

Hazard Assessment and Biomonitoring Data on Perfluorooctane Sulfonate - PFOS

I. Executive Summary

In human blood samples, PFOS has been detected in the serum of occupational and general populations in the ppm to ppb range. In the U.S., recent blood serum levels of PFOS in manufacturing employees have been as high as 12.83 ppm, while in the general population, serum collected from blood banks and commercial sources have indicated mean PFOS levels of 30–44 ppb. Levels in a very small sample of children yielded even higher results, with a mean level of 54 ppb.

Sampling of several wildlife species from a variety of sites across the United States has shown widespread distribution of PFOS. In recent analyses, PFOS was detected in the ppb range in the plasma of several species of eagles, wild birds, and fish. Endogenous levels of PFOS have also been detected in the ppb range in the livers of unexposed rats used in toxicity studies, which presumably occurred through exposure to a dietary source (fishmeal).

Studies show that PFOS is well-absorbed orally and distributes mainly in the serum and the liver. No further metabolism is expected. Elimination from the body is slow and occurs via the urine and feces. Serum PFOS levels in 3 retired male 3M chemical workers have been followed for five and a half years and suggest a mean elimination half-life ($t_{1/2}$) of 1,428 days (approximately 4 years). Based on the pharmacokinetic data obtained from a 28-day oral study in male and female monkeys, a volume of distribution (V_d) of 0.19L/kg was reported; no sex differences in the pharmacokinetic parameters were noted.

PFOS has shown moderate acute toxicity by the oral route with a rat LD₅₀ of 251 mg/kg. A one-hour LC₅₀ of 5.2 mg/l in rats has been reported. PFOS was found to be mildly irritating to the eyes and non-irritating to the skin of rabbits. PFOS was negative in mutagenicity studies in five strains of salmonella and did not induce micronuclei in an *in vivo* mouse bone marrow micronucleus assay.

Numerous repeat-dose oral toxicity studies on PFOS have been conducted in rats and primates. Adverse signs of toxicity observed in rat studies included increases in liver enzymes, hepatic vacuolization and hepatocellular hypertrophy, gastrointestinal effects, hematological abnormalities, weight loss, convulsions, and death. These effects were reported at doses of 2 mg/kg/day and above. Adverse signs of toxicity observed in Rhesus monkey studies included anorexia, emesis, diarrhea, hypoactivity, prostration, convulsions, atrophy of the salivary glands and the pancreas, marked decreases in serum cholesterol, and lipid depletion in the adrenals. The dose range for these effects was reported between 1.5–300 mg/kg/day. No monkeys survived beyond 3 weeks into treatment at

10 mg/kg/day or beyond 7 weeks into treatment at doses as low as 4.5 mg/kg/day. At doses as low as 0.75 mg/kg/day, cynomolgus monkeys exhibited low food consumption, excessive salivation, labored breathing, hypoactivity, ataxia, hepatic vacuolization and hepatocellular hypertrophy, significant reductions in serum cholesterol levels, and death.

Postnatal deaths and other developmental effects were reported at low doses in offspring in a 2-generation reproductive toxicity study in rats. At the two highest doses of 1.6 and 3.2 mg/kg/day, pup survival in the first generation was significantly decreased. All first generation offspring (F1 pups) at the highest dose died within a day after birth while close to 30% of the F1 pups in the 1.6 mg/kg/day dose group died within 4 days after birth. As a result of the pup mortality in the two top dose groups, only the two lowest dose groups, 0.1 and 0.4 mg/kg/day, were continued into the second generation. The NOAEL and LOAEL for the second generation offspring (F2 pups) were 0.1 mg/kg/day and 0.4 mg/kg/day, respectively, based on reductions in pup body weight. Reversible delays in reflex and physical development were also observed in this study, raising concerns about the potential for developmental neurotoxicity following exposure to PFOS.

Developmental effects were also reported in prenatal developmental toxicity studies in the rat and rabbit, although at slightly higher dose levels. Signs of developmental toxicity were evident at doses of 5 mg/kg/day and above in rats administered PFOS during gestation. Significant decreases in fetal body weight and significant increases in external and visceral anomalies, delayed ossification, and skeletal variations were observed. Abnormalities of the lens of the eye were also reported at doses as low as 1 mg/kg/day in one rat prenatal developmental study, but could not be repeated in a second study of similar design. At doses of 2.5 mg/kg/day and above, significant reductions in fetal body weight and significant increases in delayed ossification were observed in rabbits administered PFOS during gestation.

There are several uncertainties in the data-base. For example, since the two-generation reproductive toxicity study dosed the F0 males for only six weeks prior to mating and did not include any evaluations of sperm number, motility, and morphology, an analysis for the potential for male reproductive toxicity is incomplete. Although blood concentrations of PFOS in animals have been estimated based on limited pharmacokinetic data, it is uncertain how PFOS was assayed in these analyses. Moreover, the extent of potential interspecies and intraspecies variability in the pharmacokinetic handling of PFOS is not well understood and cannot be fully ascertained with the two-generation toxicity study alone. There presently exists uncertainties with the human exposure data as well. Data on exposure pathways for all populations is missing. For occupational exposures, only limited data on the sampled workers is available and human serum levels were not measured over time in the same individuals. Data on general population exposures come from pooled sera and must be interpreted with caution. In addition, due to the long half-life of PFOS in the body and given the limited knowledge regarding the distribution of PFOS in the body, it is uncertain whether body burden is adequately reflected by serum levels. Several on-going mechanistic and other studies may help address some of these data needs.

