific species effects data are not available, inter-species extrapolation of toxicity endpoints is an accepted practice in ecological risk assessment. The magnitude of the uncertainties in such extrapolations is unknown, and could be large (Chapman et al., 1998). If fewer steps are involved in the extrapolation process, the uncertainty will be less (Sample et al., 1996). For PFOS, or any other chemical, these uncertainties should be smaller when extrapolating from mammals to mammals (e.g., rats to mink) and larger when extrapolating from mammals to birds (e.g., rats to eagles). A potentially large source of uncertainty associated with predicting effects of chemicals on birds and mammals comes from the variability associated with

sensitivity among species to toxic chemicals. Toxicity data for laboratory rats represent the most common, relatively consistent test endpoints for human health risk assessment that can be applied to terrestrial vertebrates. These endpoints will also be applied to bird species subject to the increased extrapolation uncertainties mentioned above. Use of a tissue concentration of PFOS rather than an external dose estimate reduces this uncertainty by eliminating some of the pharmacokinetic variables that exist between species. Avian chronic studies are also underway to better characterize the effects of PFOS in birds.

The preliminary results of three recent studies (see Table 3-5) evaluated the subchronic or chronic effects of PFOS on rats and monkeys, which included measurements of PFOS concentrations in serum and liver. As explained above, these results provide the best available information for characterizing the potential effects and risks of PFOS to piscivorous wildlife.

Section C of Table 3-5 presents the results of a growth and reproduction study conducted with rats. Growth and reproduction are typical endpoints used in ecological risk assessments, and have a direct ecological effects correlation at the individual and population level. Examination of the table shows that the NOEL occurred at the 0.4 mg/kg/d dosing level. No toxicologically important effects on pup survival or growth occurred at this dose. At 1.6 mg/kg/d and higher, pre-implantation loss increased and litter size, pup viability, growth, and survival decreased.

For the ecological risk characterization for piscivorous wildlife, the NOEL from the dam pre-mating group was chosen. This value is 47.1-ppm serum PFOS. Several reasons support this choice. First, this value is taken from a study on reproduction which has direct population level relevance. Second, the mammal serum values from 3M's biosphere program are generally derived from adult, nonpregnant animals. Third, end gestation values are affected by the physiologic changes occurring during pregnancy, introducing greater intra- and interspecies variability. In addition, fetal values tend to be more uncertain than adult values, because neonatal sera are difficult to collect, and the risk for contamination or dilution during collection is higher. (Note: There is a NOEL of 62.9 ppm in Section B of Table 3-5 for female rats. This number was not used because it does not represent a reproductive effect). For the ecological risk characterization for piscivorous wildlife, the 0.4 mg/kg/day dam pre-mating value of 47.1-ppm serum PFOS NOEL was used as the PNEC concentration.

Two recent studies were done to assess human health effects related PFOS toxicity to liver concentrations—the 26-week capsule toxicity study with *Cynomolgus* monkeys and the 14-week dietary study with rats. In the 26-week monkey study, the mean NOEL for liver concentrations of PFOS at the 0.15 mg/kg/day dose was 80 ppm, (Table 3-5). For the 14-week rat study, the mean (male and female average) NOEL for liver concentrations for PFOS at the 2.0 ppm dose was 72.5 ppm. (Table 3-5). Either the monkey liver value or the rat liver value could be used as PNECs for this risk assessment. The rat liver value was chosen for this risk assessment because it results in the most conservative risk estimates. Therefore, the 72.5-ppm liver PFOS concentration was used as the PNEC.

### **3.3 Initial Assessment for the Environment**

Effects to the environment are calculated using a ratio of the PEC to PNEC for both aquatic and mammalian assessments. As indicated in the SIDS manual a ratio of greater than one ( $>1$ ) indicates a specific hazard may be posed. A ratio far below one ( $<1$ ) indicates a hazard cannot be identified and the chemical can be considered to present a low potential for risk. In this assessment actual environmental data are used to evaluate risk and safety factors are not explicitly incorporated in the PNEC's or risk calculations. The inverse of the risk ratio, or PNEC/PEC, is the margin of safety.

In addition to calculating the PEC / PNEC ratios, the effects and exposure data are presented in graphical form (Figures 1, 2 and 3). The graphics provide a method for visually comparing the effects and exposure data. From the graphs, the range of effects concentrations, or range of exposure concentrations, that are contained in the current data set can be assessed. Cumulative frequency distributions of effects and exposure are created for both the aquatic and terrestrial risk assessments, and plots of the data are presented. Unlike the PEC / PNEC ratios which focus on the highest possible risk estimates, the graphical approach provides a comprehensive assessment of the potential risk of PFOS across the entire range of effects and exposure information.

#### **3.3.1 Risks to Aquatic Biota from Exposure to PFOS in Surface Waters**

Table 3-7 presents the ratio of PEC to PNEC for each of the cities in which aquatic exposure concentrations are available. The ratios range from 0.000016 at Port St. Lucie (Site 2) to 0.0096, also at Port St. Lucie (quiet surface water). The second largest ratio (0.00037) was determined for the quiet surface water sample in Decatur. All but one of the ratios is less than one by a margin of safety greater than 2000. The quiet water at Port St. Lucie is the exception, with a margin of safety of over 100. A comparison of all toxicological endpoints to the maximum PFOS concentration obtained at each of the six cities is shown in Figure 3-1. The Figure indicates that for the currently available water column data the concentration of PFOS in all samples are well below the entire range of ecotoxicological effects data. Within the bounds of uncertainty (based on this very conservative risk approach), the current information indicates that no adverse effects to aquatic biota would be associated with measured concentrations of PFOS. It should be recognized that aquatic exposure data is limited.

#### **3.3.2. Potential Risks to Terrestrial Wildlife from Bioaccumulation of PFOS**

All PEC/PNEC ratios for blood and liver PFOS concentrations in terrestrial organisms were less than one (Tables 3-8 and 3-9, respectively). These tables provide ratios for each species using the lowest tissue concentration, the maximum tissue concentration, and the average of all available tissue samples. The largest maximum ratio for PFOS in blood was 0.0552 for bald eagles. This ratio represents the degree of risk for the individual eagle with the highest measured blood concentrations of PFOS. Note that this ratio represent a margin of safety of 18. The highest mean ratio is also associated with eagles (0.0073), and represents a margin of safety of 157. Mean PEC/PNEC ratios were less for all other species.

Figure 3-2 compares the PNEC for serum concentration with the cumulative distribution of blood PFOS concentrations for all species sampled. Each value in the cumulative distribution is the mean of all samples for a particular species. Labels on the figure indicate the species used in the analysis. Examination of the figure shows that the median PFOS serum concentration for all species is approximately 0.03 ug/ml. The 5<sup>th</sup> and 95<sup>th</sup> percentile PFOS serum concentrations are approximately .004ug/ml and 0.28 ug/ml, respectively. In other words, based on current data, only 5% of the species mean PFOS serum concentrations exceed 0.64 ug/ml. Figure 3-2 shows that for the currently available environmental data the serum concentrations of PFOS in wildlife samples are well below the PNEC.

For PFOS in liver, the largest maximum PEC/PNEC ratio was 0.0676 for the mink with the highest liver concentration. This ratio represents a margin of safety of 15. The largest mean PEC/PNEC ratio is also associated with mink liver (0.0170), representing a margin of safety of approximately 59. Figure 3-3 compares the PNEC for liver concentration to the cumulative distribution of liver PFOS concentrations for all species sampled. Again, species mean values are used in the cumulative distribution. Examination of the figure shows that the median PFOS liver concentration for all species is approximately 0.08 ug/g. The 5<sup>th</sup> and 95<sup>th</sup> percentile concentrations are approximately 0.02 ug/g and 0.4 ug/g, respectively. Figure 3-3 indicates that for the currently available environmental data the liver concentrations of PFOS in wildlife samples are well below the PNEC.

The remaining species have PEC/PNEC ratios that are much smaller than those of eagles and mink. For example, the second highest maximum serum ratio is associated with herring gull (0.0046), representing a margin of safety of 217. The largest margin of safety for the maximum serum concentrations is 10,000 for the northern fur seal and the stellar sea lion. In liver, the second highest maximum ratio is associated with the river otter (0.0137), representing a margin of safety of 73. The largest margin of safety for the maximum liver concentration is seen in swordfish (5,000).

Sources of uncertainty in these risk characterizations include the following:

1. The relative sensitivities of rats, monkeys, and piscivorous wildlife species to PFOS are unknown; therefore, using rat and monkey laboratory PFOS toxicity data to predict effects to piscivorous wildlife may over- or underestimate risks. Use of a tissue concentration of PFOS rather than an external dose estimate reduces this uncertainty by eliminating some of the pharmacokinetic variables that exist between species.
2. The amount of chronic toxicity data for PFOS available at this time for predicting risks to piscivorous wildlife is limited
3. The degree to which the limited data in the biosphere sampling program for PFOS concentrations in blood and liver in piscivorous wildlife are representative of PFOS concentrations in piscivorous wildlife in general is unknown.

In summary, it can be concluded from currently available data that the observed levels of PFOS from a wide variety of samples cannot be associated with identifiable adverse effects in wildlife or the environment. PEC/PNEC ratios are substantially less than one (<1). It should be

recognized, as indicated above, that uncertainty exists in this analysis. Additional avian chronic studies are underway that will increase the amount of data available for characterizing risk to birds. Finalizing biosphere monitoring studies also will provide more information on the presence of PFOS in the environment.

### **3.3.3 Other Effects**

Standardized whole effluent toxicity tests required under the discharge permit for the manufacturing plant located in Decatur, Alabama were reviewed. Quarterly testing with *Daphnia* and fathead minnows is required. For the past two years, there has been 100% survival in the test organisms exposed to the plant effluent, which does contain PFOS.

**Table 3-1. Environmental Concentrations (PECs) for PFOS in Surface Water**

Location	Sampling Site	PEC (ng PFOS/L) ppt			Location Maximum
		Sample 1	Sample 2	Site Average	
Columbus, Georgia  Sampling locations near the Columbus Water Works Influent	Site 1	63.8	59.9	61.9	83.3
	Site 2	76.6	83.3	80	
	Site 3	55.4	55.4	55.4	
	Quiet surface water	< 25	< 25	< 25	
Pensacola, Florida  Sampling locations in Texas Bayou (selected for ease of access)	Site 1	20.8	19	19.9	28.5
	Site 2	28.5	22.8	25.7	
	Site 3	20.9	18.5	19.7	
	Quiet surface water	15.7	17.4	16.6	
Mobile, Alabama  Sampling locations near a customer's industrial wastewater treatment plant	Site 1	23.9	22	23	42.8
	Site 2	39.6	42.8	41.2	
	Site 3	34.7	36.3	35.5	
	Quiet surface water	33.3	31.5	32.4	
Decatur, Alabama  Sampling locations upstream of the Decatur POTW effluent and downstream of Water Plant	Site 1	23.1	8.3	15.7	114
	Site 2	14.5	22	18.3	
	Site 3	< 25	< 25	< 25	
	Quiet surface water	108	114	111	
Cleveland, Tennessee  Sampling locations upstream of the Cleveland Municipal POTW	Site 1	14.7	< 25	19.9	< 25
	Site 2	< 25	< 25	< 25	
	Site 3	< 25	< 25	< 25	
Port St. Lucie, Florida  Sampling locations in the vicinity of the Northport Wastewater Treatment Plant and Port St. Lucie landfill	Site 1	5.2	4.1	4.7	2,930
	Site 2	7.7	9.3	8.5	
	Site 3	7.8	5.4	6.6	
	Quiet surface water	2,930	2,850	2,890	

<sup>a</sup>Limit of quantitation is 25 ng/L and method detection limit is 2.5 ng/L.

**Table 3-2. Environmental Concentrations (PECs) of PFOS in Blood, Plasma, and Serum Samples from Wildlife Species**

Species	Number of Samples	PEC ( $\mu\text{g PFOS/mL}$ ) ppm			
		Minimum	Maximum	Mean <sup>(b)</sup>	Standard Deviation
Albatross	13	0.0035	0.039	0.011	0.011
Bald Eagle	26	0.0012 <sup>(a)</sup>	2.6	0.34	0.64
Caspian Seal	14	0.012	0.018	0.013	0.0021
Cormorant	11	0.0012 <sup>(a)</sup>	0.43	0.17	0.12
Herring Gull	4	0.066	0.45	0.22	0.18
Northern Fur Seal	44	0.0058 <sup>(a)</sup>	0.0058 <sup>(a)</sup>	0.0058 <sup>(a)</sup>	0.0
Otter	1	0.039	0.039	0.039	—
Polar Bear	14	0.0029 <sup>(a)</sup>	0.052	0.030	0.013
Stellar Sea Lion	12	0.0058 <sup>(a)</sup>	0.0058	0.0058	0.0

<sup>a</sup> Level of Quantification for the Specific Analysis

<sup>b</sup> The mean concentrations were calculated using all data points, including those that were below the limit of quantification.

**Table 3-3. Environmental Concentrations (PECs) of PFOS in Liver Samples from Wildlife Species**

Species	Number of Samples	PEC ( $\mu\text{g PFOS/g}$ ) ppm			
		Minimum	Maximum	Mean <sup>b</sup>	Standard Deviation
Albatross	9	0.035 <sup>a</sup>	0.62	0.099	0.19
Baikal Seal	24	0.035 <sup>a</sup>	0.23	0.094	0.054
Blacktailed Gull	15	0.071	0.50	0.17	0.12
Bottlenose Dolphin	5	0.0070 <sup>a</sup>	0.43	0.22	0.16
Brown Pelican	2	0.046	0.29	0.17	0.18
Brown Trout	10	0.017 <sup>a</sup>	0.026	0.018	0.0026
California Sea Lion	6	0.035 <sup>a</sup>	0.049	0.038	0.0058
Chinook Salmon	6	0.033	0.17	0.11	0.061
Cormorant	12	0.032	0.47	0.096	0.12
Elephant Seal	5	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0
Ganges Dolphin	2	0.035	0.081	0.058	0.033
Gozzi	1	0.13	0.13	0.13	--
Green Frog	4	0.035	0.29	0.097	0.13
Harbor Seal	3	0.035 <sup>a</sup>	0.057	0.042	0.013
Lake Whitefish	5	0.033	0.081	0.067	0.02
Loon	8	0.035 <sup>a</sup>	0.69	0.22	0.21
Map Turtle	6	0.039	0.70	0.19	0.26
Mink	30	0.093	4.9	1.2	1.3
Northern Fur Seal	13	0.035 <sup>a</sup>	0.12	0.043	0.024
Polar Bear	17	0.18	0.68	0.35	0.14
River Otter	5	0.15	0.99	0.39	0.35
Sea Otter	8	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0
Striped Dolphin	4	0.065	0.16	0.19	0.041
Swordfish	5	0.0070 <sup>a</sup>	0.013	0.0084	0.0028
Terrapin	3	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0
Tuna	20	0.035 <sup>a</sup>	0.25	0.08	0.052
Turtle	3	0.099	0.36	0.23	0.13
Weddell Seal	1	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0.035	--

<sup>a</sup> Level of Quantification for the Specific Analysis

<sup>b</sup> The mean concentrations were calculated using all data points, including those that were below the limit of quantification.

**Table 3-4. Environmental Concentrations (PECs) of PFOS in Other Tissue Samples from Piscivorous Wildlife Species**

Species	Tissue	Number of Samples	PEC ( $\mu\text{g PFOS/g}$ ) ppm			
			Minimum	Maximum	Mean <sup>b</sup>	Standard Deviation
Albatross	kidney	7	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0
Brown trout	eggs	3	0.049	0.075	0.064	0.013
	muscle	10	0.0070 <sup>a</sup>	0.046	0.011	0.012
Carp	body	4	0.017	0.028	0.022	0.0057
	muscle	10	0.060	0.30	0.12	0.079
Chinook salmon	muscle	6	0.0070	0.19	0.091	0.065
Cormorant	yolk	4	0.035 <sup>a</sup>	0.32	0.19	0.13
Frog	muscle, whole body	8	0.017 <sup>a</sup>	0.024	0.019	0.0027
Green frog	eggs	4	0.017 <sup>a</sup>	0.017 <sup>a</sup>	0.017 <sup>a</sup>	0
Gull	yolk	3	0.035 <sup>a</sup>	0.15	0.078	0.059
Lake whitefish	eggs	2	0.15	0.38	0.26	0.17
	muscle	5	0.097	0.17	0.13	0.035
Sea otter	brain	2	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0
	kidney	3	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0.035 <sup>a</sup>	0

<sup>a</sup> Level of Quantification for the Specific Analysis

<sup>b</sup> The mean concentrations were calculated using all data points, including those that were below the limit of quantification.

