PFOS

3/11/05 PFOS Case Study
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Introduction
Perfluorooctane sulfonate and its salts (PFOS) are fully fluorinated organic molecules produced synthetically by electrochemical fluorination or from the degradation or metabolism of other fluorochemical products produced by electrochemical fluorination. PFOS and its precursors all belong to the larger class of fluorochemicals known as perfluoroalkyl substances and are derived from perfluorooctanesulfonyl fluoride (POSF), the basic chemical building block for many sulfonyl-based fluorochemicals. POSF is used primarily as an intermediate to synthesize numerous fluorochemicals, including PFOS.

3M Company produced POSF, PFOS, and POSF-related materials for over 40 years. The commercial uses of PFOS included predominantly surface treatments for soil and stain-resistant coating on fabrics, carpets, and leather, coatings on paper and packaging products for grease and oil resistance, including food contact papers, and performance chemicals uses, such as fire extinguishing foam concentrates, mining and oil surfactants, electroplating and etching bath surfactants, household additives, chemical intermediates, coatings and coating additives, carpet spot cleaners and insecticide raw materials (3M Company, 2003). Total worldwide POSF production by 3M Company in 2000 was approximately 8 million pounds. However, on May 16, 2000, 3M Company announced that it would globally phase out the perfluorooctanyl chemistry used to produce certain repellents and surfactant products, which included the manufacture of PFOS and related compounds (3M Company, 2000). 3M steadily reduced their production volume and discontinued the manufacture of most PFOS and POSF-based chemicals by December 31, 2002 (3M Company, 2001). Manufacture of PFOS for certain uses for which no substitutes are available (eg., use as an anti-corrosion additive in fire-resistant phosphate ester aviation hydraulic fluids) are continuing by non-U.S. producers.

Biomarker of Exposure
PFOS has been measured primarily in human blood serum (Olsen et al. 2003a; 2004a; 2004b); however, data are also available on PFOS in human whole blood (Kannan et al. 2004; Harada et al. 2004), plasma (Kannan et al. 2004; Olsen et al. 2004c), cord blood (Inoue et al. 2004) and seminal plasma (Guruge et al. 2005). PFOS was measured in the liver and serum of cadavers (Olsen et al. 2003b). The average PFOS serum and liver data for each of 23 paired samples (serum and liver from the same individual) showed a good correlation for both male and female donors—the mean liver to serum ratio was 1.3:1. Mean PFOS levels for male and female donors were similar for both serum (male = 18.2 ng/mL; female = 17.2 ng/mL) and liver (male = 19.2 ng/g; female = 28.4 ng/g).
The analytical techniques for measuring fluorochemical analytes, including PFOS, have employed high performance liquid chromatography/mass spectrometry methods including tandem mass spectrometry (Hansen et al. 2001). Briefly, analysis of PFOS and other fluorinated surfactants exhibit chemical and physical properties that can be substantially different from more hydrogenated compounds. These properties include the fact that fluorosurfactants are extremely resistant to heat as well as oxidizing or reducing agents, have lower surface tension, are typically water-soluble (although the degree depends upon the nature of the acid and length of the perfluorocarbon group), and are relatively strong organic acids. Detailed validation studies for the analysis of PFOS and other fluorinated compounds are available (Tandem Labs 1999; 2001a; 2001b). More recent laboratory analyses for PFOS have incorporated solid phase extraction techniques (Kuklenyik et al. 2004).

Prior to the development of analytical techniques for specific fluorochemical analytes, total organic fluorine was measured. In the 1970’s and 1980’s, there were multiple reports of organic fluorine in human blood (3M Company, 2003). As analytical techniques improved and the LOQ was lowered, “blank” human serum was found to contain PFOS in 1997. In 1998, PFOS was found distributed widely in human serum and fish-eating wildlife serum and liver.