II. Hazard Assessment

Metabolism and Pharmacokinetics

Absorption

PFOS is well absorbed following ingestion. After a single oral dose of PFOS-14C (mean dose, 4.2 mg/kg) in solution to groups of three male rats, at least 95% of the total carbon-14 is systemically absorbed at 24 hours (Johnson, Gibson and Ober, 1979a,). The digestive tract and contents contained on average, 3.45% of the dose. The mean fecal excretion is 1.55% of the dose at 24 hours and 3.24% at 48 hours. At 24 hours, the mean sum of total carbon-14 in feces and digestive tract plus contents is 5% of the dose. Some of this 5% likely represents systemically absorbed carbon-14 present either in the digestive tract tissues or in the digestive tract contents as a result of excretion. The data from the 48 hour post dose group of rats are consistent with the 24 hour post dose data. Thus, at least 95% of the PFOS-14C dose was absorbed from solution after administration to non-fasted rats.

Distribution

At 24 to 48 hours after a single oral dose of PFOS-14C (4.2 mg/kg) in rats, approximately 86% of the radioactivity recovered was found in the carcass (Johnson, Gibson and Ober, 1979a). The carcass data are not as reliable as the other tissue data since large volume homogenates were necessary and homogeneity of sample aliquots was difficult to assure. There is some excretion of total carbon-14 in urine (1-2%/day). The spleens from the 24 hour and 48 hour post dose rats were analyzed for total carbon-14 content, and the percent of the dose in the whole organ was ~0.2%. The concentrations of total carbon-14 in red blood cells and plasma were compared. The mean ratio of red blood cell to plasma concentration at 24 and 48 hours is 0.25 and 0.39, respectively. Thus, at 24 and 48 hours after a single oral dose of FC-95-14C, there is no selective retention of carbon-14 in red blood cells.

At 89 days after a single intravenous dose of PFOS-14C (4.2 mg/kg) in male rats, mean tissue C-14 concentrations above one ug equivalents/g were as follows: liver, 20.6; plasma, 2.2; kidney, 1.1; and lung, 1.1 (Johnson, Gibson and Ober, 1979b). Other tissues such as muscle, skin, bone marrow, and spleen had concentrations ranging from 0.2 to 0.6 ug/g. There was a difference in C-14 content of subcutaneous fat (0.2 ug/g) and abdominal fat (≤ 0.08 ug/g). Very little C-14 was found in whole eye (0.16 ug/g) and no detectable C-14 was found in brain. Only liver and plasma contained a substantial percentage of dose at 89 days post dose, 25.21% and 2.81%, respectively. The low levels of radioactivity found for kidney, lung, testes, and spleen are due in part to blood still contained in these organs when homogenized.

Placental transfer of PFOS has been demonstrated (Argus Research Laboratories, 1999). F0 rats were given oral doses of PFOS (0.1, 0.4, 1.6, or 3.2 mg/kg/day in 0.5% Tween 80). Male F0 animals

were treated 42 days prior to mating and through mating period; female F0 animals were administered PFOS daily 42 days prior to mating, through gestation, and up to 20 days following litter delivery. Liver and sera samples collected from the initial population of dosed animals (F0) and their offspring (F1) were analyzed for the presence of PFOS. The F0 results by are presented below, by dose group:

Dose group (mg/kg/day)	Average PFOS conc. in serum (ug/ml)	Average PFOS conc. in liver (ug/g)
0.0:	female 0.0307 male 0.0244	female 0.171 male 0.665
0.1:	female 5.28 male 10.5	female 14.8 male 84.9
0.4:	female 18.9 male 45.4	female 58.0 male 176
1.6:	female 82 male 152	female 184 male 323
3.2:	female NR* male 273	female NR* male 1360

*samples not received

Average PFOS concentrations in pooled liver samples from F1 animals shortly after birth were 0.0511, 6.19, 57.6, and 70.4 ug/g in the 0.0, 0.1, 0.4, and 1.6 mg/kg/day dose groups, respectively.

Elimination

Urinary excretion is the primary route of elimination for PFOS. By 89 days after a single intravenous dose of PFOS-14C (4.2 mg/kg) in male rats, mean urinary excretion was 30.2+-1.5% of total C-14 administered (Johnson, Gibson, and Ober, 1979b). Mean cumulative fecal excretion was 12.6+-1.2%. Radioactive content in feces was too low to measure after 64 days.

The half-life for elimination of total PFOS carbon-14 from plasma after a single oral dose (4.2 mg/kg) in male rats is 7.5 days (Johnson, Gibson and Ober, 1979a). This determination was based upon analysis of plasma samples from groups of three rats at 1, 2, 6, 12, 24, 48, 96, and 144 hours after the single oral dose.

