

AR 226-0548

**Perfluorooctane Sulfonate:
Current Summary of Human Sera,
Health and Toxicology Data**

**3M
January 21, 1999**

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Executive Summary

3M has prepared this document to summarize the data related to the biological effects of perfluorooctane sulfonate (PFOS). It also presents current thinking on human health risk related to PFOS and includes information about future study plans. 3M Medical Department scientists and physicians, in consultation with outside experts, are the authors.

PFOS has been found at tens of parts per billion levels in serum samples of nonoccupationally exposed employees, in commercially available human serum and in pooled samples from multiple blood banks. PFOS is an eight-carbon molecule that is perfluorinated except for the sulfonate group on the terminal carbon. 3M has manufactured PFOS and molecules that may be metabolic precursors to it since 1948. Routes of exposure to PFOS or precursor molecules are not well understood at this time.

PFOS is an example of an "organic" fluorine molecule. Human serum has been known to contain organic fluorine molecules for over 30 years. The primary constituent of this organic fluorine fraction was tentatively identified as another molecule (perfluorooctanoate) in 1976. Current analysis of stored sera samples from a variety of sources are more consistent with PFOS being a major fraction of this organic fluorine. Improved analytic techniques allowing a relatively rapid analysis at low levels of detection make the current analyses possible. These analytic techniques were first available for use in medical surveillance of exposed workers in 1992. Detection limits have been lowered to allow the more recent analysis of serum from those without occupational exposure.

Medical surveillance has been done among 3M employees occupationally exposed to PFOS precursors for over 20 years. To date, no adverse health effect associated with PFOS exposure has been found in these employees. This conclusion applies at serum levels up to 6 parts per million, about 100 times higher than levels seen in the general

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population. PFOS has a long residence time in the human body. In three retirees, the half-life in human sera ranges from 1100 to 1500 days. A mortality study at the U.S. plant primarily involved with production of PFOS related materials has found no significantly elevated standardized mortality ratios (SMR's).

Toxicology studies show that PFOS is well absorbed orally and distributes primarily in the serum and liver. It does not appear to be further metabolized. Some enterohepatic circulation of PFOS occurs, based on the observation of increased excretion in rats given cholestyramine. Elimination from the body is slow and occurs via both urine and feces.

Mutagenicity testing is negative in five salmonella species. It is not genotoxic in a mouse bone marrow micronucleus assay. The acute LD50 in rats is 250 mg/kg (moderately toxic). It does not produce dermal or ocular toxicity.

Subchronic studies have been done in rats and primates. PFOS causes liver enzyme elevations and hepatic vacuolization in rats, and hepatocellular hypertrophy at higher doses. Higher doses also cause other GI toxicity, hematological abnormalities, weight loss, convulsions, tremors and death. Monkeys show anorexia, emesis, diarrhea, hypoactivity and at higher doses prostration, convulsions and death. Atrophy of exocrine cells in salivary glands and the pancreas, and lipid depletion in the adrenals is found at high doses in the monkey.

The serum levels at which these compound related effects occurred in these early rhesus monkey studies are unknown. In a recently completed rangefinder study in cynomolgus monkeys the first observed biological effect was a decrease in serum cholesterol, first observed at a serum level of 72 ppm in one of the two monkeys in the high dose group. Using the relationship between cumulative dose and serum level found in this study, it can be estimate that significant toxicity occurred at 700 to 800 ppm in the early rhesus monkey studies, and death at 1100 ppm and above. More complete quantitative absorption, distribution and excretion data for PFOS is being obtained.

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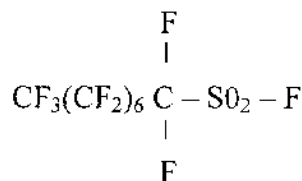
Available information therefore suggests that no identifiable health risk to humans would be expected to occur at the PFOS levels found in blood bank or commercial serum samples.

Extensive further research, which includes epidemiological and laboratory studies, is planned or underway. The purpose of this research is to explore the potential for chronic and reproductive effects, understand toxic mechanisms and obtain a better understanding of absorption, distribution, metabolism and excretion. The plan is to make as much use as possible of observational data in exposed workers and to establish no effect levels in both rats and primates for endpoints of importance.