Pharmacokinetics
The pharmacokinetic properties of PFOS are favorable for using serum PFOS concentration as a measure of internal dose. Good absorption, lack of known metabolism, distribution primarily in extracellular space, high serum protein binding (albumin and beta-lipoproteins), and poor elimination in all species studied combine to establish serum PFOS concentration as an integration of exposures from various sources. In addition, serum PFOS concentrations can be directly associated with effects in toxicology studies, as well as with results from medical surveillance studies.

Animal studies indicate that PFOS is well absorbed orally and distributes mainly in the serum and liver, with liver concentrations being potentially several times higher than serum concentrations (Johnson, et al., 1979a). The volume of distribution at steady state, as measured in cynomolgus monkeys, is approximately 200 mL/kg, suggesting distribution primarily in extracellular space (Noker and Gorman, 2003). PFOS is highly bound to albumin and has affinity for binding to β-lipoproteins (Kerstner-Wood et al., 2003) as well as albumin and liver fatty-acid-binding protein (Luebker et al., 2002a). PFOS is poorly metabolized and excreted, and undergoes extensive enterohepatic circulation (Johnson, et al., 1984). The serum elimination half-life of PFOS is approximately 100 days in rats (Johnson, et al., 1979b), 100-200 days in Cynomolgus monkeys (Seacat, et al., 2002a; Noker and Gorman, 2003) and appears to be approximately 8 years in humans, based on an initial longitudinal observation of retired PFOS workers (Burris, et al., 2002).

Exposure Assessment
The mechanisms and pathways leading to the presence of PFOS in human blood are not well characterized but likely involve environmental exposure to PFOS or to precursor
molecules and residual levels of PFOS or PFOS precursors in industrial and commercial products. Potential sources of human or environmental exposure to PFOS may have included 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. PFOS has been identified in serum and tissue samples from both occupationally and non-occupationally exposed human populations in various countries, in various species of wildlife in many parts of the world, and in surface waters and other environmental media in various countries (3M Company, 2003; Giesy and Kannan, 2001; Hansen et al., 2001; Kannan et al., 2001a; 2001b; 2002a; 2002b; 2002c; 2002d). In addition, N-alkyl-perfluorooctanesulfonamides that can degrade to PFOS have been identified in the atmosphere (Martin, et al., 2002). The strength of carbon-fluorine bonds contributes to the extreme stability and unique properties of PFOS. PFOS is highly persistent in the environment and has also been shown to bioconcentrate in fish and biomagnify in the food chain.