There is evidence of enterohepatic circulation of PFOS. After 21 days of cholestyramine treatment, the mean percentage of PFOS-14C dose eliminated via feces (75.8 +- 5.0) was 9.5-fold the mean percentage of dose eliminated via feces by control rats (8.0 +- 0.8, Johnson, Gibson and Ober, 1984). After adjustment for the amount of carbon-14 excreted in urine (18% for controls and 5% for cholestyramine-treated), the amounts of carbon-14 remaining to be excreted are 19% for cholestyramine-treated rats and 74% for control rats. After PFOS-14C administration, the mean liver

carbon-14 content at 21 days represents 11% and 40% of the dose for cholestyramine-treated and control rats, respectively. Mean plasma and red blood cell carbon-14 concentrations are significantly lower after 21 days of cholestyramine treatment. The authors conclude that the high concentration of PFOS-14C in liver at 2 to 3 weeks after dosing and the fact that cholestyramine treatment enhances fecal elimination of carbon-14 by nearly 10-fold suggest that there is a considerable enterohepatic circulation of PFOS-14C.

Acute Toxicity

Four reports of acute studies of PFOS have been submitted, one inhalation toxicity of rats, two oral studies of rats, and one dermal and eye irritation study of rabbits.

In a study to determine the median lethal concentration (LC_{50}), Rusch et al. (1979) administered PFOS dust in air to Sprague-Dawley rats, 5/sex/group, levels of 1.89 to 45.97 mg/l PFOS to eight test groups. A Wright dust-feed mechanism with dry air at a flow rate of 12 to 16 liters per minute was used to administer the PFOS dust. Rats were exposed for 1 hour. The test group rats weighed 201-299 g at study initiation. The control group rats weighed 203-263 g at study initiation. The test group rats were exposed to 1.89, 2.86, 4.88, 6.49, 7.05, 13.9, 24.09 or 45.97 g/l. The control rats were exposed to dry air at a flow rate of 12 liters per minute. All other protocols were the same as the test group rats. The rats were observed for abnormal signs prior to exposure, at 15-minute intervals during the 1-hour exposure, at removal from the exposure chamber, hourly for four hours after exposure, and daily thereafter for 14 days. Individual body weights were recorded on Day 0 (prior to exposure), Day 1, Day 2, Day 4, Day 7, and Day 14. It is reported that all animals dying spontaneously were necropsied as soon as possible after death. Blood samples were collected on Day 14 from all surviving animals, but analyses were not provided. The LC_{50} of 5.2 mg/l and 95% confidence limits of 4.4 and 6.4 mg/l were calculated using the method of Litchfield and Wilcoxon.

The highest dose group, 45.97 mg/l, was not used in the LC_{50} calculations and terminated on Day 2. At that point, only 5 animals survived and blood samples were taken at termination. The 13.9 mg/l group was also terminated early (Day 1) because of a mechanical problem during exposure. These animals were also not used in the LC_{50} determination.

In the 24.09 mg/l exposure group, all animals died by Day 6. At 7.05 and 6.49 mg/l there was 80% mortality. At 4.88, 2.86, and 1.89 mg/l there was 20%, 10%, and 0% mortality, respectively. The rats in all these 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. Therefore, the most significant treatment related abnormality was varying degrees of 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.

In a study to determine the acute oral LD₅₀, Dean et al. (1978) administered CD rats, 5/sex/group, doses of 0, 100, 215, 464, and 1000 mg/kg PFOS by gavage. The powdered test material was suspended in a 20% acetone/80% corn oil mixture. All dose levels were administered as volumes of 10ml/kg body weight. The rats weighed 172-212 g at the beginning of the study immediately prior to dosing and weights were recorded at Day 7 and Day 14. The rats were observed for abnormal signs during the four hours after exposure, and daily thereafter for 14 days. It is reported that all animals dying spontaneously were grossly necropsied, as well as all rats that survived to the end of the 14 day study.

Acute oral LD₅₀ values and 95% confidence limits were calculated for males (233 [160-339] mg/kg), females (271 [200-369] mg/kg) and combined male and female rats (251 [199-318] mg/kg).

All rats in the 464 and 1000 mg/kg dose groups died before the end of the study. Three animals in the 215 mg/kg group died prematurely. It appears signs of toxicity most frequently observed included: hypoactivity, decreased limb tone, and ataxia. At necropsy, observations included: yellow-stained urogenital region, stomach distention and signs of irritation of the glandular mucosa, and lung congestion.

In a second oral study, Gabriel (1978; cited in Dean et al., 1978) administered two groups of Sherman-Wistar albino rats (5 /sex/group) two doses of PFOS by gavage in water. The rats weighed between 200 -300 grams. It was determined the acute oral LD₅₀ was greater than 50 mg/kg and less than 1500 mg/kg.