I. INTRODUCTION

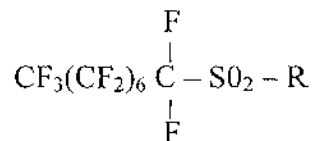
Evidence that organic compounds containing the element fluorine covalently bonded to carbon (organic fluorine compounds, OF) can be found in human sera has been available for 30 years. Although all of the specific compounds contributing to the total amount of OF present are not identified, it now appears that a compound called perfluorooctane sulfonate constitutes a significant fraction. Recent data provide evidence that PFOS is present at tens of parts-per-billion (ppb) levels in serum samples from the general population, averaging 30 ppb in blood bank samples from diverse locations in the U.S. Single digit parts per million (ppm) levels (approximately 100 times greater) are found in individuals occupationally exposed to PFOS and its precursors, averaging 2.0 ppm among participating employees at the primary U.S. manufacturing location for these compounds.

3M produces perfluorinated molecules by mixing anhydrous HF and hydrocarbon feed stock in an electrochemical cell (electrochemical fluorination). Perfluorooctane sulfonyl fluoride (POSF) is the cell product from which a group of products is developed:



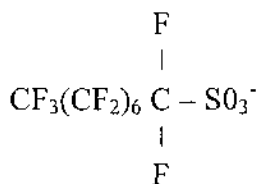
POSF

Other moieties ("R") are added to the sulfur, which leads to the creation of materials that may be polymerized or esterified. The vast majority of POSF produced is used in this way.



POSF derived molecule

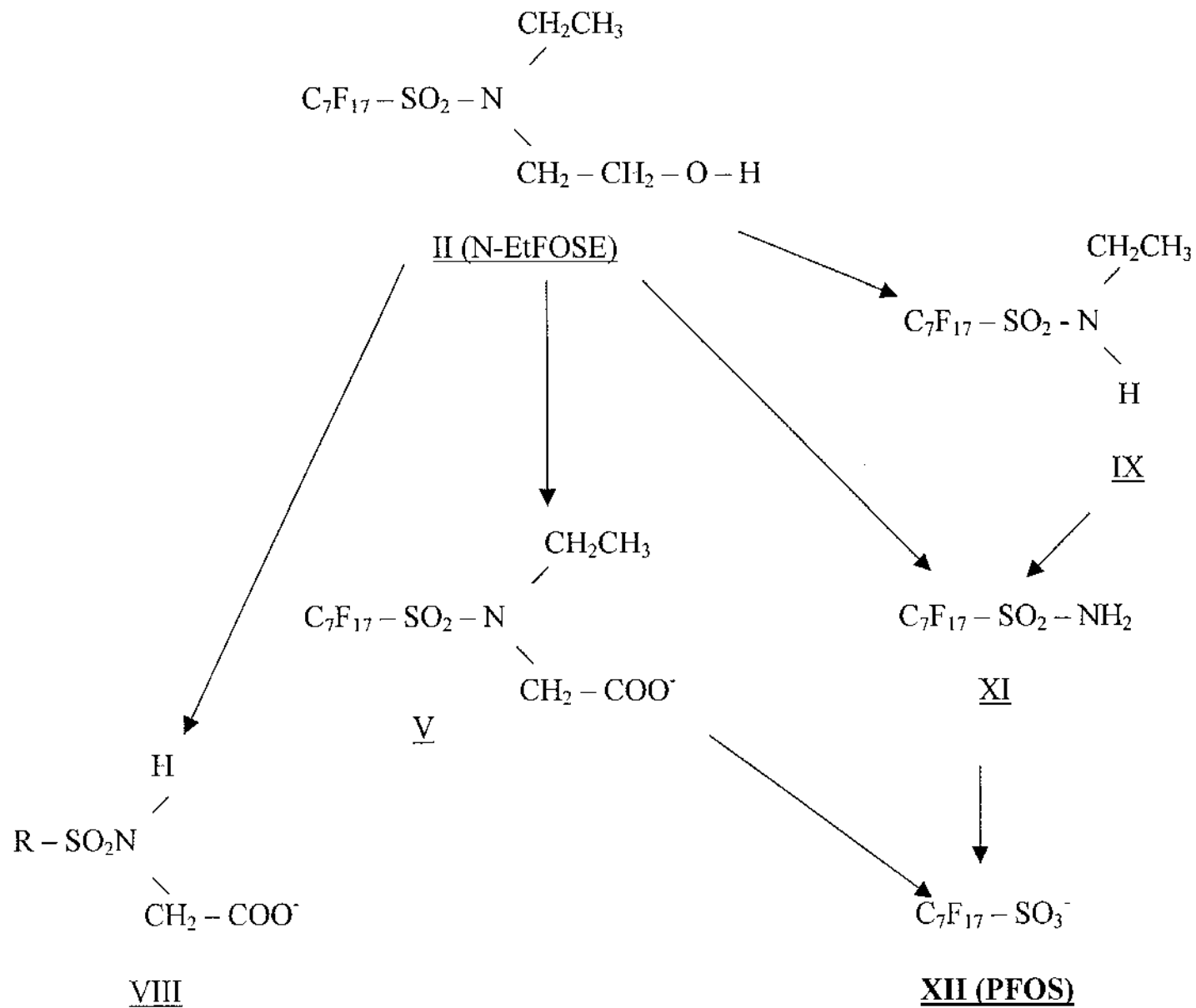
PFOS may result from the loss of the "R" moiety through metabolic processes. Current evidence would indicate that PFOS is not further metabolized. Some PFOS is produced and sold directly into industrial applications as a surfactant. This, however, amounts to only a small fraction of total POSF production.