A review of the published biomonitoring data has shown that PFOS has been measured on multiple occasions and by different investigators only in general populations from two countries: the United State (Table 1) and Japan (Table 2). The total number of samples presented in these data represents approximately 90 percent of the individual analyses published in the literature, to date. The similar distribution of averages from the individual studies presented in Table 1 suggests that large variations in serum PFOS concentration do not exist within geographic regions, age groups or sex in the United States. Average PFOS concentrations were lower among the Japanese populations presented in Table 2. In one Japanese study, Harada et al (2004) observed sex-related differences in serum PFOS concentrations with males approximately two-fold higher than females. Furthermore, Harada et al. (2005) reported higher concentrations among pre-than post-menopausal women (Harada et al. 2005) in another study. These findings were not observed in general populations in the U.S. (Olsen et al. 2003a; 2004a; 2004b; Kannan et al. 2004; Kuklenyik 2004). In the only published study of its kind, PFOS was measured in 15 pairs of maternal and cord blood (fetal) samples from Japan (Inoue, et al., 2004a). PFOS concentrations in maternal samples ranged from 4.9 to 17.6 ng/mL, whereas those in fetal samples ranged from 1.6 to 5.3 ng/mL with a high degree of correlation between pairs (r = .94). Only two studies in Tables 1 and 2 examined time trends. Serum PFOS concentrations increased three-fold over a 25 year time period in Miyaga, Japan (Harada et al. 2004) although it is not clear whether potential occupational exposure may have played a role. Occupational exposure was not a factor in the time trends analyzed by Olsen et al. (2005) where median PFOS concentrations increased approximately 25% between 1974 (median 25 ng/mL) and 1989 (median 33 ng/mL) for 58 individuals living in the vicinity of Hagerstown, Maryland (Olsen et al. 2005). However, only a 9 percent increase in median PFOS concentrations occurred in two non-paired populations residing in the same area and time period. PFOS concentrations did not appear to increase between 1989 and 2001 for this region (Olsen et al. 2003a; 2005). Individual samples from three large data sets with different age groups predominate the United States findings as reported in Table 1 (Olsen et al. 2000a; 2004a; 2004b). Sera from children (age 2-12, n = 598) in 23 states, adult blood donors (20-69 years, n = 645)
from six municipalities in the U.S., and elderly (65-96 years, n = 238) Seattle residents, were analyzed for PFOS using identical laboratory methods with comparable findings. PFOS was analyzed using identical laboratory methods in these three studies. Geometric means were 38 (95% CI 36-39), 35 (95% CI 33 – 37) and 31 (95% CI 29-33) ng/mL, respectively. Although comparable average PFOS concentrations, a small number of individuals in each studied population had relatively higher levels than the majority of individuals sampled. The factors that would lead to higher serum PFOS concentrations in some individuals are not completely understood. Some factors that may affect serum PFOS concentrations include, proximity to sources of manufacture and use, length of residence in these latter areas, potential product exposures, and possible food and environmental sources. It is notable that PFOS serum concentrations did not strongly correlate with serum concentrations of metabolites of N-alkyl-perfluorooctanesulfonamide molecules known to be present in products as manufacturing residuals or from degradation of products (Olsen et al. 2003a; 2004a;2004b). Additional data on serum PFOS concentrations in the general population of the U.S. should become available in 2007 when CDC releases its national biomonitoring report using NHANES III data collected during 2003-2004.

There is a very limited number of published PFOS data sets from other countries, and those that do consist of relatively few blood samples analyzed. Most of these data were reported by one investigator (Kannan et al. 2004). In general, the majority of these PFOS concentrations were less than those reported for the United States general populations displayed in Table 1. The highest mean PFOS concentration reported by Kannan et al. was found in samples collected from Poland (males 55 ng/mL; females 33 ng/mL). Lower mean PFOS concentrations were reported by Kannan et al for Korea (male 27 ng/mL; female 15 ng/mL), Belgium (male 18 ng/mL; female 11 ng/mL), Malaysia (male 13 ng/mL; female 12 ng/mL), Brazil (male 14 ng/mL; female 11 ng/mL), Italy (male 4 ng/mL; female 4 ng/mL) and Columbia (male 8 ng/mL; female 8 ng/mL); and India (male 3 ng/mL; female 3 ng/mL). In a pilot study, Kubwabo et al. (2004) reported mean concentrations of 30 and 28 ng/mL in 21 and 35 female and male Canadians. Guruge et al. (2005) reported a mean concentration of 5 ng/mL in adults from Sri Lanka and 0.1 ng/mL concentration in seminal plasma, with a correlation of 0.6 for PFOS between the two matrices.

Estimation of external PFOS exposure for workers is difficult. 3M manufactured perfluorooctane sulfonyl fluoride (POSF), a starting material used to produce PFOS and other fluorochemicals. POSF and some POSF-based chemistries have the potential to degrade or metabolize to PFOS. Employees may have been exposed to POSF and/or other perfluorochemicals in the manufacturing environment by one or more routes. The primary route of exposure may have varied among employees and depended on several factors, including process conditions, job tasks, work location, personal hygiene, personal habits, and general work practices. Because multiple sources and routes of exposure were probable, estimating external worker PFOS exposure is problematic.