All of the rats administered 1500 mg/kg died before the 14-day observation period ended, with the last rat dead on Day 9. None of the rats administered 50 mg/kg died before the end of the study. It is stated that rats were observed for signs of toxicity and mortality but it is not clear how frequently they were observed and no individual animal data was provided. It is stated that the high dose group rats were “depressed” at 2- 3 hours after dosing and “severely depressed or semi-comatose” by 24 hours; staying in this state until death occurred. No individual pathology data were provided. The author states: “Gross pathologic examination revealed nothing remarkable.”

Biesemeier and Harris, 1974 examined the potential for PFOS to cause skin and eye irritation. Six albino rabbits had their hair clipped from their backs and flanks, and it appears five tenths of one gram (0.5 g; the procedure states either 0.5 g or 0.5 ml and the test material as supplied by 3M was a solid) of the test material was placed on abraded or intact prepared test sites, then covered with gauze

patches. After 24 hours and 72 hours the coverings were removed and the degree of erythema and edema was recorded according to a standardized scale. No reference is provided for method or scoring of results. Concentration or total dose of test material was not provided. In all six rabbits, it is reported the primary skin irritation scores were 0; which indicates no reddening or swelling detected.

In the eye irritation study, six albino New Zealand White rabbits were placed in collars so they could not rub their eyes. It appears one tenth of a gram (0.1 g; the procedure states either 0.1 g or 0.1 ml was used and T117 was a solid as supplied by 3M) of the test substance was instilled in one eye, the other eye was left untreated as a control. The concentration or total dose of the test substance were not provided. It is reported that the reaction to the test material was read against a scale of damage to the cornea, iris, and the bulbar and palpebral conjunctivae at 1, 24, 48, and 72 hours after treatment. The scale criteria were not presented or referenced. Each time the eyes were scored, any accumulated discharge or residue of test material was flushed from the eye. There is no reference provided for the method. It appears that scores were maximal at 1 hour and 24 hours after treatment then decreased over the rest of the study (Biesemeier and Harris, 1974).

Mutagenicity

PFOS was tested for its ability to induce mutation in the Ames Salmonella/Microsome Plate Test and in the D4 strain of *Saccharomyces cerevisiae* (Litton Bionetics, Inc., 1979). It was also tested in: (1) a Salmonella – *Escherichia coli*/Mammalian-microsome reverse mutation assay (Mecchi, 1999); (2) an in vitro assay for chromosomal aberrations in human whole blood lymphocytes (Murli, 1999); and (3) an assay for unscheduled DNA synthesis (UDS) in rat liver primary cell cultures (Cifone, 1999). It was negative in all assays in which it was tested. PFOS does not induce reverse mutation at the histidine locus of *S. typhimurium* or at the tryptophan locus of *E. coli* when tested with or without metabolic activation. It does not induce chromosomal aberrations in human lymphocytes when tested with or without metabolic activation and does not induce UDS in primary cultures of rat hepatocytes. PFOS was also tested in an in vivo mouse micronucleus assay (Murli, 1996). PFOS did not induce micronuclei in the bone marrow of Crl:CD-1 BR mice and is negative in the mouse bone marrow micronucleus assay.

T-2247 CoC which is a 50% by weight solution of the diethanolammonium salt of perfluorooctanesulfonate in water was tested for its ability to induce gene mutation in 5 strains of *S. typhimurium* and also for its ability to induce recombination in *S. cerevisiae* strain D3. (Simmon, 1978). The chemical was negative in all 5 strains of Salmonella and in *S. Cerevisiae* D3 when tested with and without metabolic activation. T-2247 CoC was tested with *S. typhimurium* strains TA98 and TA100 in a desiccator assay for the detection of volatile compounds. It was nonmutagenic when tested under

these conditions.

Repeat-Dose Toxicity

Three 90-day subchronic studies of PFOS have been conducted, two gavage studies in rhesus monkeys and one dietary study in rats. In addition, a four week and a 26 week capsule study in cynomolgus monkeys have been conducted. Both reports were unaudited drafts at the time of this review. In addition, a two-year cancer bioassay is currently being conducted, but was not available at the time of this review.

In the first rhesus monkey study, Goldenthal et al. (1979) administered rhesus monkeys, 2/sex/group, doses of 0, 10, 30, 100 or 300 mg/kg/day PFOS (FC-95) in distilled water by gavage. The males weighed 3.05-3.80 kg at study initiation and the females weighed 2.75-4.10 kg. The monkeys were observed daily for general clinical signs and body weights were recorded weekly. Hematological and clinical chemistry analyses and urinalysis were conducted at the beginning of the study. The study was terminated after 20 days due to the death of the monkeys. At necropsy the heart, liver, adrenals, spleen, pituitary, kidneys, testes/ovaries and brain were weighed. The thyroid/parathyroid were weighed after fixation. Tissues were preserved in buffered neutral 10% formalin; the eyes were preserved in Russell's fixative. The following organs from control and all treated groups were examined microscopically: adrenals, aorta, brain, esophagus, eyes, gallbladder, heart (with coronary vessels), duodenum, ileum, jejunum, cecum, colon, rectum, kidneys, liver, lung, skin, mesenteric lymph node, retropharyngeal lymph node, mammary gland, nerve (with muscle), spleen, pancreas, prostate/uterus, bone/bone marrow (rib junction), salivary gland, lumbar spinal cord, pituitary, stomach, testes/ovaries, thyroid, parathyroid, thymus, trachea, tonsil, tongue, urinary bladder and vagina.