**Table 3-5. PFOS Toxicity Data for Mammals: Observed Effects, Serum and Liver PFOS Concentrations, and Cumulative Dose**

Group <sup>1</sup>	Observed Effect	Serum PFOS Concentration (ppm)	Liver PFOS Concentration (ppm)	Cumulative Dose (mg/kg)
<b>26-week Capsule-Dosing Study in Cynomolgus Monkeys</b>				
0.15 mg/kg/d	NOEL	85	80	27.3
0.75 mg/kg/d	Hepatomegaly; hepatocyte enlargement	> 100, < 300	415 (average)	> 27.3, < 137
0.75 mg/kg/d	Decreased cholesterol in females	> 134 ± 25	415 (average)	46.5
0.75 mg/kg/d	Decreased cholesterol in males	> 152 ± 30	415 (average)	67.7
0.75 mg/kg/d	Decreased T3	> 152 ± 30	415 (average)	67.7
0.75 mg/kg/d	Death or early sacrifice for 2/6 males	> 150, < 300	415 (average)	> 100, < 137
<b>14-Week Dietary Study in Sprague Dawley Rats</b>				
2.0 ppm Males	NOEL	17.9	76.8	~ 17
2.0 ppm Females	NOEL	26.9	68.25	~ 13
5.0 ppm Males	Hepatocellular hypertrophy and vacuolization	45.6	386.53	24.4
5.0 ppm Females	NOEL	62.9	362.45	38.2
20 ppm Males	Hepatocellular hypertrophy and vacuolization; decreased cholesterol; increased AAT	134	599.94	106
20 ppm Females	Hepatocellular hypertrophy and vacuolization	216	617.52	141
<b>Reproduction PK Dosing 6 weeks prior to mating and 21 days of gestation</b>				
0.4 mg/kg/d Dam PM	NOEL	47.1 ± 5.00 (n = 16)	--	16.8
0.4 mg/kg/d Fetus EG	NOEL	39.7 ± 5.90 (n = 5)	--	N/A
0.4 mg/kg/d Dam EG	NCE <sup>2</sup>	30.3 ± 17.0 (n = 6)	--	28
1.6 mg/kg/d Dam PM	Slight body weight	185 ± 14.0 (n = 16)	--	67.2
1.6 mg/kg/d Fetus EG	Survival, body weight	117 ± 14.5 (n=2)	--	N/A

**Table 3-5. PFOS Toxicity Data for Mammals: Observed Effects, Serum and Liver PFOS Concentrations, and Cumulative Dose**

<b>Group<sup>1</sup></b>	<b>Observed Effect</b>	<b>Serum PFOS Concentration (ppm)</b>	<b>Liver PFOS Concentration (ppm)</b>	<b>Cumulative Dose (mg/kg)</b>
1.6 mg/kg/d Dam EG	Slight body weight	158 ± 86.6 (n = 4)	--	112
3.2 mg/kg/d Dam PM	Body weight	368 ± 23.6 (n = 16)	--	134
3.2 mg/kg/d Fetus EG	Stillbirth, survival	191 ± 26.4 (n = 6)	--	N/A
3.2 mg/kg/d Dam EG	Body weight	180 ± 41.5 (n = 6)	--	224

<sup>1</sup> PM = Pre-Mating, after 42 days of dosing; and EG = End of Gestation, day 21 of gestation.

**Table 3-6. Aquatic Species Ecotoxicity Tests with a Survival Endpoint Using PFOS**

Ref. No.	Study Date	Species	Chronic or Acute	Toxicity Test Result (mg PFOS/L)
73	1999	<i>Daphnia magna</i>	Acute	48-h EC10 = 53
73	1999	<i>Daphnia magna</i>	Acute	48-h EC50 = 61
73	1999	<i>Daphnia magna</i>	Acute	48-h EC90 = 63
73	1999	<i>Daphnia magna</i>	Acute	24-h EC50 > 91
71	1999	Fathead minnow	Acute	96-h LC50 = 9.5
71	1999	Fathead minnow	Acute	48-h LC50 > 28
75	1999	Freshwater mussel	Acute	96-h LC50 = 59
77	1999	Mysid shrimp	Acute	96-h LC50 = 3.6
77	1999	Mysid shrimp	Acute	72-h LC50 = 4.4
504	1996	<i>Daphnia magna</i>	Acute	48-h NOEL = 6.25
504	1996	<i>Daphnia magna</i>	Acute	48-h EL50 = 11.3
503	1996	Fathead minnow	Acute	96-h NOEL < 490
503	1996	Fathead minnow	Acute	96-h LL50 = 562
87	1994	<i>Daphnia magna</i>	Acute	48-h EC50 = 210
86	1994	Fathead minnow	Acute	96-h LC50 = 19
93	1991	<i>Daphnia magna</i>	Acute	48-h EC50 = 14
90	1979	Bluegill sunfish	Acute	96-h NOEC = 18
90	1979	Bluegill sunfish	Acute	96-h LC50 = 31
184	1974	Fathead minnow	Acute	96-h LC50 = 85
185	1974	Fathead minnow	Acute	96-h LC50 = 100
79	1999	<i>Daphnia magna</i>	Chronic	21-d NOEC = 12
<b>78</b>	<b>1999</b>	<b>Fathead minnow</b>	<b>Chronic</b>	<b>47-d NOEC = 0.3<sup>a</sup></b>
78	1999	Fathead minnow	Chronic	47-d LOEC = 0.6
80	1999	Mysid shrimp	Chronic	35-d NOEC = 0.55
84	1978	Fathead minnow	Chronic	30-d NOEC = 1
84	1978	Fathead minnow	Chronic	30-d LOEC = 1.9

<sup>a</sup> Bold indicates the value used in this risk assessment.

**Table 3-7. Aquatic Species PEC/PNEC Ratios for Six Locations**

Location	PEC <sup>a</sup> /PNEC <sup>b</sup> Ratio			
	Site 1	Site 2	Site 3	Quiet Surface Water
Columbus, GA	$2.1 \times 10^{-4}$	$2.7 \times 10^{-4}$	$1.8 \times 10^{-4}$	$8.3 \times 10^{-5}$
Pensacola, FL	$6.6 \times 10^{-5}$	$8.6 \times 10^{-5}$	$6.6 \times 10^{-5}$	$5.5 \times 10^{-5}$
Mobile, AL	$7.7 \times 10^{-5}$	$1.4 \times 10^{-4}$	$1.2 \times 10^{-4}$	$1.1 \times 10^{-4}$
Decatur, AL	$5.2 \times 10^{-5}$	$6.1 \times 10^{-5}$	$8.3 \times 10^{-5}$	$3.7 \times 10^{-4}$
Cleveland, TN	$6.6 \times 10^{-5}$	$8.3 \times 10^{-5}$	$8.3 \times 10^{-5}$	—
Port St. Lucie, FL	$1.6 \times 10^{-5}$	$2.8 \times 10^{-5}$	$2.2 \times 10^{-5}$	$9.6 \times 10^{-3}$

<sup>a</sup> Site average PEC, in units of ng PFOS/L, presented in Table 3-1.

<sup>b</sup> The value used as the PNEC is 0.3 mg PFOS/L, based on study reference no. 78 as presented in Table 3-6. Note that the value 0.3 mg PFOS/L is an actual measured value. Safety factors are not used in the calculation of the PEC/PNEC ratio.

**Table 3-8. Piscivorous Wildlife Species PEC/PNEC Ratio for Serum**

Species	PEC <sup>a</sup> /PNEC <sup>b</sup> Ratio		
	Minimum	Maximum	Mean
Albatross	0.0001	0.0008	0.0002
Bald Eagle	0.0000	0.0552	0.0072
Caspian Seal	0.0003	0.0004	0.0003
Cormorant	0.0000	0.0091	0.0036
Herring Gull	0.0014	0.0096	0.0047
Northern Fur Seal	0.0001	0.0001	0.0001
Otter	0.0008	0.0008	0.0008
Polar Bear	0.0001	0.0011	0.0006
Stellar Sea Lion	0.0001	0.0001	0.0001

<sup>a</sup> Minimum, maximum, and mean PECs ( $\mu\text{g PFOS/mL}$ ) are presented in Table 3-2.

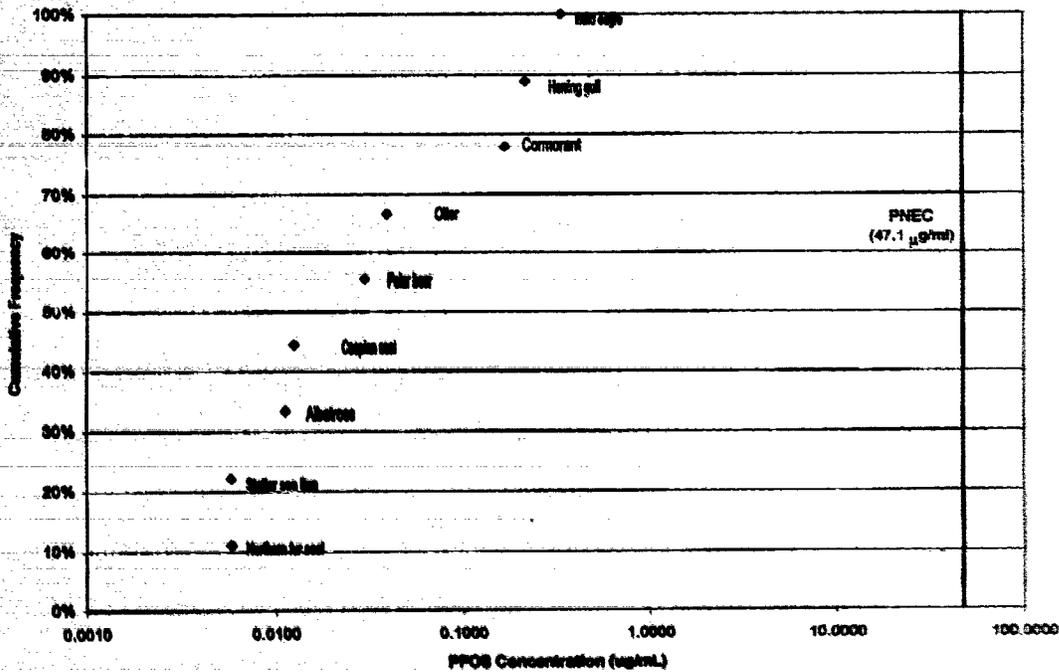
<sup>b</sup> The value used as the PNEC for serum is 47.1 mcg or  $\mu\text{g/l}$ .

**Table 3-9. Piscivorous Wildlife Species PEC/PNEC Ratios for Liver**

Species	PEC <sup>a</sup> /PNEC <sup>b</sup> Ratio		
	Minimum	Maximum	Mean
Albatross	0.0005	0.0086	0.0014
Baikal Seal	0.0005	0.0032	0.0013
Blacktailed Gull	0.0010	0.0069	0.0023
Bottlenose Dolphin	0.0001	0.0059	0.0030
Brown Pelican	0.0006	0.0040	0.0023
Brown Trout	0.0002	0.0004	0.0002
California Sea Lion	0.0005	0.0007	0.0005
Chinook Salmon	0.0005	0.0023	0.0015
Cormorant	0.0004	0.0065	0.0013
Elephant Seal	0.0005	0.0005	0.0005
Ganges Dolphin	0.0005	0.0011	0.0008
Gozzi	0.0018	0.0018	0.0018
Green Frog	0.0005	0.0040	0.0013
Harbor Seal	0.0005	0.0008	0.0006
Lake Whitefish	0.0005	0.0011	0.0009
Loon	0.0005	0.0095	0.0030
Map Turtle	0.0005	0.0097	0.0026
Mink	0.0013	0.0676	0.0166
Northern Fur Seal	0.0005	0.0017	0.0006
Polar Bear	0.0025	0.0094	0.0048
River Otter	0.0021	0.0137	0.0054
Sea Otter	0.0005	0.0005	0.0005
Striped Dolphin	0.0009	0.0022	0.0014
Swordfish	0.0001	0.0002	0.0001
Terrapin	0.0005	0.0005	0.0005
Tuna	0.0005	0.0034	0.0011
Turtle	0.0014	0.0049	0.0032
Weddell Seal	0.0005	0.0005	0.0005

- a) Minimum, maximum and mean PEC's ( $\mu\text{g PFOS/g}$ ) are presented in Table 3-1.  
b) The value used as the PNEC for liver is  $72.5 \mu\text{g/g}$  (Table 3-5)





**Figure 3-2. Cumulative frequency distribution of mean PFOS concentrations in blood samples of piscivorous wildlife species. [Note: Cumulative frequency of the exposure results is calculated by first ordering the data from lowest to highest, while keeping track of the order number. The order number is then divided by the total number of observations and then converted to a percentage. The resulting cumulative frequency is a value that ranges from 0 to 100 percent.]**

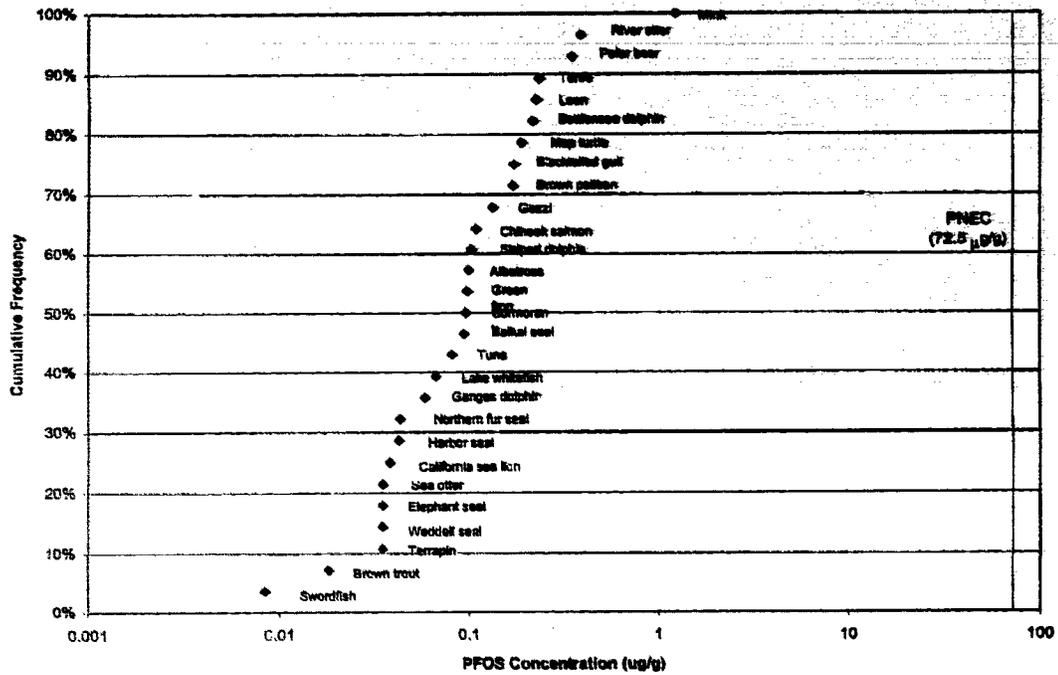


Figure 3-3. Cumulative frequency distribution of mean PFOS concentrations in liver samples of piscivorous wildlife species. [Note: Cumulative frequency of the exposure results is calculated by first ordering the data from lowest to highest, while keeping track of the order number. The order number is then divided by the total number of observations and then converted to a percentage. The resulting cumulative frequency is a value that ranges from 0 to 100 percent.]

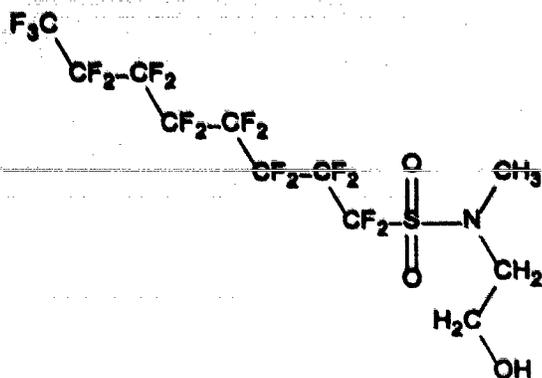
## 4.0 HUMAN HEALTH

### 4.1 Introduction

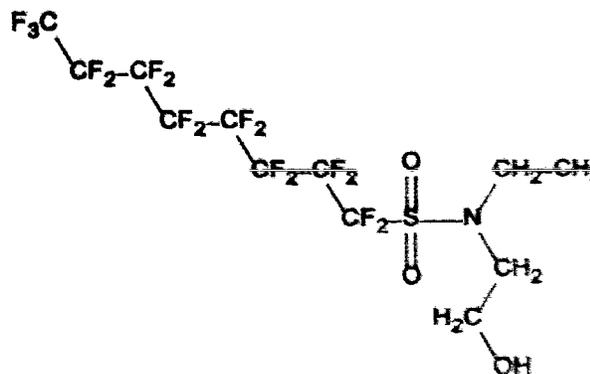
This section contains a summary of the available data relating to the potential for PFOS to induce adverse effects in humans. The available data consist of a large body of epidemiological, animal, and other types of experimental data, reported over the past 25 years. Substantial dose-response data now exist relating serum levels to adverse outcomes in experimental animals, including primates. Included are repeat-dose studies, two-generation reproduction-development studies, teratology studies, and genotoxicity studies. Still in progress, and not reported here, are chronic animal studies; results from these long-term bioassays will be available by the end of 2000. The majority of citations in this Section are from studies and reports from 3M sponsored work, the details of which are found in Robust Summaries. These Robust Summaries are contained in Appendix V of this SIAR. The authors of this section wish to acknowledge the effort of U.S. EPA scientists in preparing many initial Robust Summary drafts that were further developed and edited by the SIAR authors.

The principle focus of all of this work is PFOS. The toxicity testing program includes two related compounds, N-ethylperfluorooctane sulfonamidoethanol (N-EtFOSE) and N-methylperfluorooctane sulfonamidoethanol (N-MeFOSE). The structures of these chemicals are shown below. Both are components of commercial products, and both are known to be absorbed and undergo metabolism to yield PFOS.

N-Methylperfluorooctane sulfonamidoethanol



N-Ethylperfluorooctane sulfonamidoethanol



Both of these compounds have been subjected to repeat dose toxicity and genotoxicity testing, and the ethyl derivative has also been evaluated in teratology and two-generation reproduction studies. As will be seen, both compounds produce effects very similar to those produced by PFOS. This suggests that the toxicities of PFOS precursor molecules may be due to PFOS accumulation as opposed to the precursor molecules themselves, or to any of the intermediary metabolites leading to PFOS. This conclusion can not be verified until a careful quantitative evaluation of PFOS serum levels in relation to toxicity is completed. Thus, for the present, the data on the N-ethyl and N-MeFOSE alcohol derivatives is presented for completeness, and because they confirm, at least qualitatively, the PFOS results.

## **4.2 Human Exposure**

### **4.2.1 Background**

The data on PFOS levels in human serum samples are presented in this section. The presence of organic fluorine in human serum was observed 30 years ago. The advancement of analytical chemistry has had a significant influence on knowledge of fluorocarbons in human sera. The techniques developed and used by researchers in the 1960's and 1970's were time-intensive, requiring hours for a single analysis. The methods were generally nonspecific, measuring "organic fluorine compounds" (any compound having fluorine covalently bonded to carbon) rather than specific molecules. The development of a rapid analytic technique in the late 1970's decreased analytic time for total organic fluorine to under an hour, allowing large-scale medical surveillance of production employees at higher detection limits (about 0.5 parts per million organic fluorine) that were adequate for the levels found in occupationally exposed individuals. The advancement of chromatographic/mass spectroscopy technology enabled, by the early 1990's, rapid analysis of specific fluorochemicals from small volumes of sera. This technology was first used in medical surveillance in 1993. Detection limits for PFOS in serum were lowered to 50 parts per billion by 1997.