PFOS

Most POSF that is produced is used in 2-(N-ethylperfluorooctanesulfonamido)-ethyl alcohol (N-Et-FOSE) and 2-(N-methylperfluorooctanesulfonamido)-ethyl alcohol (N-Me-FOSE) based products. Figure 1.1 shows the chemical structure of N-Et-FOSE and metabolites that have been found in rat serum. All except compound VIII have been verified to metabolize further to PFOS. (Missing Roman numerals represent hypothesized intermediates not shown in this figure.)

Figure I.1 N-EtFOSE(*) Metabolites Identified in Rat Serum



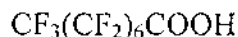
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In vitro studies in both rat and human hepatocytes lead to identification of the same compounds and hypothesized intermediates. Compound VIII has been detected in some samples of pooled human sera. A single dose absorption, distribution, metabolism and excretion study of N-Et-FOSE in cynomolgus monkeys is through the in life phase and tissue analysis is pending. N-Et-FOSE is esterified to produce larger molecules that are used on paper and packaging for oil and water repellency.

It is presumed that N-Me-FOSE, in which a methyl group replaces the ethyl group on the nitrogen, has a similar metabolism. N-Me-FOSE becomes part of very large molecules that act as protective chemicals on fabrics, leather and rugs.

Outside of the occupational setting, routes of human exposure to PFOS or its metabolic precursors are not understood, but are the subject of intense study. Exposure could occur from environmental releases of PFOS or its precursors at the Decatur, Alabama and Antwerp, Belgium manufacturing sites. It could occur from the environmental or biological degradation of products to PFOS or molecules metabolized to PFOS. Products also contain small amounts (generally less than a few percent) of residuals, such as N-Et-FOSE and other molecules found in Figure I.1, which are known or suspected metabolic precursors to PFOS. These residuals represent a source of PFOS that would not require environmental or biological degradation of large molecules. Downstream industrial users of POSF based products are also potential sources of environmental releases of PFOS or its precursors. The relative contribution of these various sources to population exposure is currently unknown.

Another surfactant is known to be found in the sera of employees and was reported in general population sera samples in 1976 (Taves). This is perfluorooctanoic acid, or PFOA:



PFOA is also made by electrochemical fluorination. It is mentioned here because following Taves' report in 1976 it was presumed to be a significant fraction of the total organic fluorine found in the sera samples analyzed by Taves and others. This report was a stimulus for investigation and subsequent medical surveillance of employees in fluorochemical production, including those producing POSF based materials. It should be recognized, however, that PFOA is a different and unrelated compound. It does not metabolize to or become PFOS. It is likely that PFOA was misidentified as a major fraction of organic fluorine in the 1976 Taves paper. The evidence for this is discussed in Section II.

The purpose of this report is to describe the data on PFOS levels in human sera, and to discuss the potential for those levels to affect health based on current scientific knowledge. A review of current findings and historical information on PFOS levels in sera is presented in Section II. This is followed in Section III with a description of 3M's epidemiology and medical monitoring database obtained from studies of its workers in plants in the United States and Belgium. The animal and other laboratory toxicology data available on PFOS are presented in Section IV. Section V offers a preliminary evaluation of the serum findings in light of the available health effects data.

3M is actively developing further human health and toxicological information. Section VI outlines the current research agenda.

II. HISTORICAL REVIEW AND CURRENT FINDINGS OF FLUORO-CHEMICALS IN HUMAN SERA

The data on fluorochemicals in human sera is presented in this section. The presence of organic forms of fluorine in human serum was observed 30 years ago, and PFOA was thought to account for most of this fraction. 3M finds little current evidence to support this view. Evidence is presented below that PFOS is more likely to be consistently found in sera. Based on the limited data provided by historical samples, there is no evidence of significant change in PFOS concentration in serum samples taken over the last two to three decades.