All of the treated monkeys died. The monkeys in the 300 mg/kg/day group died between days 2-4, the monkeys in the 100 mg/kg/day group died between days 3-5, the monkeys in the 30 mg/kg/day group died between days 7-10, and the monkeys in the 10 mg/kg/day group died between days 11-20 of treatment. The monkeys from all the groups showed similar signs of toxicity including decreased activity, emesis with some diarrhea, body stiffening, general body trembling, twitching, weakness, convulsions and prostration. At necropsy, several of the monkeys in the 100 and 300 mg/kg/day groups had a yellowish-brown discoloration of the liver; histologic examination showed no microscopic lesions. Congestion, hemorrhage and lipid depletion of the adrenal cortex was noted in all treated groups. No other lesions were noted.

In the second study, Goldenthal et al. (1978a) administered rhesus monkeys, 2/sex/group, doses of 0, 0.5, 1.5 or 4.5 mg/kg/day PFOS (FC-95) in distilled water by gavage for 90 days. The males weighed 2.55-3.55 kg at study initiation and the females weighed 2.7-3.75 kg. The monkeys were observed daily for general clinical signs and body weights were recorded weekly. Hematological and clinical chemistry analyses and urinalysis were conducted at the beginning of the study and after 30 and 90

days of treatment. The monkeys were sacrificed after 90 days of treatment and a gross necropsy was conducted. At necropsy the heart, liver, adrenals, spleen, pituitary, kidneys, testes/ovaries and brain were weighed. The thyroid/parathyroid were weighed after fixation. Tissues were preserved in buffered neutral 10% formalin; the eyes were preserved in Russell's fixative. The following organs from control and all treated groups were examined microscopically: adrenals, aorta, brain, esophagus, eyes, gallbladder, heart (with coronary vessels), duodenum, ileum, jejunum, cecum, colon, rectum, kidneys, liver, lung, skin, mesenteric lymph node, retropharyngeal lymph node, mammary gland, nerve (with muscle), spleen, pancreas, prostate/uterus, bone/bone marrow (rib junction), salivary gland, lumbar spinal cord, pituitary, stomach, testes/ovaries, thyroid, parathyroid, thymus, trachea, tonsil, tongue, urinary bladder and vagina.

All monkeys in the 4.5 mg/kg/day group died or were sacrificed in extremis between week 5 and 7 of the study. Beginning on the first or second day of the study, these monkeys exhibited signs of gastrointestinal tract toxicity including anorexia, emesis, black stool and dehydration. All of the monkeys had decreased activity and just prior to death showed marked to severe rigidity, convulsions, generalized body trembling and prostration. The mean body weight decreased from 3.44 kg at the beginning of the study to 2.7 kg at week 5. After 30 days of treatment, there was a significant reduction in serum cholesterol and a 50% reduction in serum alkaline phosphatase activity. At necropsy, mean organ weights were comparable among the control and treated monkeys. Histologic examination showed several treatment related lesions. All the male and females had marked diffuse lipid depletion in the adrenals. One male and two females had moderate diffuse atrophy of the pancreatic exocrine cells with decreased cell size and loss of zymogen granules. Two males and one female had moderate diffuse atrophy of the serous alveolar cells characterized by decreased cell size and loss of cytoplasmic granules.

All monkeys in the 1.5 mg/kg/day group survived until the end of the study. During the first week of the study, the monkeys had decreased activity. Signs of gastrointestinal tract toxicity were noted occasionally during the study and included black stool, diarrhea, mucous in the stool and bloody stool; at the end of the study, anorexia, dehydration or general body trembling were noted. Although statistical significance was not achieved, the mean body weight of the males dropped from 3.15 kg at the beginning of the study to 2.93 kg at the end of the study, and the mean body weight of the females dropped from 3.22 kg to 2.75 kg. After 90 days of treatment, the females had a significant reduction in serum alkaline phosphatase activity and serum potassium levels. One of the females had very low serum cholesterol and another had a reduction in inorganic phosphate. Necropsy revealed no treatment related lesions.

All monkeys in the 0.5 mg/kg/day group survived until the end of the study. Signs of gastrointestinal tract toxicity were noted occasionally during the study and included diarrhea, soft stools, anorexia and emesis. Occasionally, decreased activity was noted in three of the monkeys. After 90 days of treatment, a slight decrease in serum alkaline phosphatase was noted. Necropsy revealed no treatment

related lesions.