This section presents: 1) a brief summary of the historical information regarding organic fluorine in human sera; 2) data from 3M employees involved in fluorochemical production; and 3) data from various sources of human sera that may represent non-occupational exposures.

#### **Historical Finding of the Organic Form of Fluorine in Blood**

Taves (1968a) described two forms of fluorine in serum, one that was exchangeable with radioactive fluorine-18 and one that was not. Pothapragada et al. (1971) also described two forms, ionic and nonionic. Taves (1968b) showed that the non-exchangeable fluorine was bound to albumin. This finding, along with results of extraction and precipitation and the need for ashing to release this form of fluorine, led to the conclusion that the non-exchangeable or nonionic fluorine was "organic", i.e. covalently bound to carbon (Taves et al. 1976). Using NMR spectroscopy, these authors tentatively identified a component of the organic fluorine as perfluorooctanoic acid (PFOA). There was some variation in the observed spectra from an authentic sample of PFOA, however, leading the authors to suggest that branching, or the presence of a sulfonate, was possible. Subsequent efforts by 3M researchers identified both PFOS and PFOA in blood.

A number of studies over the past 25 years reported levels of organic fluorine in human blood serum from presumably non-occupationally exposed persons. Table 4-1 presents the study author, level measured, populations studied and methods of analysis. The variety of methods used for determination of fluorine suggests that some caution be used in interpreting results. All reported means were in the tens-of-parts per billion levels. The average of reported values from United States sources is 0.038 ppm.

**Table 4-1. Historical Findings of Serum Organic Fluorine Levels in the General Population**

Year	Author	OF* (ppm)	N	Method**	Source
1972	Guy	0.030	65	Ash	US
1975	Pothapragada	0.036	2	O bomb	US
1976	Guy, Taves	0.025	106	Ash	US
1978	Belisle	0.020	9	O bomb	US
1979	Singer	0.045	264	Ash	US
1980	Paez	0.085	Pooled	Ash	Argentina
1980	Ubel	0.045	4	Mod O bomb	US
1981	Belisle	0.011	8	O bomb	China
1989	Yamamoto	0.032	11	LOPA	Japan

\* Organic fluorine, specific identities not provided.

\*\* Varied methods were used to measure organic fluorine. See papers for details.

#### **4.2.2 Occupational Exposures**

3M manufactures POSF, a starting material for other fluorochemicals that may then degrade or metabolize, to an undetermined degree, to PFOS. Employees may be exposed by one or more routes (i.e., inhalation, skin contact/absorption, or ingestion) to fluorochemicals in the manufacturing environment. The primary route of exposure varies among employees and depends on several factors, including process conditions, job tasks, work location, personal hygiene, personal habits and general work practices. Exposure estimation has been exceedingly difficult when multiple sources of exposure are probable. Biological monitoring data (e.g., serum levels) may address this problem as it allows for an internal measurement assessment from all exposure sources. Biological monitoring data are especially relevant where they reflect dose to the target organ (e.g., liver). This is likely to be the situation for PFOS as it has been observed in cynomolgus primates that the liver to serum ratio is approximately 1:1 up to serum levels approaching 100 ppm (see section 4.3.1).

Table 4-2 presents PFOS serum values obtained from plant employees in Decatur (Alabama, USA), Antwerp, (Belgium), and Sagamihara Japan [RS6, RS8, RS9]. The Decatur and Antwerp plants are involved in fluorochemical production, whereas the Sagamihara facility handles, but does not produce, sulfonated perfluorochemicals. Although voluntary biennial medical surveillance of production employees began in the late 1970's, routine specific measurement of serum PFOS levels did not commence until the mid-1990's. [Note: Prior to this time period, total organic fluorine was measured. Fluorine is 65% of the molecular weight of PFOS. The contribution of PFOS to organic fluorine, in ppm, will therefore be 0.65 x (PFOS value in ppm). PFOS was measured in 5 Decatur employee sera samples in 1979 but analytical techniques were too time consuming and required too large a volume of serum for routine medical surveillance.]

A voluntary medical surveillance program may not lend itself to an adequate characterization of the distribution of employee fluorochemical serum levels if participation rates are low as a consequence of respondent (i.e., selection) bias. Because the extent of this potential bias was unknown for the fluorochemical medical surveillance programs at the Decatur and Antwerp

manufacturing plants, a cross-sectional study was designed in 1998 to randomly sample employees at the Decatur (Alabama) manufacturing site (RS6). The purpose of the study was to determine whether the distribution of employee serum fluorochemical levels observed in the voluntary medical surveillance programs was a reasonable reflection of the plant population. A total of 232 Decatur employees were randomly sampled; 186 (80%) participated. Respondents and non-respondents (n = 46) were comparable with respect to age, gender and employment duration. Of the randomly sampled participating employees, 126 were from the chemical plant and 60 from the film plant (where fluorochemicals were not manufactured, although in one production run a fluorochemical is occasionally used). Blood levels of the fluorochemicals were analyzed according to the employees' demographics, current or longest-held job, and the locations of jobs within the chemical plant. Serum PFOS levels were weakly associated in a linear fashion with years worked in the chemical plant ( $r^2 = 0.11$ ). No positive association was observed between frequency of self-reported hand-to-mouth usage or hand cleanliness and serum PFOS levels.

**Table 4-2. PFOS Serum Concentrations: Occupational Populations**

<i>Location &amp; Year</i>	<i>Mean (ppm)</i>	<i>Range (ppm)</i>
<b>Decatur (Alabama): Plant</b>		
1994 (n = 100) <sup>a</sup>	2.44	0.25 – 12.83
1997 (n = 84) <sup>a</sup>	1.96	0.10 – 9.93
1998 Chemical (n = 126) <sup>b</sup>	1.51	0.09 – 10.60
1998 Film (n = 60) <sup>b</sup>	0.17	0.02 – 0.95
<b>Antwerp (Belgium): Plant</b>		
1995 (n = 88) <sup>a</sup>	1.93	0.00 – 9.90
1997 (n = 65) <sup>a</sup>	1.48	0.10 – 4.83
<b>Sagamihara (Japan): Plant</b>		
1999 Production (n = 32) <sup>c</sup>	0.14	<0.03 – 0.63
1999 Management (n = 32) <sup>c</sup>	0.04	<0.03 – 0.06
<sup>a</sup> Voluntary study. Estimated participation rates < 50% of employees who routinely or periodically worked in the chemical plant. <sup>b</sup> Random sample cross-sectional study. <sup>c</sup> Voluntary cross-sectional study.		

The distribution of serum PFOS levels measured in this random sample was similar to that previously reported from the voluntary medical surveillance examinations. Thus, it was unlikely that employee serum PFOS levels higher than that observed in the medical surveillance programs existed in these fluorochemical manufacturing populations. Results from this random sample assessment are currently being used in the construction of an exposure matrix for the updated retrospective cohort mortality study of the Decatur employee population (see Section 4.4.3). These biological monitoring data were also used in the ongoing analysis of health claims comparison analysis between chemical and film plant employees from 1993-1998 (see Section 4.4.3).

There are many industrial uses of fluorochemical-containing compounds, and it is likely that PFOS could be found in serum samples from workers in these various user industries. 3M production employees are exposed to concentrated PFOS precursors whereas downstream workers are generally exposed to PFOS precursors in concentrations of less than 1% as residual starting materials in polymer products. This suggests downstream workers should have lower serum levels of PFOS than those observed in 3M production employees. The Sagamihara sampling data is consistent with this viewpoint.

#### **4.2.3 Non-occupational Exposures**

In 1998, three questions were addressed to delineate the extent to which PFOS might be present in the blood of members of the general population not exposed occupationally to precursor molecules:

- 1) Is PFOS detectable in human blood samples from a corporate-based 3M employee population known not to have worked in 3M fluorochemical manufacturing or use plants?
- 2) Is PFOS detectable in pooled blood samples from the general population and from

- different geographical locations across the United States and outside the United States?
- 3) Is PFOS detectable in historical human blood samples collected prior to the introduction of POSF-based chemicals into the marketplace?

To address the first two of questions several studies were conducted and the data from them are summarized in Table 4-3. PFOS could be detected in the serum of adults in the United States (RS27, RS29, RS30) and could be detected in children using a very small amount of serum (0.1 ml) (RS31). PFOS could also be detected in the serum of adults in Belgium, the Netherlands, Germany, Sweden and Japan (RS27, RS29, RS28). No inferences could be developed regarding associations between PFOS and demographics (e.g., age, and gender), time trends and source(s).

**Table 4-3. PFOS Serum Concentrations: Non-Occupational Populations (1998-1999)**

<i>Population</i>	<i>Mean (ppm)</i>	<i>Range (ppm)</i>
3M Corporate Center (n = 31)	0.047	0.028 - 0.096
Tokyo (Japan): Head Office (n = 30)	0.052	<0.03 - 0.097
<i>Commercial Laboratories<sup>a</sup></i>		
Intergen (pooled: approx 500 donors)	0.044	0.043 - 0.044
Sigma (pooled: approx 200 donors)	0.033	0.026 - 0.045
35 Lots Commercial Labs	0.035	0.005-0.085
US Blood Banks (n = 18 pooled samples) <sup>b</sup>	0.030	0.009 - 0.056
<i>European Blood Banks (pooled samples)<sup>c</sup></i>		
Belgium (n = 5)	0.017	0.005-0.022
Netherlands (n = 6)	0.053	0.039-0.061
Germany (n = 6)	0.037	0.032-0.046
Sweden (n = 39 individuals) <sup>d</sup>		
28 individuals	< 0.032 (LLOQ)	-
11 individuals	0.048	0.032-0.085
Children (U.S., n = 10 individuals) <sup>e</sup>	0.054	0.031 - 0.115
<sup>a</sup> Donor pool information, such as age, sex, or geographical location, not available. <sup>b</sup> 3 to 6 samples per blood bank, 5 to 10 donors per sample. Geographically distributed across the continental US and Alaska. Not a statistically valid sample of the US population (RS29). <sup>c</sup> pooled samples, 10 donors per sample in Belgium and the Netherlands; 30 donors per sample in Germany (RS28). <sup>d</sup> RS7 <sup>e</sup> Pilot analysis. Limited serum (0.1 ml) from children aged 6 or 12 who were enrolled in a group A streptococcal study. Study is in progress. RS31		

To address the third exploratory question, historical samples were obtained to learn whether PFOS could be detected in samples obtained prior to the manufacture of precursor compounds (the late 1940's). PFOS was not detected in ten pooled samples (10 donors per sample) from U.S. military recruits of the Korean War era (1948-1951). Analysis of 10 Swedish samples collected in 1958 resulted in a range of values from non-detect to 2 ppb. A limited number of samples taken during the conduct of several post-1969 epidemiological studies conducted in the United States were analyzed and serum PFOS levels ranging from non-detect to 59 ppb could be identified. Analysis of serum samples from two Chinese rural provinces (Linxian, Shandong) that were collected in 1984 and 1994 showed no detectable PFOS.

It appears from this limited sampling that PFOS presence in human serum coincides with the introduction of PFOS-precursor molecules; the conclusion is highly uncertain because of the sparseness of the database. Definitive statements regarding time trends cannot be made at this time.

#### **4.2.4 Forthcoming Studies**

Several additional studies to address human exposure are being sponsored. These include the following:

- 1) An analysis of 500 individual, contemporary adult blood samples from the American Red Cross in order to obtain a cross sectional analysis of serum PFOS levels in adults by age, gender and in up to 5 U.S. geographical locations;
- 2) An analysis of approximately 250 individual elderly adult samples (ages 65 - 99) from an ongoing study of cognitive function among the elderly in the Seattle, Washington area;
- 3) An analysis of 600 children's samples (ages 2 - 12) from 23 states who were enrolled in a group A streptococcal clinical trial in the mid-1990's;
- 4) A comparison of liver to serum PFOS ratios from 30 human organ donors; and
- 5) A time trend analysis of fluorochemicals, including PFOS, in sera that were collected in Maryland in 1974 and 1989 from the same 59 individuals as well as 120 different individuals in the two time periods (ages 20-60+).

All of these research efforts are scheduled for completion by the first quarter of 2001.

#### **4.2.5 Indirect Exposure via the Environment**

Human exposure via the environment is discussed as part of section 3.1.1.

### **4.3 Effects on Human Health**

#### **4.3.1 Mode of Action, Toxicokinetics, Metabolism**

##### **4.3.1.1 Mode of Action**

The mechanisms governing the biological responses to PFOS exposure observed in toxicological studies are currently under investigation. Several studies provide clues to the potential modes of toxicity. Competition with fatty acids for carrier protein binding sites (Nabbefeld et al 1998, Nabbefeld 1988), cholesterol synthesis (Haugham and Øystein, 1992) and bioenergetics (Wallace and Starkov, 1998) have been studied. In addition PFOS has been reported to induce peroxisome proliferation (Sohlenius et al., 1993, Ikeda et al., 1987). No conclusions have been reached on the importance of any of these possible mechanisms toxicity at this time.

#### **4.3.1.2 Toxicokinetics and Metabolism**

The absorption, tissue distribution, potential metabolism and excretion of PFOS have been studied most extensively in rats by both radiolabel and direct quantitation. Data relating oral dose to serum and liver concentrations of PFOS in the cynomolgus monkey during dosing and recovery is available from direct quantitation. In addition, serum PFOS concentrations in retired 3M chemical workers have been followed in an attempt to estimate an elimination rate constant for the human.

##### **Absorption**

PFOS is well absorbed from the digestive system. A radiolabel study in which adult male rats were given a single oral dose of 4.2 mg/kg [<sup>14</sup>C]PFOS demonstrated that > 95 % of the dose was absorbed in the first 24 hours (RS60).

Dermal absorption of PFOS appears to be possible but is limited. In one study, PFOS was applied under occlusion to approximately 40 % of the body surface area of male and female New Zealand White rabbits at 5,000 mg/kg and left in place for 24 hours (RS54). Blood samples were obtained on days 1, 7, 14, and 28. Analysis for total blood fluoride was performed on day one and day 28 samples from a single male and single female. Total serum fluoride values for the male were 10.3 ppm for day one and 130 ppm for day 28. The respective values for the female were 0.9 ppm and 128 ppm. Although this study indicated some dermal absorption at a high dose, it is limited in that the values from only two animals were measured, and only from the day one and day 28 samples (O'Malley and Ebbens, 1981).

No quantitative information is available on the absorption of PFOS from inhalation exposure. Due to the exceptionally low vapor pressure of PFOS, inhalation exposure would be unlikely. If it does occur it would be associated with aerosols or particulates containing PFOS.

##### **Distribution**

PFOS distributes predominantly to the blood and liver, with liver concentrations being potentially several times higher than serum concentrations, depending on species and dose. A radiolabel study in which adult male rats were given a single intravenous dose of 4.2 mg/kg [<sup>14</sup>C]PFOS demonstrated that the carbon-14 in liver and plasma represents 25 and 3% of the dose, respectively, after 89 days. During the 89-day post-dose period, the rats excreted a mean of 30.2% of the total carbon-14 via urine and the mean cumulative fecal excretion was 12.6%. At 89 days, mean tissue concentration of total carbon-14 expressed as µg [<sup>14</sup>C]PFOS equivalents/g were: liver, 20.6; plasma, 2.2; kidney, 1.1; lung, 1.1; spleen, 0.5; and bone marrow, 0.5. Lower concentrations (≤0.5) were measured in adrenals, skin, testes, muscle, fat and eye. No radioactivity (<0.05) was detected in brain. (RS57).

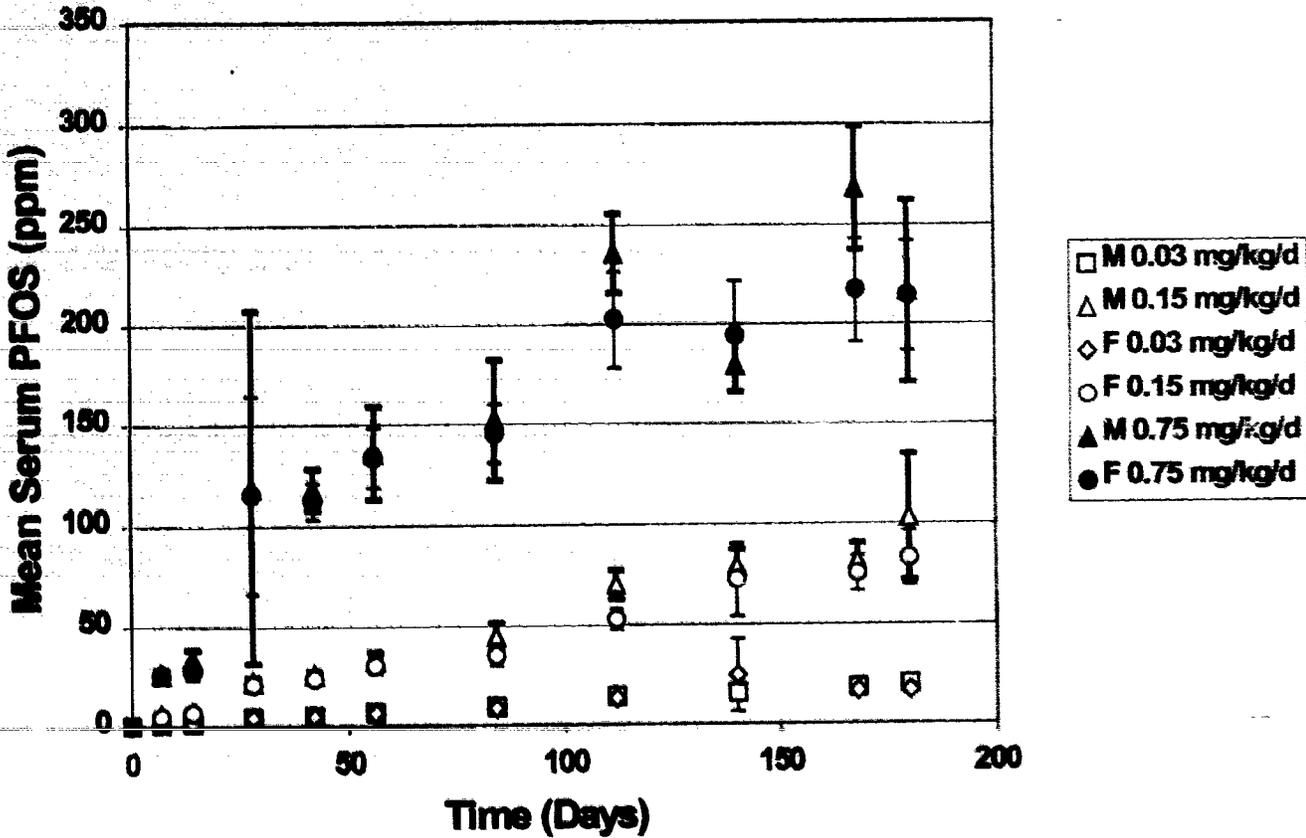
Significant enterohepatic circulation of PFOS has been reported as evidenced by the fact that cholestyramine (four percent by weight in diet) treatment of rats given single intravenous doses of PFOS increased fecal elimination 9.5 times over control (RS58).