Biological biomonitoring allows for the assessment from all routes of exposure.
Occupationally, PFOS serum levels have been measured in 3M employees involved in both the manufacturing of perfluorochemicals and the processing of these compounds into products, such as fire protection and surface protection products. Since the mid-1990s measurement of serum PFOS concentrations was performed as part of employee medical surveillance examinations at the 3M manufacturing facilities in Decatur, Alabama and Antwerp, Belgium (Olsen et al. 1999; 2003c). Between 1994 and 2000, mean PFOS concentrations approximated 1.0 μg/mL to 2.5 μg/mL (1,000 to 2,500 ng/mL) and ranged between less than 0.1 to 12.8 μg/mL. Because employee participation is voluntary, biomonitoring data from these medical surveillance programs may not have provided an adequate characterization of the distribution of serum PFOS concentrations due to possible nonresponse bias. To address the potential for this bias, a random sample of 3M Decatur employees participated in serum analysis of PFOS. An eighty percent response was achieved. Of the 126 chemical plant employees who participated, their range of serum PFOS concentrations was 0.1 to 10.6 μg/mL. The mean, median and geometric mean PFOS levels were 1.5, 0.9 and 1.1 μg/mL, respectively. By job category the geometric mean PFOS serum concentrations (95% CI in parenthesis) were: cell operators 2.0 μg/mL (95% CI 0.7-5.3); chemical operators 1.5 μg/mL (95% CI 1.3 - 1.8); waste treatment plant operators 1.5 μg/mL (0.5-4.6); maintenance workers 1.3 μg/mL (0.8-2.1); supervisors 0.9 μg/mL (95% CI 0.5-1.6); mill operators 0.6 (0.4-0.8); engineers/laboratory workers 0.4 (0.3-0.6) and clerical workers 0.4 (0.2 - 0.8). These randomly sampled data indicated that serum PFOS concentrations measured during the course of medical surveillance examinations likely presented an unbiased analysis of the production employee serum PFOS distribution. The data also indicate serum PFOS concentrations among actively engaged production workers (i.e., cell and chemical operators) were approximately 50 times higher than that measured in the United States general population as displayed in Table 1.

Toxicity Data
The toxicological profile of PFOS has been extensively studied (reviewed in Organization for Economic Cooperation and Development, 2002; 3M, 2003; Lau et al., 2003). Available studies include subchronic and chronic studies in multiple species, reproduction and developmental studies, and mode-of-action studies. In addition, a number of epidemiological and medical surveillance studies of exposed workers have been conducted.

Several repeat-dose toxicology studies on PFOS have consistently demonstrated that the liver is the primary target organ. Liver response to subchronic PFOS treatment is characterized by hepatocellular hypertrophy and vacuolation in rats (Seacat et al., 2003) and monkeys (Seacat et al., 2002a), and, at lethal doses in rats, necrosis (Goldenthal et al., 1978a). The dose-response curve for mortality in repeat-dose studies is very steep for sexually mature rats and primates (Goldenthal et al., 1978a,b; Seacat et al., 2002a) as well as neonatal rats and mice that were exposed in utero (Butenhoff et al., 2002; Lau et al., 2003). Although PFOS is not genotoxic, liver tumors (hepatocellular adenoma) were increased in the high-dose (20 μg KPFOS/g feed) males and females in a chronic (two-year) dietary study of PFOS in Sprague Dawley rats (Seacat et al., 2002b). A
A number of studies have been conducted to investigate the possible modes of action of PFOS. Induction of peroxisome proliferation and associated peroxisomal enzymes (Ikeda et al., 1987; Sohlenius et al., 1993; Berthiaume and Wallace, 2002), activation of nuclear receptors (Shipley et al., 2004), interference in lipid metabolism and decreases in serum cholesterol (Haughom and Spydevold, 1992; Luebker et al., 2002a,b), interference in mitochondrial bioenergetics (Starkov and Wallace, 2002; Berthiaume and Wallace, 2002), delays in lung maturation (Grasty et al., 2004), inhibition in gap junctional intercellular communication processes (Hu et al., 2002; 2003), and alterations in thyroid hormone homeostasis (Butenhoff et al., 2002; Thibodeaux et al., 2003; Lau et al., 2003; Tanaka et al., 2005; Butenhoff et al., 2005) have all been investigated as possible modes of action; however, at present, the mechanisms of action related to the toxicity of PFOS are still not clearly understood.