In the rat subchronic study, Goldenthal et al. (1978b) administered CD rats, 5/sex/group, dietary levels of 0, 30, 100, 300, 1000 or 3000 ppm PFOS (FC-95) for 90 days. The males weighed 196-232 g and the females weighed 165-206 g at study initiation. The dietary levels were equivalent to doses of 0, 2, 6, 18, 60 and 200 mg/kg/day. The rats were observed daily for general clinical signs; body weights and food consumption were recorded weekly. Hematological and clinical chemistry analyses and urinalysis were conducted at the beginning of the study and after 30 and 90 days of treatment. The rats were sacrificed after 90 days of treatment and a gross necropsy was conducted. At necropsy the heart, liver, adrenals, spleen, pituitary, kidneys, testes/ovaries and brain were weighed. The thyroid/parathyroid were weighed after fixation. Tissues were preserved in buffered neutral 10% formalin; the eyes were preserved in Russell's fixative. The following organs from control and all treated groups were examined microscopically: adrenals, aorta, brain, esophagus, eyes, gallbladder, heart (with coronary vessels), duodenum, ileum, jejunum, cecum, colon, rectum, kidneys, liver, lung, skin, mesenteric lymph node, retropharyngeal lymph node, mammary gland, nerve (with muscle), spleen, pancreas, prostate/uterus, bone/bone marrow (rib junction), salivary gland, lumbar spinal cord, pituitary, stomach, testes/ovaries, thyroid, parathyroid, thymus, trachea, tonsil, tongue, urinary bladder and vagina.

All of the rats in the 300, 1000 and 3000 ppm groups died. Death occurred between days 13-25 and days 18-28 for the males and females, respectively, in the 300 ppm group. At 1000 ppm, death occurred between days 8-14, and at 3000 ppm, the rats died between days 7-8 of treatment. The rats in all groups showed signs of toxicity including emaciation, convulsions following handling, hunched back, red material around the eyes, yellow material around the anogenital region, increased sensitivity to external stimuli, reduced activity and moist red material around the mouth or nose.

Three males and two females in the 100 ppm group died prior to scheduled sacrifice. Two of the males and the two females died during week 5 and the third male died during week 11 of the study. At study termination, mean body weights were reduced by 16.7% and 16.3% in the male and female groups, respectively. Average food consumption during the entire study period (g/rat/day) was significantly reduced for males and females at 100 ppm. After 30 days of treatment, hematologic values were comparable among the control and 100 ppm groups. Clinical chemistry analyses at one month showed a significant increase in mean glucose in males, blood urea nitrogen values in males and females, and creatinine phosphokinase and alkaline phosphatase values for females. After 90 days of treatment at 100 ppm, the two surviving males had significantly reduced erythrocyte, hemoglobin, hematocrit and leukocyte counts; the three surviving females had significantly reduced hemoglobin and reticulocyte counts, as well as slightly lower erythrocyte, hematocrit and leukocyte counts. Two of the surviving females showed slight to moderate increases in plasma glutamic oxalacetic and pyruvic transaminase activities. Urinalysis results were comparable among treated and control groups at 30 and 90 days. Relative liver weight was significantly increased in the males and absolute and relative liver weights were

significantly increased in the females. Relative kidney weights were significantly increased in both sexes.

All rats in the 30 ppm group survived until the end of the study. At study termination, mean body weights were reduced by 8.7 and 8% in the males and females, respectively. Average food consumption during the entire study period (g/rat/day) was significantly reduced for the males at 30 ppm. Hematologic values were comparable among the control and 30 ppm group at 30 and 90 days. One female showed a slightly elevated glucose level and one male showed a slightly increased alkaline phosphatase level at 30 days. At 90 days, one male showed moderate increases in glucose, blood urea nitrogen and γ -glutamyl transpeptidase activity. The females had significant increases in absolute and relative liver weights. The males had significant decreases in absolute and relative adrenal weights, absolute thyroid/parathyroid weight and absolute pituitary weight. The biological significance of the changes in male organ weights is unclear since similar changes were not noted in higher dose groups.

At necropsy, treatment related gross lesions were present in all treated groups and included varying degrees of discoloration and/or enlargement of the liver and discoloration of the glandular mucosa of the stomach. Histologic examination also showed lesions in all treated groups. Centrilobular to midzonal cytoplasmic hypertrophy of hepatocytes and focal necrosis was observed in the liver; the incidence and relative severity were greater in the males. In addition, especially among rats in the 300, 1000 and 3000 ppm groups, treatment related histologic lesions were noted in the primary (thymus, bone marrow) and secondary (spleen, mesenteric lymph nodes) lymphoid organs, stomach, intestines, muscle and skin. In the thymus, this consisted of depletion in the number and size of the lymphoid follicles and in the bone marrow hypocellularity was noted. The spleen was slightly atrophied with a corresponding decrease in the size and number of lymphoid follicles and cells and a similar depletion was noted in the mesenteric lymph nodes. Mucosal hyperkeratosis and/or acanthosis was observed in the forestomach and mucosal hemorrhages were noted in the glandular portion of the stomach. Decreases ~~atrophy~~ in the height and thickness of the villi were noted in the small intestine. Atrophy of the skeletal muscle was noted, as well as epidermal hyperkeratosis and/or acanthosis was noted in the skin.