The volume of distribution in male and female cynomolgus monkeys on daily dosing has been

estimated as 0.2 L/kg (RS34). Monkeys dosed by oral capsule with PFOS (0.02 and 2.0 mg/kg/day) demonstrated a linear ( $r$ -squared > 0.99) increase in serum concentration throughout the exposure period (28 days). There was no apparent sex difference and the individual slopes of the cumulative PFOS dose versus serum PFOS concentration curves appeared to be virtually identical for the monkeys in the two dose groups. The average slope of the curve in the 0.02 mg/kg/day group ( $n = 6$ ) was  $5.22 \pm 0.74$  ppm PFOS in serum per mg/kg cumulative dose. The two monkeys in the 2.0 mg/kg/day dose group had an average slope of  $5.40 \pm 0.61$  ppm PFOS in serum per mg/kg PFOS cumulative dose. At the end of the 28-day dosing period, serum concentration in the 0.02 and 2.0 mg/kg/day groups were approximately 3 ppm and 300 ppm. These data suggest a volume of distribution of 0.2 L/kg for continuous dosing over a two order of magnitude range.

In a 26-week capsule-dosing study in cynomolgus monkeys, a similar pattern of increasing serum concentration with cumulative dose was observed (RS32). At the lower doses, 0.03 and 0.15 mg/kg/day, serum levels increased in fairly linear fashion and reached means of 18 ppm and 85 ppm at the end of the dosing period, respectively. At the 0.75 mg/kg/ dose, the increase in serum PFOS appeared to saturate, reaching a mean of 215 ppm by the end of the dosing period. The accumulation of PFOS in the serum of male and female monkeys appeared similar in all dose groups. Figure 4.1 shows the trend in group mean serum concentrations during the dosing period.

**Figure 4-1. Mean serum PFOS concentrations for males and females during 182 days of oral dosing at either 0.03, 0.15 or 0.75 mg/kg/day.**



Male and female CR:CD rats continuously exposed to PFOS in the diet for 14 weeks (RS39) also showed a linear relationship between dose and serum concentration as is shown by the data in Table 4-4.

**Table 4-4. Serum concentrations in male and female rats after 14-weeks of exposure to PFOS in the diet.**

Males	Dose Group <sup>a</sup>			
	0.5 ppm (0.036 mg/kg) <sup>b</sup>	2.0 ppm (0.1 mg/kg) <sup>b</sup>	5.0 ppm (0.35 mg/kg) <sup>b</sup>	20 ppm (1.37 mg/kg) <sup>b</sup>
Estimated Cumulative Dose (mg/kg)	3.2	12.6	31.1	123.3
Serum PFOS concentration	4.22 ppm (8.5 µM)	17.9 ppm (35.9 µM)	45.6 ppm (91.4 µM)	134 ppm (304.6 µM)

Females	Dose Group <sup>a</sup>			
	0.5 ppm (0.04 mg/kg) <sup>b</sup>	2.0 ppm (0.16 mg/kg) <sup>b</sup>	5.0 ppm (0.41 mg/kg) <sup>b</sup>	20 ppm (1.6 mg/kg) <sup>b</sup>
Estimated Cumulative Dose (mg/kg)	3.6	14.6	37.0	144.0
Serum PFOS concentration	6.7 ppm (13.3 µM)	26.9 ppm (53.9 µM)	62.9 ppm (126.0 µM)	216 ppm (432.9 µM)

<sup>a</sup> Dietary concentration of PFOS in ppm (µg PFOS/g diet)

<sup>b</sup> Estimated dose based on feed analysis, feed consumption and body weight during study

Distribution across the placenta and exposure of the fetus *in utero* has been demonstrated. Table 4-5 presents serum concentrations from a pharmacokinetic study conducted during pregnancy (RS52). Dams were treated with vehicle only (control), 0.1, 0.4, 1.6 or 3.2 mg/kg/day PFOS by oral gavage for 42 days prior to mating, during mating and during gestation. Serum was obtained from dams prior to mating and on gestation days 7, 14 and 21. Serum was obtained from pooled fetal litters on gestation day 21. The pre-mating and gestation day 21 values are represented in the Table 4-5.

**Table 4-5. Maternal and fetal PFOS serum and liver PFOS concentrations associated with gestation (rats).**

Dose Group Mg/kg/d <sup>a</sup>	Media	Mean Serum and Liver [PFOS] in ppm		
		Pre-mating <sup>b</sup>	Gestation Day 21	
		Dams (n)	Dams (n)	Fetal Litter (n)
0.1	Serum	10.3 ± 1.26 (16)	4.91 ± 1.23 (7)	10.5 ± 1.01 (7)
	Liver	---	23.4 ± 3.76 (8)	9.17 ± 1.08 (7)
0.4	Serum	47.1 ± 5.00 (16)	30.3 ± 17.0 (6)	39.7 ± 5.90 (5)
	Liver	---	107 ± 25.2 (7)	42.5 ± 19.4 (6)
1.6	Serum	185 ± 14.0 (16)	158 ± 86.6 (4)	117 ± 14.5 (2)
	Liver	---	440 ± 316 (5)	100 ± 30.6 (2)
3.2	Serum	367 ± 23.6 (16)	180 ± 41.5 (6)	191 ± 26.4 (6)
	Liver	---	598 ± 83.9 (6)	265 ± 70 (6)

- a) Dams were treated daily by oral gavage for 42 days prior to mating, during mating and through gestation.  
 b) After 42 days dosing

The apparent lack of correspondence in the relationship of dose to serum level when comparing the 14-week dietary study and the reproduction study may be explained by the fact that the reproduction study was a gavage study, as opposed to the 14-week dietary study. In the latter study, mg/kg dose levels were estimated based on feed analysis, feed consumption and body weight during the course of the study. Feed consumption is an error-prone measurement, due to the possibility of spilled (unconsumed) feed. Dietary doses also represent a continuous source of exposure as opposed to pulse dosing by gavage.

Serum levels at the end of lactation after exposure in the PFOS reproduction study are represented in Table 4-6.

**Table 4-6. Comparison of serum PFOS levels at the end of lactation after dosing rats with PFOS for 42 days pre-mating, during mating, gestation and through lactation (approximately 13 weeks).**

PFOS Dose	[PFOS] in Serum
0.0 mg/kg	0.037 ± 0.020
0.1 mg/kg	5.28 ± 0.358
0.4 mg/kg	18.9 ± 1.30
1.6 mg/kg	82 ± 17.5

There is conclusive evidence from the cross-fostering study that PFOS distributes to milk and also crosses the placenta. These data are discussed in Section 4.3.4.

### Metabolism

PFOS is not known to undergo further metabolism or to form conjugates. Preliminary data from analysis of urine, feces and tissues of rats as well as the inherent stability of perfluorinated anions suggest that PFOS is not metabolized (Johnson et al., 1984). Analysis by LC/MS of serum and liver samples from recent studies has not revealed any evidence of metabolism.

Certain chemicals made from perfluorooctanesulfonyl fluoride (POSF) may undergo a degree of metabolism to PFOS. For example, N-EtFOSE can be metabolized to PFOS. In one study, in which rats were administered  $^{14}\text{C}$ -N-EtFOSE in feed, at least 28% of the radioactivity found in the liver at 48 hours was PFOS (RS56). This represented 4.4% of the administered dose.

### Excretion

Single intravenous doses (mean 4.2 mg/kg) of [ $^{14}\text{C}$ ]PFOS in 0.9% NaCl were administered to male rats (RS57). By 89 days after dosing, 30.2% of the administered  $^{14}\text{C}$  had been excreted in the urine and 12.6% had been excreted in the feces. Whole body elimination in the male rat appeared to be biphasic. Initial redistribution from the plasma yielded a plasma elimination half-life of  $^{14}\text{C}$  of 7.5 days following single oral administration of [ $^{14}\text{C}$ ]PFOS (mean dose 4.2 mg/kg) to male rats (RS60). In the aforementioned intravenous study, elimination of only 42.8 % of the dose through urine and feces after 89 days indicates that the half-life of elimination from the body is > 89 days in the male rat.

Cynomolgous monkeys have been followed for one year in recovery after six months of daily oral dosing by capsule at 0.15 or 0.75 mg/kg/day (RS32). While the numbers of animals are limited (two per sex per dose group), the values suggest mean serum elimination half-lives of 189 days for the mid-dose recovery group and 175 days for the high-dose recovery group. There are likely no true differences in serum PFOS elimination rates between the mid-dose and high-dose groups. A low-dose recovery group was not part of the study design.

Fecal and total excretion of  $^{14}\text{C}$  were markedly increased in male rats administered cholestyramine (~ 2.7 g/kg/d) in their diet following single intravenous doses of [ $^{14}\text{C}$ ]PFOS (Johnson and Gibson, 1984 and RS58). The results suggest that there was significant enterohepatic circulation of PFOS. Cholestyramine administered at 4% by weight in feed to male rats decreased the retention of carbon-14 in liver, plasma, and red blood cells and increased the elimination of carbon-14 via feces after iv dosing with PFOS- $^{14}\text{C}$ . Groups of five rats were dosed intravenously with PFOS- $^{14}\text{C}$  (mean dose, 3.4 mg/kg). Rats were sacrificed at 21 days post dose. The mean liver, plasma, and red blood cell concentration as well as fecal and urinary excretion of  $^{14}\text{C}$  for cholestyramine-treated rats were compared to mean control rat values. Mean cholestyramine-treated rat  $^{14}\text{C}$  concentrations in liver (9.4 $\mu\text{g/g}$ ), plasma (0.9 $\mu\text{g/ml}$ ), and red blood cells (0.3  $\mu\text{g/g}$ ) represent a decrease from mean control rat concentrations of 3.8, 7.7, and 6.0 fold, respectively. Fecal elimination (75.9% with cholestyramine treatment) was increased 9.5 fold. The extent of urinary  $^{14}\text{C}$  elimination, as a result of the relatively high rate of fecal elimination of  $^{14}\text{C}$  was lower in cholestyramine-treated rats. The extent of total elimination of  $^{14}\text{C}$  (urine plus feces) was higher in the cholestyramine-treated rats.

### Human Data

Serum PFOS levels in three retired male 3M chemical workers followed for five and one-half years suggested a mean serum elimination half-life of 1,428 days. A recent initial analysis of 27 3M fluorochemical production workers retirees' sera, collected three times over a 12-month period, has suggested that the serum elimination half-life of PFOS in the human may be much lower, approximately 300 days [RS53]. The range of the initial serum PFOS levels in these retirees was from 0.2 to 4.6 ppm. These retirees have their serum collected and analyzed every six months. More definitive serum PFOS half-life estimates are expected within the next year upon collection of two more samples.

### Summary

The data provide no evidence for PFOS metabolism in any species. PFOS is readily absorbed after oral exposure but absorption by the dermal route is low. There is evidence that absorbed PFOS is bound to protein and distributed primarily in blood and liver. PFOS undergoes entero-hepatic recirculation. There is slow whole body elimination in both sexes. At lower and moderate doses, body-burden is proportional to cumulative dose. In rat studies it is clear that PFOS can traverse the placenta and expose the fetus *in utero*. PFOS is also distributed in to the milk of lactating females.

### 4.3.2 Acute Toxicity Studies

Numerous reports of acute studies of PFOS have been performed. Data from an inhalation study in rats, two oral studies of rats, one dermal study of rabbits and one dermal and eye irritation study of rabbits are noted below.

### Inhalation Exposure

In a study to determine the median lethal concentration ( $LC_{50}$ ), Rusch et al. (1979) administered the potassium salt of PFOS as dust in air to Sprague-Dawley rats at levels of 1.89 to 45.97 mg/l PFOS. An  $LC_{50}$  of 5.2 mg/l was estimated from this study (RS2).

The rats in all groups showed signs of toxicity including emaciation, red material around the nose or other nasal discharge, yellow material around the anogenital region, dry rales or other breathing disturbances, and general poor condition. Abnormal in-life observations were reported to be less frequent in the lower exposure groups.

At necropsy, the most common abnormality was discoloration of the liver and lung. Discoloration of the lung was also observed in control rats and therefore may not be treatment related. The most significant treatment related abnormality was discoloration of the liver. Among animals that died prematurely, decreased body weight, discoloration of the lung, and discoloration and distention of the small intestine were also observed.

### Oral

The study of Dean et al 1978 determined an acute oral  $LD_{50}$  and 95% confidence limits of

251 (199-318) mg/kg. The study report by Gabriel 1978, tested only two doses and determined the acute oral LD<sub>50</sub> was greater than 50 mg/kg and less than 1500 mg/kg (RS3).

### **Dermal Exposure**

No significant toxicity was observed in a 1979 percutaneous absorption study in which male and female albino rabbits were dosed dermally under occlusion with 5000 mg/kg PFOS for 24 hours and observed for 28-days post-dose (RS54).

### **4.3.3 Repeated Dose Toxicity**

#### **4.3.3.1 PFOS**

PFOS has been studied in 90-day subchronic dietary studies in rats (RS37), in a 90 day gavage study in rhesus monkeys (RS35, RS36), and in a 26-week oral (capsule) study in cynomolgus monkeys (RS32). A two-year chronic feeding study in rats is currently in final stages of completion (RS39).

The studies in rhesus monkeys and the 90-day rat study were reported in 1978. The more recent chronic study in rats and the 26-week study in cynomolgus monkeys were also designed to provide serum data. The earlier studies are summarized in Table 4-7, and it can be seen that the pattern of toxic effects observed in those studies is similar to that seen in the more recent studies. The older studies included much higher doses on both rats and primates. Areas of overlap on dose showed consistency of toxic effects. In the following, the recent studies are described in detail.

In the recent 26-week cynomolgous study, groups of six monkeys of each sex (4/sex at low dose) received PFOS by capsule at doses of 0, 0.03, 0.15, and 0.75 mg/kg/day (RS32). Two animals per sex from the control, 0.15 and 0.75 mg/kg/day groups were assigned to a recovery group and were followed for at least 52 weeks following the last administration of PFOS. At the end of the dosing period, high-dose females showed reduced body weights compared to controls, but the differences were no longer obvious by the end of the recovery period.

Two males from the 0.75 mg/kg/day group did not survive to the scheduled sacrifice. One animal died after dosing on Day 155 (Week 23). Clinical signs noted in this animal included constricted pupils, pale gums, few, mucoid, liquid and black-colored feces, low food consumption, hypoactivity, labored respiration, dehydration, and recumbent position. In addition, the animal was cold to the touch. An enlarged liver was detected by palpation. Cause of death was determined to be pulmonary necrosis with severe acute inflammation. On day 179, the second male was sacrificed in a moribund condition. Clinical signs noted included low food consumption, excessive salivation, labored respiration, hypoactivity and ataxia. Cause of death was not determined.

Males and females in the 0.75 mg/kg/day dose-group had lower total cholesterol and males and females in the 0.15 and 0.75 mg/kg/day groups appeared to have lower high density lipoprotein cholesterol during treatment. HDL cholesterol values, however, were only determined on study days 153 and 182, and no prestudy values are available for comparison. The effect on total cholesterol was reversed within 5 weeks of recovery and high density lipoprotein cholesterol

increased within 9 weeks of recovery. Triiodothyronine values were lower in males in the 0.75 mg/kg/day dose group on day 182. However, total thyroxine and thyroid stimulating hormone levels were normal and thyroid gland showed normal histology.

Perhaps related to the observed decrease in cholesterol at the 0.75 mg/kg dose was a progressive decrease in estradiol in males.

At terminal sacrifice, females in the 0.75 mg/kg/day dose-group had increased absolute liver weight, liver-to-body weight percentages, and liver-to-brain weight ratios. In males, liver-to body weight percentages were increased in the high-dose group compared to the controls. "Mottled" livers were observed in two high-dose males and in one high-dose female. Of the two males not surviving until the scheduled terminal sacrifice, one had a "mottled" and large liver. Three of 4 high-dose males (including those that did not survive to scheduled sacrifice) had centrilobular or diffuse hepatocellular hypertrophy which was also observed in all high-dose females. Centrilobular or diffuse hepatocellular vacuolation occurred in 2 of 4 females and 2 of 4 males in the high-dose group.

No PFOS related lesions were observed either macroscopically or microscopically at recovery sacrifice indicating that the effects seen at terminal sacrifice were reversible.

The LOAEL for this study is 0.75 mg/kg/day based upon death, liver effects, and effects on cholesterol. The NOAEL is 0.15 mg/kg/day. All effects appeared to be reversible.

Interim results at weeks 14 and 53 are available from the ongoing chronic rat study (RS39). That study involves groups of 60 or 70 CrI:CD<sup>®</sup> (SD) IGS BR rats of each sex fed diets containing PFOS at 0, 0.5, 2.0, 5.0, and 20.0 ppm. Through week 53, high dose females showed reduced body weight gain and reduced food consumption. Reduced serum cholesterol and increased serum alanine aminotransferase (males only) was seen in high-dose animals. Mildly increased urea nitrogen was seen in animals fed 5 or 20 ppm, and serum glucose was reduced in high dose males and females, and in males at 2 and 5 ppm at week 53.