The advancement of analytical chemistry technology has had a significant influence on our 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 also nonspecific, measuring organic fluorine (fluorine covalently bonded to carbon) rather than specific molecules. The development of a rapid analytic technique in the late 1970's decreased analytic time 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 rapid analysis of specific fluorochemicals from small volumes of sera in the early 1990's. This technology was first used in medical surveillance in 1992. Detection limits for PFOS were lowered to 50 parts per billion by 1997. The first report to 3M of PFOS in commercially available pooled sera occurred in late summer of 1997, prompting more research into the technique, and confirming its validity over a period of several months.

Since older published data described organic fluorine content rather than a specific molecule, it is useful to understand the relationship between PFOS levels currently observed and organic fluorine content. Fluorine is 65% of the molecular weight of PFOS. The contribution of a PFOS value to organic fluorine, in ppb, will therefore be $[0.65 \times (\text{PFOS value in ppb})]$. Conversely, if the measured organic fluorine is entirely PFOS, the value of PFOS in ppb will be $[1.54 \times (\text{OF level in ppb})]$.

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, 3) data from a small group of non-occupationally exposed 3M employees, 4) data from commercially available human pooled serum samples, 5) data from pooled sera from 18 regional blood banks and 6) data from current analysis of stored serum samples.

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.

A number of studies over the past 25 years reported levels of organic fluorine in human blood serum. Table II.1 presents the study author, level measured, population 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 part per billion levels. The average of reported values from United States sources is 37.6 ppb.

Table II.1.
Historical Findings of Serum Organic Fluorine Levels

Year	Author	OF* (ppb)	N	Method**	Source
1972	Guy	30	65	ash	US
1975	Venkateswarlu	36	2	O bomb	US
1976	Guy, Taves	25	106	ash	US
1978	Belisle	20	9	O bomb	US
1979	Singer	45	264	ash	US
1980	Paez	85	pooled	ash	Argentina
1980	Ubel	45	4	mod O bomb	US
1981	Belisle	11	8	O bomb	China
1989	Yamamoto	32	11	LOPA	Japan

* Organic fluorine, specific identities not provided.

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

Occupationally Exposed Employees

3M has produced PFOA (the ammonium salt) by electrochemical fluorination since the early 1950's. It is a surfactant used in fluoropolymer production. The company began medical monitoring of employees involved in PFOA production in 1976, by measuring serum levels of organic fluorine (OF) and performing medical assessments. Employee monitoring was expanded significantly in 1980 following the development of a more rapid test for organic fluorine. Measured serum levels of OF in these employees averaged less than 10 parts per million (ppm).

As noted earlier, PFOS is a surfactant used as a wetting and foaming agent in industrial and commercial processes. Certain fluorochemicals that may transform metabolically to PFOS have been produced since the early 1950's by electrochemical fluorination. Since 1980 this has occurred at primarily one location in the United States (Decatur, Alabama). This 3M site consists of a fluorochemical plant and a film plant that are physically separate entities. Chemical plant employees have been offered a medical monitoring program that includes standard medical testing as well

as measurement of serum levels of OF. Among employees with six or more measurements, OF levels averaged 2.9 to 6.5 ppm from 1981 to 1992¹ (Figure II.1). With the introduction of high performance liquid chromatography-mass spectrometry, serum PFOS was measured in 1994 and 1997 (see also Figure II.1). In these two years, mean PFOS levels were 2.44 ppm (range 0.25 – 12.83 ppm) and 1.96 ppm (range 0.10 – 9.93 ppm), respectively.

Another 3M plant in the United States where PFOS has been measured in employees' serum is Cottage Grove, Minnesota. Some PFOS is manufactured at this plant. In 1997, the mean serum level of PFOS among 74 Cottage Grove fluorochemical production employees was 0.82 ppm (range 0.05 - 6.25 ppm). Outside the United States, 3M manufactures PFOS related materials at its Antwerp, Belgium plant. PFOS levels were measured in Antwerp employees in 1995 (mean = 1.9 ppm, range 0.0 - 9.9 ppm) and in 1997 (mean 1.5 ppm, range 0.1 - 4.8) ppm.

The cross-sectional stratified analysis presented in section III, examining the relationship between PFOS sera level and various clinical chemistry and hormone parameters, was conducted at the Decatur, Alabama and Antwerp, Belgium plants. The Cottage Grove facility was not included because little PFOS related product is manufactured there. It is also the primary site for PFOA production.

¹ We are aware of one occasion in 1979 where the serum of 5 Decatur employees was measured for PFOS by electron capture gas chromatograph and microwave plasma detection methods [Central Analytical Laboratory, 1979]. Total serum organic fluorine levels for these five employees were 10.1, 5.7, 9.4, 11.8 and 4.1 ppm. The percent of PFOS found was 60%, 70%, 80%, 55% and 65% of the total serum organic fluorine levels, respectively.