In order to determine the dose range for a six-month study, Thomford et al. (unaudited draft, 1998) conducted a 4-week range-finding study in cynomolgus monkeys. Male and female cynomolgus monkeys were administered doses of 0 (2/sex/group), 0.02 (3/sex/group), or 2.0 mg/kg/day (1/sex/group) PFOS in capsules placed directly into the stomach. The monkeys weighed 2.1- 2.4 kg at study initiation. It appears the monkeys were observed at least daily for general clinical signs and body weights were recorded twice weekly. Hematological and clinical chemistry analyses were conducted on samples collected before the beginning of the study at day -7(baseline values) and day 29. Additional blood samples for clinical chemistry were collected on study days 2, 7, and 14. Blood samples for serum PFOS concentrations were taken on days -7, 2, 3, 7, 14, and 29. In addition, samples from day -7 and day 29 were analyzed for levels of estradiol, estrone, estriol, thyroid stimulating hormone, triiodothyronine, and thyroxine. The study animals were terminated as scheduled at 30 days. At necropsy a sample of liver was collected from

each animal for palmitoyl CoA oxidase activity analyses. Samples of liver, testes, and pancreas were collected for proliferation cell nuclear antigen evaluation. A sample of liver was also collected from each animal for PFOS concentration analysis. The following organs from control and all treated groups were examined microscopically: adrenals, eye, kidney, liver, lung, spleen, pancreas, femoral bone marrow, testes, and thymus.

None of the monkeys died before the study was ended. There were no test-related effects on clinical observations, body weight, food consumption, body temperatures, hematology, or macroscopic or microscopic pathology findings. No test-related effects were noted in the levels of estrone, estriol, thyroid stimulating hormone, and thyroxine. Cell proliferation, as measured by immunohistochemical detection of proliferating cell nuclear antigen, was not increased in the liver, testes, or pancreas of monkeys.

Both the male and female monkey that received 2.0 mg/kg/day showed reductions in serum cholesterol. Serum cholesterol levels for the male dropped from a baseline value of 150 mg/dl to 91 mg/dl at day 29. Serum cholesterol levels for the female dropped from a baseline value of 141 mg/dl to 62 mg/dl at day 29. The decreases in serum cholesterol were first evident in samples from day 7 for the high-dose animals. The monkeys in the 2.0 mg/kg/day group both showed estradiol levels that were less than their prestudy values and controls at day 29. Similarly, the monkeys in the 2.0 mg/kg/day group both showed triiodothyronine levels that were less than their prestudy values and controls at day 29. However, pre-treatment, the high-dose monkeys also had triiodothyronine values lower than controls in baseline samples as well. However, since the numbers of tested animals are small and baseline levels are variable, it is not clear if these hormone level changes are treatment-related effects.

In the final study, Thomford (unaudited draft, 2000) administered PFOS to cynomolgus monkeys by oral capsule at doses of 0 (6 monkeys per sex), 0.03 (4 monkeys per sex), 0.15 (6 monkeys per sex), or 0.75 mg/kg/day (6 monkeys per sex) for 26 weeks. Two animals from the control, 0.15 and 0.75 mg/kg/day groups were assigned to a recovery group and were not treated for at least 52 weeks following the last administration of PFOS. Animals were observed twice daily for mortality and moribundity and were examined at least once daily for abnormalities and signs of toxicity; food consumption was assessed qualitatively. Ophthalmic examinations were done before initiation of treatment and during weeks 26 and 52. Body weight data were recorded weekly before the start of treatment, on Days -1 and 1 and weekly thereafter. Blood and urine samples were collected for clinical hematology, clinical chemistry, and urinalysis before the start of treatment and at specified intervals during treatment and recovery. Blood samples were also taken for hormone determinations. The following organs were weighed at scheduled and unscheduled sacrifices; paired organs were weighed separately: adrenal (2), brain, epididymis (2), kidney (2), liver, ovary (2), pancreas, testis (2), and thyroid (2) with parathyroid. The following tissues were collected for histopathology: adrenals (2), aorta, brain, cecum, cervix, colon, duodenum, epididymis (2), esophagus, eyes (2), femur with bone marrow, gallbladder, heart, ileum, jejunum, kidneys (2), lesions, liver, lung, mammary gland, mesenteric

lymph node, ovary (2), pancreas, pituitary, prostate, rectum, salivary gland [mandibular (2)], sciatic nerve, seminal vesicle (2), skeletal muscle (thigh), skin, spinal cord (cervical, thoracic, and lumbar), spleen, sternum with bone marrow, stomach, testis (2), thymus, thyroid (2) with parathyroid, trachea, urinary bladder, uterus, and vagina.

Males weighed 3.3-3.4 kg and females weighed 2.8-2.9 kg at the beginning of the study. At the end of 26 weeks of treatment, males weighed 3.7, 3.8, 3.5, and 3.3 kg for the 0, 0.03, 0.15 and 0.75 mg/kg/day treatment groups respectively. Females weighed 3.1, 3.1, 3.1 and 2.8 kg for the 0, 0.03, 0.15 and 0.75 mg/kg/day treatment groups respectively. The difference between the control and the 0.75 mg/kg/day female treatment groups was statistically significant. At the end of the recovery period, differences in weight between the control and treated animals were no longer obvious.