3M has conducted several health studies using over 20 years of medical surveillance data collected on perfluorochemical production workers. A battery of clinical tests (including lipids, hematological parameters, enzymes and 11 different hormone assays) in both cross-sectional and longitudinal studies in workers have not shown consistent patterns of associations between PFOS serum levels and hematology, hormonal and other clinical chemistry parameters (Olsen et al., 1999; 2003c). A mortality study showed no statistically significant excess mortality for most cancer types and for non-malignant causes (Alexander, 2003). However, bladder cancer mortality was elevated in a cohort of 2083 employees. Three bladder cancer deaths were observed, all of them occurring in male workers who had high PFOS exposure jobs for at least 5 years. However, it is
unclear whether fluorochemicals are responsible for the excess of bladder cancer deaths, whether other carcinogens may be present in this plant, or that the findings are not related to occupational exposures. Worker insurance claims data categorized as episodes of care have also been evaluated (Olsen et al. 2004d). For a priori interests, the observed to expected episodes of care experience were comparable for the fluorochemical and a neighboring film plant (control) employee population for liver tumors, bladder cancer, thyroid and lipid metabolism disorders, and reproductive, pregnancy, and perinatal disorders and higher for biliary tract disorders and cystitis recurrence. Non-a priori associations among the fluorochemical plant workers included benign colon polyps, malignant colorectal tumors, and malignant melanoma. Research is currently being conducted to further investigate these associations.

Environmental Public Health Use of Biomonitoring Data
The evaluation of PFOS exposure pathways is a new field of research. Based on the biomonitoring data available, no unusually exposed populations have been identified. However, PFOS concentrations in Charlotte, North Carolina were the highest of the geographical regions investigated by 3M (Olsen et al. 2003a), and that a preliminary screening study conducted by CDC to validate methodology showed slightly higher values in Atlanta, Georgia (Kuklenyik et al. 2004). The southeast United States is an area of high carpet and fabric production; however, it is not possible to establish that this is the reason for the somewhat higher values measured from these locations. In addition, few data are available that can describe exposure trends; however, as previously discussed a Japanese study evaluated trends over time in blood concentrations of PFOS in Japan and reported a three-fold increase in serum PFOS concentrations over a 25-year time period. Olsen et al. (2005) presented data collected in the vicinity of Hagerstown, Maryland that suggested PFOS concentrations in the blood may have increased 10 to 25 percent between 1974 and 1989 but no subsequent increase since 1989. It is assumed that with the discontinuation of the global manufacture of PFOS and POSF-based chemicals that PFOS exposures will eventually diminish. However, PFOS is expected to persist in humans and the environment for many subsequent years because of its unusual physical-chemical and pharmacokinetic properties. It is too soon to determine how and whether the removal of PFOS from market will impact exposure to U.S. human populations.

Several research needs have been identified that could strengthen the database on PFOS. Recommendations include:

- Strengthen the database to allow conversion of whole blood and plasma PFOS concentration values to serum PFOS concentration. Various reports give whole blood measurements converted to estimated serum concentrations by making the assumption that all PFOS is in serum.
- Strengthen the relationship between serum and liver concentrations of PFOS. Although this information is available from toxicology studies, the human data are very limited.
- Bank samples of blood, plasma, or serum for future needs, including early screening investigations.
- Obtain additional data for children, especially children under two years of age.
- Obtain matched serum and urine samples from humans and research animals, where possible.
- Obtain placental, cord blood, and milk samples.
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