At the 53-week sacrifice, high-dose rats showed increased absolute (males only) and relative liver weight. Centrilobular hepatocyte hypertrophy and midzonal to centrilobular vacuolation was increased in incidence in males at 20 ppm, and high-dose females showed an increased incidence of centrilobular hepatocyte hypertrophy and pigment.

Data on serum PFOS levels are available from the 26-week cynomolgus monkey study and for week 14 of the chronic rat study. The relationships between PFOS serum levels and toxic responses for these two studies are presented in Table 4-8. The serum levels presented in Table 4-8 represent preliminary analyses available as of July, 2000. These values will change in the final analytical reports based on adjustments for purity of the samples and other possible corrections.

000036

**Table 4.7. Summary of Repeat-Dose Studies for PFOS**  
**Clinical Observations; Clinical Pathology; Gross Pathology;**  
**Histopathology (M = Male; F = Female)**

Study	Species (Strain)	Dose (units)	n	Clinical Observations; Clinical Pathology; Gross Pathology; Histopathology (M = Male; F = Female)
90-Day Dietary (Goldenthal et al. 1978a)	Rat (CD)	0 (ppm)	5 M / 5 F	<ul style="list-style-type: none"> <li>■ No effect</li> <li>■ ↓ body weight, ↑ plasma glutamate-pyruvate transaminase, ↑ plasma glutamate-oxalacetate transaminase, liver discoloration</li> <li>■ 3 deaths; ↑ sensitivity to external stimuli, red material around the eyes or mouth, ↓ food consumption, ↑ plasma creatinine phosphokinase, ↑ alkaline phosphatase, ↑ blood glucose, ↑ blood urea nitrogen, ↓ hemoglobin, ↓ hematocrit, ↓ erythrocyte count, ↓ reticulocyte count (F), ↓ leukocyte count, liver enlargement, necrosis &amp; hepatocellular hypertrophy, stomach discoloration &amp; hemorrhage</li> <li>■ Death; emaciation, convulsions, stomach mucosal hyperkeratosis, bone marrow hypocellularity, thymic follicular atrophy, splenic lymphoid follicular atrophy, atrophy of mesenteric lymph nodes, atrophy of villi in small intestines, skeletal muscle atrophy &amp; dermal acanthosis, hyperkeratosis</li> <li>■ Death; hunched posture</li> <li>■ Death; hypoactivity</li> </ul>
		30	5 M / 5 F	
		100	5 M / 5 F	
		300	5 M / 5 F	
		1000	5 M / 5 F	
14-Week Dietary (Part of ongoing 2-yr study, Covance 1999a)	Rat (Sprague Dawley)	0 (ppm)	10 M / 10 F	<ul style="list-style-type: none"> <li>■ No effect</li> <li>■ No effect</li> <li>■ No effect</li> <li>■ Hepatocellular hypertrophy and vacuolization in M at 5 ppm</li> <li>■ ↓ body weight, ↓ cholesterol (M), ↑ liver weight, enlarged &amp; vacuolated liver cells, ↑ palmitoyl CoA oxidase activity</li> </ul>
		0.5	10 M / 10 F	
		2	10 M / 10 F	
		5	10 M / 10 F	
		20	10 M / 10 F	

**Table 4.7. Summary of Repeat-Dose Studies for PFOS**

Study	Species (Strain)	Dose (units) (mg/kg/day)	■	Clinical Observations; Clinical Pathology; Gross Pathology; Histopathology (M = Male; F = Female)
90-Day Gavage (Goldenthal et al. 1979)	Rhesus Monkey	0 10 30 100 300	2 M / 2 F 2 M / 2 F 2 M / 2 F 2 M / 2 F 2 M / 2 F	<ul style="list-style-type: none"> <li>■ No effect</li> <li>■ Death within 11 - 20 days; ↓ body weight, marked weakness, anorexia, ↓ activity, emesis, diarrhea, tremors, prostration, congestion, hemorrhage &amp; lipid depletion of adrenal cortex</li> <li>■ Death within 7 - 10 days; ↓ body weight, marked weakness, anorexia, ↓ activity, emesis, diarrhea, tremors, prostration, congestion, hemorrhage &amp; lipid depletion of adrenal cortex</li> <li>■ Death within 3 - 5 days; ↓ body weight, marked weakness, anorexia, ↓ activity, emesis, diarrhea, tremors, prostration, congestion, hemorrhage &amp; lipid depletion of adrenal cortex</li> <li>■ Death within 2 - 4 days; ↓ body weight, marked weakness, anorexia, ↓ activity, emesis, diarrhea, tremors, prostration, congestion, hemorrhage &amp; lipid depletion of adrenal cortex</li> </ul>
90-Day Gavage (Goldenthal et al. 1978b)	Rhesus Monkey	0 0.5 1.5 4.5	2 M / 2 F 2 M / 2 F 2 M / 2 F 2 M / 2 F	<ul style="list-style-type: none"> <li>■ No effect</li> <li>■ No Adverse Effect; Slight &amp; intermittent ↓ activity in 3 of 4 animals</li> <li>■ Blood &amp; mucus in stools, diarrhea, dehydration, tremors, ↓ body weight, ↓ cholesterol, marked ↓ activity</li> <li>■ Death within 7 weeks; marked ↓ cholesterol, black or bloody stool, dehydration, rigidity, convulsions, prostration, ↓ serum cholesterol, diffuse lipid depletion of adrenals, atrophy of pancreatic exocrine cells &amp; atrophy of submandibular salivary gland serous alveolar cells, ↓ serum alkaline phosphatase, ↑ SGOT</li> </ul>

**Table 4.7. Summary of Repeat-Dose Studies for PFOS**  
**Clinical Observations; Clinical Pathology; Gross Pathology;**  
**Histopathology (M = Male; F = Female)**

Study	Species (Strain)	Dose (units)	n	Histopathology (M = Male; F = Female)
26-Week Capsule (Thomford 2000)	Cynomolgus Monkeys	0 (mg/kg/day)	6 M / 6 F	■ No effect
		0.03	4 M / 4 F	■ No effect
		0.15	6 M / 6 F	■ No adverse effect
		0.75	6 M / 6 F	■ 2 deaths; ↓ body weight, ↓ food consumption, black & mucoid stools, ↓ activity, dehydration, labored respiration, ↓ cholesterol, ↓ HDL cholesterol, ↓ triiodothyronine (normal T4 & TSH), ↓ estradiol, liver discoloration, ↑ liver weight, vacuolated liver cells

**Table 4.8 PFOS Toxicity Data for Mammals:  
Key Observed Effects, Serum and Liver PFOS Concentrations, and Cumulative Dose**

Group <sup>1</sup>	Observed Effect	Serum PFOS Concentration (ppm)	Liver PFOS Concentration (ppm)	Cumulative Dose (mg/kg)
<b>26-week Capsule-Dosing Study in Cynomolgus Monkeys (Thomford 2000)</b>				
0.03 mg/kg/d	NOEL	18	25	5.46
0.15 mg/kg/d	NOEL	85	80	27.3
0.75 mg/kg/d	Hepatomegaly; hepatocyte enlargement	> 100, < 300	415 (average)	> 27.3, < 137
0.75 mg/kg/d	Decreased cholesterol in females	> 134 ± 25	415 (average)	46.5
0.75 mg/kg/d	Decreased cholesterol in males	> 152 ± 30	415 (average)	67.7
0.75 mg/kg/d	Decreased T3 (normal T4 & TSH)	> 152 ± 30	415 (average)	67.7
0.75 mg/kg/d	Death or early sacrifice for 2/6 males	> 150, < 300	415 (average)	> 100, < 137
<b>14-Week Interim of Chronic Dietary Study in Sprague Dawley Rats (Covance 1999a)</b>				
0.5 ppm Males	NOEL	4.22	26.38	~ 4
0.5 ppm Females	NOEL	6.65	18.59	~ 3
2.0 ppm Males	NOEL	17.9	76.8	~ 17
2.0 ppm Females	NOEL	26.9	68.25	~ 13
5.0 ppm Males	Hepatocellular hypertrophy and vacuolization	45.6	386.53	24.4
5.0 ppm Females	NOEL	62.9	362.45	38.2
20 ppm Males	Hepatocellular hypertrophy and vacuolization; decreased cholesterol; increased AAT	134	599.94	106
20 ppm Females	Hepatocellular hypertrophy and vacuolization	216	617.52	141

#### 4.3.3.2 N-EtFOSE

N-EtFOSE has been studied in ninety-day studies in rats (RS49) and rhesus monkeys (RS50). A two-year chronic toxicity study was completed in 1987. That study used a "wide range" material that included many short-chain fluorochemicals and was not representative of the typical material currently used in commercial products. A robust summary of this study is included (RS33). Subsequently, a two-year chronic study in rats using a more representative "narrow-range" product was initiated and is currently in progress (RS51). The pattern of toxic effects seen in these studies is similar to those seen with PFOS. The primary target is the liver, with dose-related increases in liver weight and macroscopic and microscopic liver lesions in rats.

In the 90-day rat study, N-EtFOSE was fed in the diet at levels of 0, 30, 100, 300, 1,000, 3,000 and 10,000 ppm to groups of five Charles River CD rats of each sex (RS49). All rats at the 1,000-, 3,000- and 10,000-ppm dosage levels died between days 9 and 29 of the study.

Findings in high dose animals were consistent with those found in animals exposed to high doses of PFOS. These included compound-related gross and microscopic liver lesions with consistent changes in biochemical parameters.

N-EtFOSE was administered to groups of two male and two female rhesus monkeys by gavage at dosage levels of 1, 3, 10 or 30 mg/kg/day (RS50). A control group received the vehicle, propylene glycol. On and after the second day of study, all the monkeys, including the control group showed anorexia, slight to marked decrease in activity and ataxia. The ataxia disappeared from all the monkeys directly after the amount of propylene glycol used was reduced from 5 to 2 ml/kg on study day 3.

Most of the monkeys, including those in the control group lost body weight early in the study. At 12 weeks of study all the monkeys were at or near the original body weight except for the groups receiving 10 and 30 mg/kg/day. At the end of the study the differences in the mean body weights of the treated and control groups were not statistically significant.

Microscopically, the adrenals from one male and two female rhesus monkeys at the 30 mg/kg/day dosage level had compound-related slight to severe lipid depletion, and the pancreas from the two female monkeys at the 30 mg/kg/day dosage level had compound-related moderate atrophy of exocrine cells. No liver lesions were seen, however.

In the ongoing two-year bioassay using a test material that is more representative of most material currently used in commercial products, groups of 60 or 70 CrI:CD®(SD)IGS BR rats of each sex were fed diets containing 0, 1, 3, 30, 100, and 300 ppm N-EtFOSE (RS51). Due to excessive toxicity (reduced body weight, reduced food consumption) the 300 ppm group was terminated at about week 8 and the 1 ppm and additional concurrent control group were added. At sacrifice, the 300 ppm animals showed hematologic changes (reduced red blood cell count, hematocrit, and hemoglobin), clinical chemistry changes (lower glucose, globulin, and cholesterol, and higher BUN, albumin, total bilirubin (males only) aspartate aminotransferase (males only) and alanine aminotransferase), liver enlargement, and hepatocellular hypertrophy and necrosis, and hemorrhage in the liver.

A similar (though less severe) pattern of effects was seen at the 30 and 100 ppm groups at interim sacrifices at later measurement times. This pattern included: reduced body weight gain over the first 53 weeks; mildly decreased red blood cell count, hemoglobin, and hematocrit for females in the 100 ppm dose group; mildly lower glucose and mildly higher urea nitrogen for

animals given 100 ppm (predominantly at Weeks 14 and 27; moderately higher albumin and moderately lower globulin (predominantly at Weeks 27 and 53) in 100 ppm males. Hepatocellular hypertrophy and vacuolation were observed in 100 ppm animals at week 53, and hepatocellular hypertrophy was also seen at week 14 in males given 30.

Decreases in body weight and total serum cholesterol were prominent effects in this study. Male body weights for the 30 ppm and 100 ppm dose groups were significantly lower than control values through week 53 of the study. Females also experienced lower body weights. In the 3 ppm dose group females, transient but significantly lower body weights occurred on weeks 14, 15 and 16. Females in the 30 ppm dose group also had significantly lower body weights through week 29 and again on week 37 and weeks 43-53. The 100 ppm dose group females had significantly reduced body weight through week 53.

Cholesterol was significantly lower in males in the 3 ppm, 30 ppm and 100 ppm dose groups at week 14. This effect was present at weeks 27 and 53 in males in the 30 and 100 ppm dose groups. In contrast, females in the 30 and 100 ppm dose groups had significantly lower cholesterol only on week 14.

#### 4.3.3.3 N-MeFOSE

N-MeFOSE has been studied in a 13-Week dietary study in CrI:CD® (SD) IGS BR rats at doses of 3, 30, and 100 ppm (20/sex/dose) (RS38). The only effect seen at 3 ppm was a slightly reduced body weight gain.

Effects seen at 30 ppm were: lower serum globulin, cholesterol and triglycerides in males; lower terminal body weight in males; increased liver-to-body weight ratio in males and females; ~~increased absolute liver weight in females; increased incidence of centrilobular hepatocellular hypertrophy in males and females, and a slight increase in minimal hepatocellular vacuolation in males.~~

At 100 ppm, the same effects as at 30 ppm were seen (but at higher incidence and/or greater severity), plus lower serum cholesterol and triglycerides in females; lower hematocrit and higher BUN in both sexes; higher serum albumin in males; higher serum AAT in males increases in all liver weight parameters in both sexes (relative and absolute); liver coagulative necrosis, hepatocellular pigment, and erosion of small portions of stomach mucosa in both sexes (RS38).

#### 4.3.3.4 Summary

PFOS, N-EtFOSE, and N-MeFOSE produce similar toxic effects in subchronic studies in rats and monkeys. The effects occurring at the lowest doses are liver cell hypertrophy, in some cases with vacuolation, a decline in weight gain, and a reduction in serum cholesterol levels. The most recent data, summarized in Table 4-9, provides dose-response information on these effects. The fact that the three compounds produce similar effects suggests that these effects may be due to the presence of PFOS and not the precursor compounds. This suggestive evidence can not be confirmed until all of the serum data have been collected and evaluated. Results from the chronic studies of PFOS and N-EtFOSE will become available in the future.

**Table 4-9 Comparative Effects Among Three Perfluorooctanesulfonyl Fluoride-Based Chemicals**

<i>Effect</i>	<b>Dose at which effect occurs after 14 weeks of dietary compound administration in rats.</b>		
	<b>N-EtFOSE<sup>a</sup></b>	<b>N-MeFOSE<sup>b</sup></b>	<b>PFOS<sup>c</sup></b>
<b>Hepatocellular enlargement</b>	30 ppm males 100 ppm females	30 ppm males 100 ppm females	5 ppm males 20 ppm females
<b>Cholesterol lowering</b>	3 ppm males 30 ppm females	30 ppm males 100 ppm females	20 ppm males -- ND females*
<b>Body weight lowering</b>	30 ppm males 3 ppm females <sup>d</sup>	30 ppm males 100 ppm females	20 ppm males 20 ppm females
<b>Liver to Body weight increase</b>	100 ppm males 100 ppm females	30 ppm males 30 ppm females	20 ppm males 20 ppm females

\* ND, not detected.

<sup>a</sup> N-Ethyl-perfluorooctanesulfonamido ethanol

<sup>b</sup> N-Methyl-perfluorooctanesulfonamido ethanol

<sup>c</sup> Perfluorooctane sulfonate

<sup>d</sup> Slight but statistically significant effect occurring only at the terminal weighing

#### **4.3.4 Reproductive and Developmental Toxicity**

Developmental toxicity studies in rats and rabbits and 2-generation studies in rats for PFOS and N-EtFOSE were reviewed. The N-EtFOSE studies are included for comparative purposes since, as noted above (Section 4.3.1) it is believed to be readily metabolized to PFOS. In addition, the results of a PFOS cross-fostering study are presented and discussed. All studies employed the oral (gavage) route for administering the chemicals.

#### **Developmental Studies**

Separate studies with PFOS and N-EtFOSE assessed the effects of pregnant rat exposure on prenatal development of their embryos and fetuses. Each chemical caused maternal and fetal toxicity and in the case of N-EtFOSE, a low litter incidence of anatomical malformations were seen at very high doses. Initial studies with both chemicals reported a lesion in the lens of the eye in all treated groups (RS41, RS45). The causal association between this effect and chemical exposure was subsequently retracted by the study director when it was established that the "lesion" was an artifact associated with the method of free hand sectioning used in the fetal examination. These lesions were not observed in repeat studies in this laboratory. Additional prenatal developmental toxicity studies with PFOS and N-EtFOSE have been performed in the rat and rabbit. Key aspects of all studies are summarized in Tables 4-10 and 4-11.

**Table 4-10.**

<b>Oral (gavage) PFOS Developmental Toxicity Studies</b>				
<b>Design</b>	<b>NOAEL*</b>	<b>LOAEL*</b>	<b>Effects</b>	<b>Reference</b>
Rat SD Group size: 22 Dose:* 0, 1, 5, 10	<u>Mat. 5</u> <u>Dev. 10</u>	<u>Mat. 10,</u> <u>Dev. None</u>	<u>Mat. Body</u> weight.	RS45
Rat SD Group size: 25 Dose:* 0, 1, 5, 10	<u>Mat. 1</u> <u>Dev. 1</u>	<u>Mat. 5</u> <u>Dev. 5</u>	<u>Mat. Body wt.</u> <u>Clinical signs,</u> g.i. lesions. <u>Dev. Body wt,</u> visc. anom., skel. var.	RS46
Rabbit NZW Group size: 22 Dose:* 0, 0.1, 1, 2.5, 3.75	<u>Mat. 0.1</u> <u>Dev. 1</u>	<u>Mat. 1</u> <u>Dev. 2.5</u>	<u>Mat. Body wt.</u> Abortions <u>Dev. Body wt.</u> Delayed ossification	RS44

\* (mg/kg). Rats dosed on GD 6-15. Rabbits dosed on GD 7-20.

Results from the PFOS studies were similar. Maternal toxicity and developmental toxicity was consistently seen and expressed as reductions in maternal weight gain or fetal body weight. Reductions in food consumption commonly paralleled the effect on maternal weight. Fetal effects were primarily associated with maturational delays, e.g., skeletal variations and delayed ossification. Abortions were observed in rabbits at a dose of 2.5 mg/kg and higher. The lowest developmental toxicity NOAEL for rat and rabbit are the same, 1 mg/kg body weight. The maternal toxicity NOAEL was 0.1 and 1.0 mg/kg for rabbit and rat, respectively.

Table 4-11.

Oral (gavage) N-EtFOSE Developmental Toxicity Studies				
Design	NOAEL*	LOAEL*	Effects	Reference
Rat SD Group size: 22 Dose:* 0,25,37.5,75	<u>Maternal 25</u> <u>Develop. 25</u>	<u>Maternal 37.5</u> <u>Develop. 37.5</u>	<u>Mat. Body wt., deaths</u> at 75 <u>Dev. Body wt., cleft</u> <u>palate, sternbrae</u> <u>malif.</u>	RS41
Rat SD Group size: 25 Dose:* 0, 1, 5, 10, 20	<u>Maternal 5</u> <u>Develop. 5</u>	<u>Maternal 10</u> <u>Develop. 10</u>	<u>Mat. Body wt. Dev.</u> <u>Body wt, delayed</u> <u>ossification</u>	RS42
Rabbit NZW Group size: 18 Dose:*0,1,5,15	<u>Maternal 5</u> <u>Develop. 5</u>	<u>Maternal 15</u> <u>Develop. 15</u>	<u>Mat. Body wt.</u> <u>Dev. Fetal &amp;</u> <u>Neonatal</u> <u>Viability, resorptions</u>	RS55
Rabbit NZW Group size: 22 Dose:* 0, 0.1, 1, 2.5, 3.75	<u>Maternal 0.1</u> <u>Develop. 1</u>	<u>Maternal 1</u> <u>Develop. 2.5</u>	<u>Mat. Body wt.</u> <u>abortions</u> <u>Dev. Late resorptions</u>	RS40

\* (mg/kg). Rats dosed on GD 6-15. Rabbits dosed on GD 6-18 or 7-20.

The more recent rat study with N-EtFOSE (RS42) showed maternal and developmental toxicity expressed as effects on body weight, this is similar to that of the earlier study (RS41). Concordance is not good between the 2 rat studies as to the NOAEL or LOAEL doses. Morphological defects in fetuses were seen only at doses of 37.5 mg/kg and higher. The results of the rabbit studies (RS40, RS55) are similar as to the nature of the effects but there are differences as to doses that caused maternal toxicity. Fetal survival during the 24 hour incubation period was significantly lower at the 15 mg/kg dose (RS55). The rabbit and the rat study conducted at similar and slightly higher dose levels indicate that the primary early maternal effect is associated with depressed body weight. The lowest NOAELs occurred in the rabbit study; 0.1 and 1.0 mg/kg for maternal and developmental endpoints, respectively.

When results of the PFOS and N-EtFOSE developmental studies are compared, the type of effects, and doses that cause those effects, are similar. Fetal toxicity, as contrasted to anatomical malformations, characterizes the principal effect of both PFOS and N-EtFOSE. Maternal toxicity also occurs at doses associated with developmental toxicity. Rabbits exposed to N-EtFOSE have a tendency to abort litters or resorb fetuses. These effects are possibly causally linked to the maternal effect. This type of response was not prominent in rats exposed to either PFOS or N-EtFOSE.

## Two-Generation Studies

Reproductive parameters generally were not affected by PFOS exposure in either generation of either sex in a 2-generation study in the rat (RS47). The exception was a decrease in implantations and litter size in F<sub>0</sub> females at 3.2 mg/kg, the highest dose tested. The early adverse response in adults and in pups is reduced body weight gain in both sexes. Most significant was the death of all F<sub>1</sub> pups in the perinatal period at the maternal dose of 3.2 mg/kg bw/day. Mortality was also seen in F<sub>1</sub> pups from dams that received 1.6 mg/kg. The dose-response for this effect is steep as demonstrated by viability indices (survival from birth to LD 4) of 98.7, 98.3, 98.3, 66.1 and 0.0% for the 0, 0.1, 0.4, 1.6 and 3.2 mg/kg dose, respectively. Severity of effect on F<sub>1</sub> pups in the lactation phase of the study resulted in post weaning dose groups being reduced to 0, 0.1 and 0.4 mg/kg. These 3 dose groups proceeded through a mating, pregnancy and postnatal evaluation phase until F<sub>2</sub> pups were 21 days of age. The F<sub>1</sub> rats in all these groups developed normally as measured by an array of developmental milestones, including neurobehavioral performance. Effects on reproduction, lactation and on postnatal viability of the F<sub>2</sub> pups were modest and transient. The NOAELs from the study and the effect(s) seen at the next higher dose are:

- F<sub>0</sub> generation - 0.1 mg/kg; at the 0.4 mg/kg dose effects on body weight gain  
- 1.6 mg/kg; for reproductive effects at 3.2 mg/kg reduced implantations and litter size
- F<sub>1</sub> generation - 0.4 mg/kg; at the 1.6 mg/kg dose pup mortality and decreased body weight  
- 0.4 mg/kg for reproductive effects, the highest dose tested
- F<sub>2</sub> generation - 0.4 mg/kg, the highest dose tested.

The N-EtFOSE 2-generation study (RS43) was of a design similar to the PFOS study and conducted in the same laboratory. A design difference was that dosing of the parental (F<sub>0</sub>) generation in the N-EtFOSE study commenced 28 days prior to cohabitation of the sexes as contrasted to 42 days in the PFOS study. The doses were 0, 1, 5, 10, 15 mg/kg/day. There was a decrease in F<sub>1</sub> litter size and pup viability in the 10 and 15 mg/kg dose groups during the perinatal period. The dose-response for this effect was steep as seen in viability indices (survival from birth to LD 4) of 92.8, 99.1, 92.0, 30.2 and 1.20% for the 0, 1, 5, 10 and 15 mg/kg dose, respectively. The last 2 pups in the high dose group died on LD 5 and an additional 6 of 60 pups alive on LD 4 in the 10 mg/kg group died between LD 5 and 14. Due to the severe effects seen in F<sub>1</sub> pups at the two higher doses, post weaning portions of the study were reduced to 0, 1, and 5 mg/kg groups. These dose groups proceeded through a mating, pregnancy and postnatal evaluation phase until F<sub>2</sub> pups were 21 days of age. F<sub>1</sub> rats in the 0, 1, and 5 mg/kg groups developed normally in the post weaning period as measured by an array of developmental milestones, including neurobehavioral performance. Effects on F<sub>1</sub> reproduction and lactation and on post natal viability of the F<sub>2</sub> pups were seen at the 5 mg/kg dose. The NOAELs from the study and the effect(s) seen at the next highest dose are:

- F<sub>0</sub> generation - 1 mg/kg; at the 5 mg/kg dose body weight effects  
- 5 mg/kg for reproductive; at the 10 mg/kg dose higher incidence of stillborn pups
- F<sub>1</sub> generation - Less than 1 mg/kg, the lowest dose tested, based on body weight effects  
- 5 mg/kg for reproductive effects, the highest dose tested

**F<sub>2</sub> generation – 1 mg/kg; at 5 mg/kg reduced litter size, pup viability and growth**

The results of the 2-generation studies with PFOS and N-EtFOSE are very similar with respect to the types of effect seen, dose response, and lowest doses that cause effects. Maternal body weight changes are observed in the pre-natal teratology studies and the two generation studies with both chemicals. However, the mortality seen in the perinatal period of life has no parallel in the prenatal studies. While modest increases in resorptions were seen in the 2-generation studies, in the main, pup development until the time of birth was fairly normal. Gross appearance notwithstanding, the incidence of pup mortality was severe (at the higher doses) on the day of birth and in the immediate perinatal period. The study design did not permit insight as to the factor(s) that contribute to the lethal response. Results of the 2-generation studies indicate that fertility and reproductive performance are not impaired at doses that cause adverse body weight effects on males and females. It is not clear whether the resorptions are due to direct effects on the fetus or secondary to altered maternal physiology associated with decreased food consumption and weight gain.

A PFOS cross-foster study was performed to ascertain the role of pre-natal, post-natal, or combined exposure on pup mortality and health (RS48). A single gavage dose, 1.6 mg/kg PFOS, was used. Female Sprague Dawley rats were treated with 0 or 1.6 mg/kg daily during a 42 days pre-mating, mating, pregnancy, and a lactation period of 21 days. At birth, 25 litters from control or treated dams were cross-fostered with 12–13 control or PFOS treated dams. Thus four groups were established. The results of the study that ended on post-natal day 21 is summarized in Table 4-12.

**Table 4-12. Cross-foster PFOS Study  
Post-natal Pup Effects During 21 Day Lactation Period<sup>a</sup>**

PFOS Exposure <sup>b</sup>		Number Total Dead Pups	Percent Mortality	Litters Affected	Pup Weight <sup>c</sup>	
Gestation	Lactation					
0	0	3	191	1.6	3	29.0
0	1.6	2	181	2.0	2	26.2
1.6	0	16	166	9.6	10	26.7
1.6	1.6	34	177	19.2	8	24.6

<sup>a</sup> extracted from RS48

<sup>b</sup> refers to daily female dose of 0 or 1.6 mg/kg PFOS.

<sup>c</sup> mean weight in Grams on LD 14

Mortality was increased (9.6%) in pup litters whose exposure was solely *in utero*. Mortality was greatest (19.2%) in pup litters exposed *in utero* who also nursed treated females. There was no increase in mortality in pup litters not exposed *in utero* that nursed treated females; body weight gain was reduced. The greatest reduction in weight gain was in pup litters who had *in utero* and lactation exposure. PFOS serum levels were determined in litters and dams from this study.

These data are summarized in Table 4-13.

**Table 4-13. PFOS Serum Values at Time of Necropsy (LD 21/22) in ug/mL (ppm)**

PFOS Exposure <sup>a</sup>		Nursing Dams Mean	Litters Pooled Mean
Gestation	Lactation		
0	0	0.05* (12)**	0.05* (6)
0	1.6	82.96 (13)	22.35 (6)
1.6	0	2.02 (13)	53.88 (6)
1.6	1.6	88.97 (12)	89.71 (6)

\* 0.05 uG/mL is Lower Limit of Quantitation.

\*\* Number in parentheses is number of samples

The data clearly indicate that treatment of a pregnant dam can result in significant levels of *in utero* exposure to PFOS. This is demonstrated by serum values of about 54 ppm in 21 day old pups who had only *in utero* exposure. PFOS also appears to be readily secreted in milk, as evidenced by pups with no gestational exposure having serum levels of about 22 ppm after nursing treated dams. Drawing upon results from a pharmacokinetic study discussed in 4.3.1 (RS52) it appears that a PFOS fetal serum level of ~117 ppm just preceding birth is associated with perinatal toxicity and death, e.g., fetuses from dams with exposure to 1.6 mg/kg PFOS. The premating sera concentration of dams in this dose group averaged 185 ppm.

In summary, *in utero* exposure to 1.6 mg/kg PFOS via the dam lead to perinatal mortality and reduced growth. In a separate study, maternal exposure to 1.6 mg/kg led to serum levels of 117 uG/mL in fetuses just prior to birth. *In utero* and peri-natal exposure to 1.6 mg/kg appear to be additive with respect to toxic effects and perinatal death in pups. Finally, exposure via milk from mothers receiving 1.6 mg/kg did not cause death although a decrease in pup weight was observed. The serum levels support a hypothesis that the degree and severity of developmental and peri-natal toxicity is directly associated with PFOS concentration.

#### Ongoing Study

A study is planned that will assess the role of reduced cholesterol metabolism as a cause of perinatal mortality in rats.

#### 4.3.5 Genetic Toxicity

PFOS. PFOS has been tested for genotoxic activity in a battery of microbial and mammalian systems. These included assays for induction of gene mutations in *Salmonella typhimurium* and *Escherichia coli*, (RS14, RS15, RS16, RS17, RS18) a test for gene conversion in the D4 strain of *Saccharomyces cerevisiae* (RS18); an *in vitro* assay for chromosomal aberrations in human whole blood lymphocytes (RS21), the mouse micronucleus assay (RS19), and an assay for

unscheduled DNA synthesis (UDS) in primary rat liver cell cultures (RS20). PFOS was negative in all assays in which it was tested.

Potassium perfluorooctylsulfonate did not induce reverse mutation at the histidine locus of *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, or at the tryptophan locus of *E. coli* WP2uvrA, and did not induce gene conversion at the try locus in the D4 strain of *S. cerevisiae* when tested with or without metabolic activation from Aroclor-induced rat liver microsomes at doses up to 5,000 µg/plate (RS15, RS18).

The diethanolamine salt of PFOS was likewise without genotoxic activity in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 when tested at up to 5,000 µg/plate, with and without metabolic activation, and in the D3 strain of *Saccharomyces cerevisiae* gene recombination assay at up to 5% (RS14).

Potassium perfluorooctylsulfonate did not induce chromosomal aberrations in human lymphocytes when tested at up to cytotoxic concentrations, with or without metabolic activation by Aroclor-induced rat liver microsomes (RS21). Nor did it induce UDS in primary cultures of rat hepatocytes when tested at up to cytotoxic levels (RS20).

In the *in vivo* mouse micronucleus assay, potassium perfluorooctylsulfonate did not induce micronuclei in the bone marrow of CrI:CD-1 BR mice given a single gavage dose of 237.5, 450, or 950 mg/kg (RS19).

N-EtFOSE. Negative results have been obtained in batteries of genotoxicity tests of N-ethyl perfluorooctane sulfonamidoethanol (N-EtFOSE).

N-EtFOSE gave negative results in micronucleus assays in rats (RS12) and mice (RS11) at doses up to lethal levels by oral gavage. N-EtFOSE, did not induce UDS in liver cells of rats that had received a single dose of 203, 405, or 810 mg/kg by gavage 2-3 hours earlier, or 15-16 hours earlier (RS13). A mammalian cell gene mutation assay in mouse lymphoma cells (RS10), which the authors considered as providing evidence of mutagenicity in the presence of metabolic activation, suffers from a number of methodological and interpretative problems that render it uninterpretable. These deficiencies include:

- Inadequate identification of mouse lymphoma test strain;
- Use of excessive, potentially toxic levels of S9 mix;
- Use of an inappropriate positive control chemical for the non-activation assay;
- Poor detection of small colony mutants;
- Use of excessively high, toxic concentrations of test chemical in the mutation assays;
- Use of an excessively long mutant expression period (3 days);
- Use of insufficiently large numbers of cells for mutation assays; and
- Over-interpretation of study results.

N-MeFOSE. N-methyl perfluorooctane sulfonamidoethanol (N-MeFOSE) gave uniformly negative results in an Ames assay in *Salmonella typhimurium* (RS22), a mammalian cell gene

mutation assay in L5178Y mouse lymphoma cells (RS24), a human lymphocyte chromosome aberration assay (RS23), a rat liver cell UDS assay (RS26), and a rat bone marrow micronucleus assay (RS25).

#### **4.3.6 Any other Human Health Relevant Information**

##### **Ocular Irritation**

PFOS was found to be mildly irritating to the eyes of albino rabbits when as powder. The ocular irritation was limited to the conjunctivae in the six test rabbits. Irritation was noted at the 1, 24, and 48 hour post-instillation reading times. The maximum irritation score was 9.3 out of a highest possible score of 110 at the one-hour reading. By 72 hours post-instillation the score subsided to 0.0 (RS1).

##### **Dermal Irritation**

PFOS was found to be non-irritating to the skin of albino rabbits when tested under conventional Draize procedures. No signs of dermal irritation were observed in any of the test animals at any time during the study period. The primary skin irritation score was 0.0 out of a highest possible score of 8.0 (RS4).

##### **Sensitization**

No reports on the sensitization potential of PFOS are available.

##### **Human Data**

There are no known cases of irritation or sensitization associated with human exposure.

##### **Conclusions**

PFOS is potentially a mild irritant on contact with eyes and is not expected to irritate skin.

#### **4.4 Data from Studies in Humans**

##### **4.4.1 Background and Early Medical Surveillance**

There have been two major types of initiatives to examine the health of the 3M fluorochemical production workforce: periodic medical surveillance examinations and a retrospective cohort mortality study. There have been no epidemiological studies of the general (non-occupational) population nor have any other occupational cohorts studies been published.

Following reports of the finding of organic fluorine in sera samples, a fluorochemical medical surveillance program began at 3M's Decatur (Alabama) manufacturing facility in the late 1970's. The voluntary program has generally consisted of biennial tests of clinical chemistries, pulmonary function, blood counts, accompanied by biomonitoring of fluorochemical exposure. A total organic fluorine measurement was routinely done until the mid-1990's. A total organic

fluorine assay measures the amount of fluorine that was covalently bound to carbon in the serum sample and is not specific for PFOS. When test data were available, a company physician reviewed each employee's results. These physicians did not, and have not, found abnormalities in individuals that they believed were related to fluorochemical exposure. That is, medical conditions, medications and lifestyle factors adequately explained any observed laboratory abnormalities.

#### **4.4.2 Medical Surveillance Studies**

Beginning in the mid-1990's, the 3M medical surveillance programs at the Decatur and Antwerp (Belgium) plants incorporated serum measurements of PFOS and perfluorooctanoate (PFOA) rather than total organic fluorine (RS8). High performance liquid chromatography-mass spectrometry was the analytical method used to detect and quantify these chemicals. An aggregate analyses was conducted of the Decatur and Antwerp male employees participating in 1994/1995 (n = 178) and 1997 (n = 149). (There were too few female employees to afford data analysis.) Sixty-one employees participated in the program during both time periods. Results from hematological, standard clinical chemistry tests and several hormone assays (cortisol, dehydroepiandrosterone sulfate, estradiol, follicle stimulating hormone, 17-alpha hydroxyprogesterone, luteinizing hormone, prolactin, sex hormone binding globulin, free testosterone, bound testosterone, and thyroid stimulating hormone) were analyzed in relation to serum PFOS levels.

During both time periods, serum PFOS levels in 95 percent of the employees were below 6 ppm. The two plant populations differed by age, body mass index, and alcohol consumption, resulting in differences between the populations in several clinical chemistry parameters. Multivariable analyses adjusted for these potential confounders. When analyzed in aggregate, no consistent significant associations were observed between the employees' serum PFOS levels and the clinical chemistries or hematology parameters for either time period. (Total bilirubin levels appeared to trend downwards; further analysis found that this was restricted to Decatur employees and the values were all within the reference range.) Multivariable regression models were fitted with PFOS level (analyzed as a continuous variable) using linear, as well as non-linear, transformations in order to maximize the possibility of finding associations between PFOS and the parameters of interest while adjusting for potential confounders.

No consistent associations were observed by plant, by year, or by both. As discussed in the toxicology section (4.3), the most sensitive clinical chemistry endpoint in rats and monkeys with increasing exposure to PFOS or N-EtFOSE appears to be a reduction in serum cholesterol levels. It is of note, therefore, that mean serum cholesterol levels in these production workers remained constant or increased with increasing serum PFOS levels. An aggregate analysis of both plants' HDL levels appeared to show negative association with increasing PFOS level; however, this was confounded by the fact that all the workers with PFOS levels of 6 ppm or greater were older than workers in the lowest PFOS category, had higher body mass indices (BMIs), and, in 1997, were only employed at the Decatur plant. Multivariable analyses and stratification by plant found no consistent associations between HDL and PFOS levels. In 1995, hormone values were also obtained from a subsample of employees with the higher PFOS measurements. After adjusting for age and body mass index, no significant associations were observed between these hormones and serum PFOS levels, with the exception of estradiol. The latter quadratic

association was highly influenced by one employee with high PFOS measurement (12.83 ppm) and a large BMI; removal of this employee from the analysis resulted in no significant association with estradiol.

The results from these analyses suggested that, among these Decatur and Antwerp male fluorochemical production employees, significant hematological, clinical chemistry, and hormonal abnormalities were not associated with serum PFOS levels up to 6 ppm. (It was not possible to draw conclusions regarding the small number of employees with serum PFOS levels > 6 ppm.) Limitations of these surveillance analyses included its cross-sectional design, the voluntary participation rates of less than 50 percent, the small number of subjects exposed at the highest levels and a single hormone measurement, rather than multiple hormone measurements.

#### **4.4.3 Mortality Studies**

A retrospective cohort mortality study of employees who worked at least one year (1961-1990) at the 3M Decatur manufacturing site was conducted to determine whether the mortality experience of these production workforce was significantly different from that which would be expected [RS5]. A total of 1,957 employees (1,639 males and 318 females) constituted the cohort, which represented 37,915 person-years of follow-up. Only six employees (0.3%) were lost to follow-up. Vital status was searched through 1991 using company records, credit bureaus, Social Security Administration and the National Death Index. A total of 74 deaths were reported and 72 (97%) death certificates were obtained.

Observed deaths were compared to an expected number calculated by using indirect standardization techniques with three comparison populations: United States; Alabama; and regional Alabama counties. Analyses were also stratified by whether male employees ever and only worked in the chemical and film plants at the Decatur site.

No statistically significant elevations in Standardized Mortality Ratios (SMRs) were found for any specific cause of death or for any of the comparisons. Table 4-14 provides the data for the most common causes of death.

**Table 4-14. Retrospective Cohort Mortality Analysis for Male Employees of the Decatur Chemical Plant (n = 1,050)**

Cause of Death*	Observed	SMR	95% Confidence Interval
All Causes	57	70.0	53.0 – 96.0
All Malignant Neoplasms	13	76.9	40.9 – 131.5
Cancer of the Bronchus, Trachea, or Lung	7	120.7	48.5 – 248.7
Cardiovascular Heart Disease	11	48.8	24.4 – 87.4
External Causes	20	90.2	55.1 – 139.3

\* Three or fewer deaths were observed for all other categories.

Despite the excellent follow-up of the cohort, there were three important limitations to this study: 1) the few person-years of follow-up; 2) the short latency period; and 3) the lack of a PFOS-specific job exposure matrix.

#### 4.4.4 Work In Progress

3M, in conjunction with epidemiologists from the University of Minnesota Division of Occupational and Environmental Health, is in the midst of completing an update of the cohort mortality study. Several methodological improvements have occurred since the original study, including the computerization of the work history record for all past and present employees, which, in conjunction with information regarding serum fluorochemical levels acquired from medical surveillance exams and the random sample assessment (described above), will allow for the construction of a PFOS-specific job exposure matrix. Estimated date of completion of this updated study is November, 2000. (A comparable retrospective cohort mortality study cannot be done among the Antwerp employee population due to the confidential nature of death certificate registration in Belgium.)

An additional health-related research effort that is scheduled for completion in 2000 is the analysis of health claims data from January 1, 1993, through December 31, 1998, of the Decatur chemical and film plant employees. Health claims data are not available for analysis purposes prior to 1993. Clinical Care Groups™ methodology will be used to group all visits (inpatient and outpatient), procedures, ancillary services, and prescription drugs considered in the diagnosis, treatment, and management of approximately 400 diseases or conditions. An episode will be considered a constellation of one or more claims data records representing an occurrence of a disease or condition for a particular condition. The observed group claims data will be compared to an expected number calculated by indirect standardization methods to adjust for age and gender. Corrected for their different age structures, the ratio of the observed to expected chemical plant claims experience will be compared to the film plant's [Ederer and Mantel, 1974].

## **4.5 Initial Assessment for Human Health**

### **4.5.1 Approach to Assessment**

PFOS has been identified in serum samples from both occupationally and non-occupationally exposed populations. This initial assessment is focused on the question of whether and to what extent the levels of PFOS found in serum samples from those populations pose a human health risk. Both epidemiological and animal toxicology data are available for use in the assessment.

PFOS comes to be present in human serum from a variety of sources and there is as yet no clear understanding of the relative importance of those different sources. Some may arise from exposure to precursor molecules that degrade and metabolize to PFOS (N-EthylFOSE Alcohol, for example), while other exposure may be to PFOS itself through underdetermined environmental pathways. It is for this reason that the typical approach to risk assessment, involving comparisons of external (administered) doses known to be associated with adverse health effects with doses experienced by the populations under evaluation, is not appropriate or even possible for PFOS. The approach to be taken here involves, instead, comparisons of serum levels that have been the subject of epidemiological and toxicological studies with serum levels found in exposed populations. This approach is, for several reasons, likely to provide greater scientific certainty than the more traditional approach.

One reason for this conclusion has already been noted: PFOS reaches and accumulates in blood from several different sources, so that the serum findings reflect total human exposure. Moreover, because PFOS is relatively persistent, with an elimination half-life in humans currently estimated to be 300 days, sera levels integrate exposure over time. External doses, especially for substances having multiple sources, are highly variable over time, and it is often difficult to obtain information on the degree of variability. Serum levels are likely to be a far more stable estimate of long-term exposure.

Uncertainty is reduced when risk assessments are based on direct comparisons of serum levels. In the traditional assessment, based on intra- and interspecies comparisons of external doses, ADME differences are often unknown and are accounted for by the introduction of uncertainty factors that are general, not chemical-specific, in nature. The PFOS assessment described herein does not suffer from this important source of uncertainty and interspecies extrapolations have greater reliability than they do when external dose is used.

Most of the recently produced epidemiology and toxicology data have involved the development of health effects information in relation to serum levels; current and future studies have been designed to acquire similar type of data.

#### **4.5.2 Health Effects of PFOS and Dose-Response Relationships**

Data from studies of 3M fluorochemical production workers have thus far revealed no adverse effects from the PFOS serum levels identified in those populations. The data derive from medical surveillance investigations and from a retrospective cohort mortality study.

Beginning in the late 1970's, biennial hematological and clinical chemistry tests, along with tests of pulmonary function, were performed on workers at 3M's Decatur manufacturing facility. Until the mid-1990's, fluorochemical exposure was based only on the level of serum organic fluorine and was not PFOS-specific. In none of the years of testing did occupational physicians report abnormalities they believed to be related to organic fluorine exposures.

In 1994/1995 and again in 1997, the health of male employees at 3M's Decatur and Antwerp production facilities was assessed in relationship to serum levels of PFOS. In addition to the standard sets of clinical chemistry and hematological tests, assays for 11 different hormones were performed on a subset of the workers' blood. In the 1994/95 sampling 178 employees were evaluated and in 1997, 149 were tested; all were volunteers. No significant hematological, clinical chemistry, or hormonal abnormalities were associated with serum levels up to 6 ppm in either of the study periods. Serum cholesterol levels were not affected; this finding is significant because of the experimental observations that PFOS at higher doses cause declines in this parameter.

A 1995 retrospective cohort mortality study of 1,957 employees who had worked at least one year at the 3M Decatur production facility revealed no statistically significant elevations in risk for any specific cause of death, including cancer. This study did not include PFOS serum measurements.

These studies of production workers, although limited in several ways, provide important information for risk assessment. First, they involve direct attempts to identify adverse health effects in the most highly exposed human populations. Second, they involve not only an examination of cancer and other causes of mortality, but also a wide range of clinical parameters that are likely to represent sensitive indicators of adverse effects based on experimental data. At the same time, it must be recognized that the studied populations are not representative of the general population in that they do not include children, the elderly, or those suffering from ill-health, and represent women in only a very limited way. Studies now underway may address some of these limitations.

More extensive data on the effects of PFOS are available from studies in monkeys, rats, and rabbits (teratology only). As discussed in the introduction to this section (4.1), repeat-dose animal studies on N-EtFOSE and N-MeFOSE have been included because both compounds undergo metabolism leading to PFOS. Thus, comparative toxicology studies of these compounds and PFOS could reveal whether any of the effects of the former two PFOS precursors are due entirely to the end product of their metabolism (PFOS), or may also involve one or more of the intermediary breakdown products or metabolites. The substantial database now available on PFOS, N-EtFOSE, and N-MeFOSE demonstrates a consistency of effects, and some data suggest that these effects may be due to PFOS. Additional study will be necessary to

confirm this initial impression.

In recent repeat-dose studies in rats, PFOS and these precursor compounds reduce serum cholesterol levels, cause reductions in body weight gain, and cause liver enlargement and vacuolization. The same pattern of effects is observed in PFOS exposure studies involving monkeys. At the highest doses tested, PFOS has caused unexplained deaths in monkeys and rats. Similar effects were observed in earlier repeat-dose studies of PFOS.

Both PFOS and N-EtFOSE have been evaluated for teratologic effects in rats and rabbits and for adverse reproductive and developmental effects in a two-generation rat study. Neither compound has been demonstrated to produce teratogenic effects. In the two-generation studies, however, both compounds affected fetal survival and body weight gains in dams and fetuses.

The dose-response relationships for some effects, as identified in PFOS dosing studies, are presented in Table 3-5, which is reproduced below as Table 4-15. At this time, the N-MeFOSE and N-EtFOSE data, as summarized in Sections 4.2.3 and 4.2.4, are used to confirm the PFOS results, but are not sufficiently complete to be used for quantitative analysis.

**Table 4-15. PFOS Toxicity Data for Mammals: Observed Effects, Serum and Liver PFOS Concentrations, and Cumulative Dose**

Group <sup>1</sup>	Observed Effect	Serum PFOS Concentration (ppm)	Liver PFOS Concentration (ppm)	Cumulative Dose (mg/kg)
<b>26-week Capsule-Dosing Study in Cynomolgus Monkeys</b>				
0.15 mg/kg/d	NOEL	85	80	27.3
0.75 mg/kg/d	Hepatomegaly; hepatocyte enlargement	> 100, < 300	415 (average)	> 27.3, < 137
0.75 mg/kg/d	Decreased cholesterol in females	> 134 ± 25	415 (average)	46.5
0.75 mg/kg/d	Decreased cholesterol in males	> 152 ± 30	415 (average)	67.7
0.75 mg/kg/d	Decreased T3	> 152 ± 30	415 (average)	67.7
0.75 mg/kg/d	Death or early sacrifice for 2/6 males	> 150, < 300	415 (average)	> 100, < 137
<b>14-Week Dietary Study in Sprague Dawley Rats</b>				
2.0 ppm Males	NOEL	17.9	76.8	~ 17
2.0 ppm Females	NOEL	26.9	68.25	~ 13
5.0 ppm Males	Hepatocellular hypertrophy and vacuolization	45.6	386.53	24.4
5.0 ppm Females	NOEL	62.9	362.45	38.2
20 ppm Males	Hepatocellular hypertrophy and vacuolization; decreased cholesterol; increased AAT	134	599.94	106
20 ppm Females	Hepatocellular hypertrophy and vacuolization	216	617.52	141
<b>Reproduction PK Dosing 6 weeks prior to mating and 21 days of gestation</b>				
0.4 mg/kg/d Dam PM	NOEL	47.1 ± 5.00 (n = 16)	--	16.8
0.4 mg/kg/d Fetus EG	NOEL	39.7 ± 5.90 (n = 5)	--	N/A
0.4 mg/kg/d Dam EG	NOEL	30.3 ± 17.0 (n = 6)	--	28
1.6 mg/kg/d Dam PM	Slight body weight	185 ± 14.0 (n = 16)	--	67.2
1.6 mg/kg/d Fetus EG	Survival, body weight	117 ± 14.5 (n=2)	--	N/A

**Table 4-15. PFOS Toxicity Data for Mammals: Observed Effects, Serum and Liver PFOS Concentrations, and Cumulative Dose**

Group <sup>1</sup>	Observed Effect	Serum PFOS Concentration (ppm)	Liver PFOS Concentration (ppm)	Cumulative Dose (mg/kg)
1.6 mg/kg/d Dam EG	Slight body weight	158 ± 86.6 (n = 4)	--	112
3.2 mg/kg/d Dam PM	Body weight	368 ± 23.6 (n = 16)	--	134
3.2 mg/kg/d Fetus EG	Stillbirth, survival	191 ± 26.4 (n = 5)	--	N/A
3.2 mg/kg/d Dam EG	Body weight	180 ± 41.5 (n = 6)	--	224

<sup>1</sup> PM = Pre-Mating, after 42 days of dosing; and EG = End of Gestation, day 21 of gestation

Examination of Table 4-15 reveals that the effects of PFOS occurring at serum levels of 45.6 ppm (hypertrophy and vacuolization in the livers of male rats in the 14-week study) represents the minimum effect level for this compound. The No Observed Effect Level (NOEL) for these liver effects in male rats is 17.9 ppm. The NOEL for this effect in female rats is 62.9 ppm. It is noteworthy that the liver effects are not observed in monkeys until serum levels exceed 100 ppm; declines in cholesterol levels are also observed in monkeys at serum levels over 100 ppm. Recovery studies in monkeys have shown that the hepatic enlargement resolves upon cessation of dosing and serum cholesterol levels return to normal. The NOEL from the 6-month monkey study is 85 ppm (serum PFOS).

Pup survival is affected adversely when dam serum levels reach 185 ppm, measured after 42 days of dosing but pre-mating. The NOEL for this effect, measured in dams at the same pre-mating time, is 47.1 ppm. Thus, although the serum levels in dams declines during gestation, the fetal effects are not observed unless the dam enters pregnancy with a serum PFOS level of ca. 185 ppm; the pups of a dam having a serum level of up to 47.1 ppm are not at risk. Thus, 47.1 ppm in the rat dam will be taken as the relevant NOEL for assessing perinatal effects.

The NOELs from the animal studies useful for assessing human risk are shown in Table 4-15.

**Table 4-16. NOELs from Animal Studies to be Used for Initial Assessment of Human Risk**

<b>NOEL (PFOS Serum Level)</b>	<b>Source</b>	<b>Effect at Next Higher Serum Level</b>	<b>Estimated Cumulative Dose</b>
17.9 ppm	14-week, repeat-dose, male rats	Liver enlargement, vacuolization	~17 mg/kg
47.1 ppm	2-generation reproduction, rats	Reduced fetal survival as measured in dams, pre-mating	16.8 mg/kg
85 ppm	6 month, repeat-dose, monkey	Liver enlargement; decreased cholesterol levels	27.3 mg/kg

#### **4.5.3 Other Experimental Data Related to Health Effects**

PFOS, N-EtFOSE, and N-MeFOSE have been subjected to an extensive battery of *in vitro* and *in vivo* tests for genotoxic potential. There is no evidence of any such potential for these compounds.

These substances are also relatively weak inducers of peroxisomes in rodents. It is not known whether this effect has any relationship to the observed toxic properties of these compounds. At this time, the mechanisms underlying toxicity are not understood. 3M has under consideration several types of exploratory investigations that may begin to shed light on how these compounds produce toxicity.

#### **4.5.4 Initial Assessment of Risk**

##### **Occupational Exposures and Risks**

Serum levels of PFOS in 3M production workers average less than 2 ppm, and some workers have exhibited levels in the range of 10–13 ppm. Direct studies of production workers have revealed no evidence of excess mortality and no evidence of effects as measured by standard hematological and clinical chemistry tests and by assays of 11 different hormones, at serum PFOS levels up to 6 ppm. Serum cholesterol levels are not affected in this range of serum PFOS levels. Within the limitations of these studies, this information suggests that workers are not at risk at the serum levels reported. Animal studies of PFOS, N-EtFOSE, and N-MeFOSE reveal that PFOS is associated with some effects that would not be expected to be found in the occupational health studies because of lower serum PFOS concentrations. The NOELs from the animal studies, as shown in Table 4-16, range from serum levels of 17.9 ppm to 85 ppm. Assuming the non-human primate is taken as the best animal model for effects in humans, then the most highly exposed workers bear serum levels approximately 15 percent of the NOEL and average worker levels are 50 times lower than the NOEL in monkeys. On the other hand, using the results from the 14-week rat study, production worker exposures are, at the upper end, more than one-half of the NOEL and, on average, are about 10 times lower than the NOEL.

As explained earlier, the direct interspecies comparisons of serum levels rather than external dose reduces many of the usual uncertainties associated with interspecies extrapolation, most

especially those associated with ADME differences. This, in turn, reduces the need for a significant fraction of the uncertainty factors typically used to extrapolate from animals to humans. Moreover, uncertainty factors used for the general (non-occupational) population (see below) are generally larger than those used for worker populations, because the latter are not expected to exhibit the same high degree of variability in sensitivity to toxic effects.

Little serum PFOS data are available for occupational exposures in various user facilities. 3M production workers are exposed to unreacted, concentrated starting materials. The majority of downstream workers are exposed to fluorochemical products that typically contain less than 1% residual unreacted starting material that could be absorbed and metabolized to PFOS. Although it seems likely that such workers exhibit lower exposure levels, and therefore would demonstrate larger safety margins than do 3M production workers, this conclusion can not be fully documented. The study of non-production workers in 3M's Japanese facility, where PFOS precursors are handled, seems to support it.

#### General (Non-Occupational) Exposures

The currently available data from sampling of blood from selected human populations and from blood banks reveals that non-occupational exposures to PFOS range from *ca.* 0.01 to 0.1 ppm. The upper end of this range is about 60 times lower than the level (6 ppm) found to be without associated adverse effects in the occupational studies. It is also about 180 to 850 times lower than the NOELs from the rat and non-human primate studies, respectively. Again, the direct interspecies comparisons of serum levels reduces uncertainties related to ADME differences. Taken together, the data from human and animal studies suggest that PFOS serum levels in members of the general population are substantially below levels associated with adverse effects.

#### 4.4.5 Uncertainties in Assessment and Work in Progress

The initial assessment presented above is based on a substantial body of health effects data. It is based on an interspecies comparison of serum PFOS levels and is more certain than typical assessments, which are based on cross-species comparisons of external doses. This reduced uncertainty translates to a need for smaller uncertainty factors for cross-species extrapolations. In light of this conclusion, the margins separating NOELs from human exposure levels described above should not be compared with the larger margins observed or used in the more typical assessment.

The limitations associated with the use of human data have already been identified, and will be reduced when additional epidemiological investigations are completed. Results from chronic rodent studies of PFOS and N-EtFOSE are still under evaluation. Definitive conclusions regarding the effects of chronic exposures will become available in the future. Mechanistic understanding of the underlying causes of toxicity, particularly those relating to reduced survival of offspring in the two-generation study is under study.

Additional data are forthcoming pertaining to the blood levels and distribution of PFOS in human sera. The distribution of PFOS levels according to age, gender, and geographic location will be available for future assessments. As detailed in Section 4.2.4 several additional studies will add substantially to understanding this area.

## **5.0 CONCLUSIONS AND RECOMMENDATIONS**

This report summarizes the information that is available as of July 20, 2000. There is a substantial body of data relating human and environmental exposures to PFOS and the possible biological effects of these exposures. This information suggests that human serum PFOS levels found in occupational and non-occupational populations are not associated with adverse health effects. Similarly, levels found in the environment and in wildlife are not associated with adverse effects. Additional research now underway will be used to refine this initial assessment.

Ongoing studies in several areas will improve this initial assessment of risk. Areas under study include environmental source assessment, human exposure (through sera measurement), chronic studies in laboratory animals and additional tissue measurements of PFOS from previous studies. Much of this information will be available in the next year.

## 6.0 REFERENCES

3M Company. Perfluorooctane Sulfonate: Current Summary of Human Sera, Health and Toxicology Data. January 21, 1999.

Baril, A., and P. Mineau. 1996. A distribution-based approach to improving avian risk assessment. Presented at the 17<sup>th</sup> Annual Meeting of the Organization for Economic Cooperation and Development, Washington, D.C.

Belisle J, Hagan DF (1978). *Anal Biochem.* 87, 545 (Note Error: In this report the blank was erroneously reported as 0.02 mg; it should be 0.02µg.)

Belisle, J (1981). *Science* 212, pp. 1509-1510.

Bisemeier, JA and Harris, DL, 1974. Report T-1117. WARF No. 4102871, WARF Institute, Inc., Madison, WI.

Chapman, P.M., A. Fairbrother, and D. Brown. 1998. A critical evaluation of safety (uncertainty) factor for ecological risk assessment. *Environ. Tox. Chem.* 17: 99-108.

ECOFRAM. 1999. ECOFRAM Terrestrial Draft Report. Ecological Committee on FIFRA Risk Assessment Methods, Washington, D.C.

Ederer, F, Mantel, N (1974). Confidence limits on the ratio of two Poisson Variables. *Am. J. Epidemiol.* 100:165-167.

Environment Canada. 1999. *Guidance Document on Application and Interpretation of Single-species Tests in Environmental Toxicology.* EPS 1/RM/34. Environmental Technology Centre, Environment Canada, Ottawa, Ontario.

Guy, WS (1972). PhD. Thesis, University of Rochester, Rochester, NY.

Haughom, B and Øystein, S. 1992. The mechanism underlying the hypolipemic effect on perfluorooctanoic acid (PFOA), perfluorooctane sulphonic acid (PFOSA) and clofibrate acid. *Biochim. Biophys. Acta.* 1128. 65-72.

Ikeda, T., Fukuda, K., Mori, I., Enomoto, M., Komai, T. and Suga, T. 1987. Induction of cytochrome P-450 and peroxisome proliferation in rat liver by perfluorinated octanesulfonic acid. In: *peroxisomes in Biology and Medicine*. H.D. Fahimi and H. Sies, Eds. Springer Verlag, New York, 304-208.

Johnson, J.D., Gibson, S.J. and Ober, R.E. 1984. Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [<sup>14</sup>C]perfluorooctanoate or potassium [<sup>14</sup>C]perfluorooctanesulfonate. *Fund. Appl. Toxicol.* 4, 972-976.

Luttik, R., and T. Aldenberg. 1995. *Extrapolation factors to be used in case of small samples of toxicity data (with a special focus on LD50 values for birds and mammals)*. Report No. 679102029. National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.

Nabbefeld D. 1998. An Investigation of the Effects of Fluorochemicals on Liver Fatty Acid-Binding Protein. Masters Thesis, University of Minnesota. Thesis research performed at and supported by 3M.

Nabbefeld D., Butenhoff J., Bass N. and Seacat A. 1998. Displacement of a fluorescently labeled fatty acid analogue from fatty acid carrier proteins by wyeth-14,643, ammonium perfluorooctanoate, potassium perfluorooctane sulfonate and other known peroxisome proliferators. (SOT Abstract. Accepted, *Toxicologist* 1998).

Nishioka M., Strauss W. 2000. Design and Structure of the Multi-City Study, Battelle Memorial Institute. Columbus, OH.

Paez, DM, deBianchi, LP, Gil BA, Dapas O, Coronato, RG (1980). *Fluoride* 13:65.

Pothapragada V, (1975). Determination of total fluorine in serum and other biological materials by oxygen bomb and reverse extraction techniques. *Analytical Biochem* 68:512-521.

Pothapragada V, Singer R, Armstrong W.D (1971). Determination of ionic (plus ionizable) fluoride in biological fluids. Procedure based on adsorption of fluoride ion on calcium phosphate. *Anal Biochem* 42:350-359.

Roach DE (1982). Fluorochemical Control Study. Unpublished report. St. Paul:3M Company, May 25, 1982.

Sample, B. E., D. M. Opresko, and G. W. Suter. 1996. *Toxicological benchmarks for wildlife: 1996 revision*. ES/ER/TM-86/R3. Risk Assessment Program, Health Assessment Research Division, Oak Ridge National Laboratory, Oak Ridge, TN.

Screening Information Data Set Manual Of The OECD Programme On The Co-Operative Investigation of High Production Volume Chemicals. 1997. Third Revision. OECD Secretariat.

Screening Information Data Set Manual Of The OECD Programme On The Co-Operative Investigation of High Production Volume Chemicals. 1997. Third Revision. OECD Secretariat.

Singer L and Ophaug RH (1979). Concentrations of ionic, total, and bound fluoride in plasma. *Clin Chem* 25:523-525.

Sohlenius, A-K., Eriksson, A.M., Högström, C., Kimland, M and DePierre, J.W. 1993. Perfluorooctane sulfonic acid is a potent inducer of peroxisomal fatty acid B-oxidation and other activities known to be effected by peroxisome proliferators in mouse liver. *Pharmacol. Toxicol.* 72, 90-93.

Suter, G.W. 1993. *Ecological Risk Assessment*. Lewis Publishers, Boca Raton, FL.

Taves D (1968a). Evidence that there are two forms of fluoride in human serum. *Nature* 217:1050-1051.

Taves D (1968b). Electrophoretic mobility of serum fluoride. *Nature* 220:582-583.

Taves D, Guy W, Brey W (1976). Organic fluorocarbons in human plasma: Prevalence and characterization. In: Filler R, eds. *Biochemistry Involving Carbon-Fluorine Bonds*. Washington, DC:American Chemical Society, pages 117-134.

Ubel FA, Sorenson SD, Roach DE (1980). Health status of plant workers exposed to fluorochemicals, a preliminary report. *Am Ind Hyg Assoc J.* 41:584-589.

U.S. EPA. 1998. *Guidelines for Ecological Risk Assessment*. EPA/630/R-95/002F. Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency. 1998. *Guidelines for Ecological Risk Assessment*. EPA/630/R-95/02F. Risk Assessment Forum, U.S. EPA., Washington, D.C.

Wallace K.B. and Starkov A. 1998. The effect of perfluorinated arylalkylsulfonamides on bioenergetics of rat liver mitochondria. Dept. of Biochemistry and Molecular Biology, University of MN School of Medicine. Duluth, MN 55812, USA. Supported by a grant from 3M Company.

Yamamoto G, Yoshitake K, Sato T, Kimura T and Ando T (1989). Distribution and forms of fluorine in whole blood of human male. *Analytical Biochem* 182:371-376.

**APPENDIX I**  
**SUMMARY REPORTS FOR PHYSICAL/CHEMICAL PROPERTIES**  
**CONTENTS**

	<b>Boiling Point</b>
<b>Reference 55</b>	<b>Melting Point</b>
<b>Reference 57</b>	<b>Vapor Pressure</b>
<b>Reference 58</b>	<b>Octanol/Water Coefficient</b>
<b>Reference 59</b>	<b>Air/Water Partition Coefficient</b>
<b>Reference 60</b>	<b>Water Solubility</b>

**BOILING POINT**

**TEST SUBSTANCE**

**Identity:** Perfluorooctanesulfonate; may also be referred to as PFOS or FC-95. (1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptafluoro-, potassium salt, CAS # 2795-39-3)

**Remarks:** Testing was not conducted. Boiling point would be in excess of 400°C.

**MELTING POINT**  
(Reference No. 55)**TEST SUBSTANCE**

**Identity:** Perfluorooctanesulfonate; may also be referred to as PFOS or FC-95. (1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptafluoro-, potassium salt, CAS # 2795-39-3)

**Remarks:** The test substance is a white powder. Sample was taken from 3M lot number 217. Sample was stored under ambient conditions prior to testing. Purity determined to be 90.49% by LC/MS, <sup>1</sup>H-NMR, <sup>19</sup>F-NMR and elemental analyses techniques.

**METHOD**

**Method:** OECD 102

**GLP:** Yes

**Year completed:** 1998

**Remarks:** Study utilized a Büchi Melting Point B-540 instrument, calibrated and inspected just prior to use using anthraquinone and 1,8-naphthalimide.

**RESULTS**

**Melting point value in °C:** >400°C (No melting observed).

**Decomposition (yes-temperature °C/ no /ambiguous):** No

**Sublimation (yes/no/ambiguous):** No

**Remarks:** Measurements of the melting point / melting range were limited to □400□C, the maximum specification for the instrument used. Fine droplets were not observed to adhere uniformly or otherwise to the walls of the melting point tubes.

**CONCLUSIONS**

The melting point/melting range was not observed and therefore could not be determined.

**Remarks:** While no melting of the test substance was evident, discoloration of the test samples was observed. The white powder turned to a light brown and eventually black as temperatures rose.

**Submitter:** 3M Company, Environmental Laboratory  
P.O. Box 33331  
St. Paul, MN 55133

**DATA QUALITY**

**Reliability:** Klimisch ranking 1.

**REFERENCES**

*Draft Initial Assessment Report PFOS - Appendix I*

**Study conducted at the request of 3M Company by Wildlife International, Ltd. of Easton, Maryland.**

**OTHER**

**Last changed: 5/3/00**

**VAPOR PRESSURE**  
**(Reference No. 57)****TEST SUBSTANCE**

**Identity:** Perfluorooctanesulfonate; may also be referred to as PFOS or FC-95. (1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptafluoro-, potassium salt, CAS # 2795-39-3)

**Remarks:** The test substance is a white powder. Sample was taken from 3M lot number 217. Sample was stored under ambient conditions prior to testing. Purity determined to be 90.49% by LC/MS, <sup>1</sup>H-NMR, <sup>19</sup>F-NMR and elemental analyses techniques.

**METHOD**

**Method:** OECD 104, U.S. EPA OPPTS 830.7950

**GLP (Y/N):** Yes

**Year completed:** 1999

**Remarks:** Determination of the vapour pressure was done by using the Spinning Rotor Gauge method.

**RESULTS**

**Vapor Pressure:**  $3.31 \times 10^{-4}$  Pa

**Temperature °C:** 20°C

**Decomposition (yes/no/ambiguous):** No

**Remarks:** The measured vapour pressure was repeatable.

**CONCLUSIONS**

**Remarks:** The vapor pressure of the test substance was determined to be  $3.31 \times 10^{-4}$  Pa at 20°C using the spinning rotor gauge method.

**Submitter:** 3M Company, Environmental Laboratory, P.O. Box 33331, St. Paul, Minnesota, 55133

**DATA QUALITY**

**Reliability:** Klimisch ranking 1.

**REFERENCES**

Study conducted at the request of 3M Company by Wildlife International, Ltd. of Easton, Maryland.

**OTHER**

**Last changed:** 5/3/00

*Draft Initial Assessment Report PFOS - Appendix I*

**OCTANOL/WATER PARTITION COEFFICIENT****(Reference No. 58)****TEST SUBSTANCE**

**Identity:** Perfluorooctanesulfonate; may also be referred to as PFOS or FC-95. (1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-, potassium salt, CAS # 2795-39-3)

**Remarks:** The test substance is a white powder. Sample was taken from 3M lot number 217. Sample was stored under ambient conditions prior to testing. Purity determined to be 90.49% by LC/MS, <sup>1</sup>H-NMR, <sup>19</sup>F-NMR and elemental analyses techniques.

**METHOD**

**Method:** OECD 107

**GLP (Y/N):** See Remarks

**Year completed:** Study completed 1999. Report completed 2000

**Remarks:** A feasibility test was conducted to determine if the physical properties of the test substance were compatible with shake flask methodology proposed for use in an n-octanol/water partition coefficient determination.

Upon completion of the test procedure, a definitive partition interface was not obtained. Instead, a beige/white emulsion was observed throughout the sample.

**RESULTS**

**Log P<sub>ow</sub>:** Not determined.

**Remarks:** The observation of an inseparable emulsion in the preliminary test precluded conduct of a definitive test, as indicated in the protocol (No 454/120298/107F/SUB454, 3M Lab Request U2723). Therefore, a study cancellation report was generated by the laboratory conducting the testing after consultation with 3M.

**CONCLUSIONS**

The study substance exhibits physical/chemical characteristics that make determination of the n-octanol/water partition coefficient infeasible by the Shake Flask Method.

**Submitter:** 3M Company, Environmental Laboratory, P.O. Box 33331, St. Paul, Minnesota, 55133

**DATA QUALITY**

**Reliability:** Klimisch ranking NA. Study not feasible.

REFERENCES

Study conducted at the request of 3M Company by Wildlife International, Ltd. of Easton, Maryland.

OTHER

**Last changed: 5/3/00**

**AIR/WATER PARTITION COEFFICIENT**  
**(Reference No. 59)**

**TEST SUBSTANCE**

**Identity:** Perfluorooctanesulfonate; may also be referred to as PFOS or FC-95. (1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptafluoro-, potassium salt, CAS # 2795-39-3)

**Remarks:** The test substance is a white powder. No information was recorded on the purity.

**METHOD**

**Method:** There is no standardized methodology used to determine this value for regulatory purposes. The experiment was designed by Dr. Richard Purdy of 3M's Environmental Laboratory and Don Mackay of D. Mackay Environmental Research Limited.

**GLP (Y/N):** No

**Year completed:** 1999

**Remarks:** The following method was devised and used:

- Weigh approximately 0.01 gram of the test substance directly into a tared 250-mL Pyrex<sup>®</sup> beaker. Record weight.
- Transfer 200 mL of NANOpure<sup>®</sup> water into the beaker using a Class A glass volumetric pipet.
- Prepare solvent blank sample. Using a gas-tight syringe, transfer a 250 µL aliquot of NANOpure<sup>®</sup> water into a 25-mL Class A glass volumetric flask partially filled with 50% methanol / 50% ammonium acetate buffer reagent. Bring to volume with 50% methanol / 50% ammonium acetate buffer reagent. Ampulate in an amber glass autosampler vial.
- Mix and sonicate the test substance in water sample (50 µg test substance/mL target nominal concentration) for approximately 10 minutes to ensure dissolution of the test material.
- Prepare the control sample. Transfer a 250 µL aliquot of the test substance in water sample into a 25-mL Class A glass volumetric flask partially filled with 50% methanol / 50% ammonium acetate buffer reagent. Bring to volume with 50% methanol / 50% ammonium acetate buffer reagent. Ampulate in an amber glass autosampler vial.
- Place the test substance in water sample beaker on a hotplate and bring solution to a boil. After approximately 10 mLs (5%) of water has evaporated, remove beaker from hotplate and cool to room temperature in an ice-water bath. Transfer contents of sample into graduated cylinder and record actual volume.
- Process a 250 µL aliquot of sample as described above for solvent blank and control samples.
- Return sample to original beaker and bring sample to boil.
- Repeat steps 6-8 until sample has evaporated to 100 mLs. Submit all ampulated samples for LCMS analysis.