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 had lower high density lipoprotein cholesterol during treatment. The effect on total cholesterol was reversed within 5 weeks of recovery and the effect on high density lipoprotein cholesterol was reversed within 9 weeks of recovery.

Estradiol values were lower in males given 0.75 mg/kg/day on days 62, 91, and 182 but because of variation only the day 182 value was significant. Estrone values were generally higher in the treated females on days 37, 62 and 91 but again because of variation in the data none of these values were significantly different from the controls. Triiodothyronine values were notably lower on days 91 and 182 in males and females given 0.15 and 0.75 mg/kg/day. There were other instances in which hormone values in treated groups were different from those of controls but these differences were not consistent over time or between sexes, were not clearly dose-related and did not appear to be related to the administration of the test material. Apparent differences in the sexual maturity of both males and females used in the study complicates the interpretation of the hormone data.

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 may be reversible.

Developmental Toxicity

Three prenatal developmental toxicity studies of PFOS have been conducted, two studies in rats and one study in rabbits.

The first study administered four groups of 22 time-mated Sprague-Dawley rats 0, 1, 5, and 10 mg/kg/day PFOS in corn oil by gavage on gestation days (GD) 6-15 (Gortner, 1980). Doses were adjusted according to body weight. Dams were monitored on GD 3-20 for clinical signs of toxicity. Individual body weights were recorded on GD 3, 6, 9, 12, 15, and 20. Animals were sacrificed on GD 20 by cervical dislocation and the ovaries, uteri and contents were examined for the number of corpora lutea, number of viable and non-viable fetuses, number of resorption sites, and number of implantation sites. Fetuses were weighed and sexed and subjected to external gross necropsy. Approximately one-third of the fetuses were fixed in Bouin’s solution and examined for visceral abnormalities by free-hand sectioning. The remaining fetuses were subjected to a skeletal examination using alizarin red.

Signs of maternal toxicity consisted of significant reductions in mean body weights during GD 12-20 at the high-dose group of 10 mg/kg/day. No other signs of maternal toxicity were reported. Under the conditions of the study, a NOAEL of 5 mg/kg/day and a LOAEL of 10 mg/kg/day for maternal toxicity were indicated.

Developmental toxicity evident at 10 mg/kg/day consisted of reductions in the mean number of implantation sites, corpora lutea, resorption sites and the mean numbers of viable male, female, and total fetuses, but the differences were not statistically significant. In addition, unusually high incidences of unossified, asymmetrical, bipartite, and missing sternebrae were observed in all dose groups; however, these skeletal variations were also observed in control fetuses at the same rate and therefore these effects were not considered to be treatment-related. The most notable sign of developmental toxicity observed in all dose groups consisted of abnormalities of the lens of the eye, which was not seen in controls. The proportion of fetuses with the lens abnormality in one or both lenses was significantly higher in the high dose group. All eye abnormalities appeared to be localized to the area of the embryonal lens nucleus, although a variety of morphological appearances were present within that location. According to the authors, this abnormality appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus. Secondary lens fiber development progressed

normally except immediately surrounding the abnormal embryonal nucleus. Under the conditions of the study, a LOAEL for developmental toxicity of 1 mg/kg/day was indicated; a developmental NOAEL could not be established.

A second prenatal developmental toxicity study administered four groups of 25 pregnant Sprague-Dawley rats 0, 1, 5, and 10 mg/kg/day PFOS in corn oil by gavage on gestation days (GD) 6-15 (Wetzel, 1983). Sexually mature Sprague-Dawley rats, one per sex per cage, were paired until confirmation of mating or until two weeks had elapsed. Mating was confirmed by daily vaginal examinations for the presence and viability of sperm or the presence of a copulatory plug. The day of confirmation of mating was designated as day 0 of gestation. Doses were adjusted according to the most recently recorded body weight measurements. Dams were observed twice daily for signs of mortality and moribundity and once daily for clinical signs of toxicity. Individual body weights and food consumption were recorded on GD 6, 8, 12, 16, and 20. Animals were sacrificed on GD 20 by CO₂ asphyxiation and the fetuses were delivered by cesarean section on GD 20. A gross necropsy was performed on all dams. The uterus from each female was excised, weighed and examined for the number and placement of implantation sites, number and of live and dead fetuses, number of early and late resorptions, and any abnormalities and then weighed again after the contents were removed. The ovaries were examined for the number of corpora lutea. Each female was examined by gross necropsy. Each fetus was sexed, weighed, and examined externally. Approximately one-third of the fetuses were fixed in Bouin's solution and examined for visceral abnormalities by the Wilson technique, with particular attention to the eyes, palate, and brain. The remaining fetuses were subjected to a skeletal examination that included evaluation of the skull, long bones, vertebral column, rib cage, extremities, and pectoral and pelvic girdles using alizarin red; bone alignment and degree of ossification were also evaluated.

Evidence of maternal toxicity, that was observed at the 5 and 10 mg/kg/day dose groups both during and following treatment and considered to be treatment-related, consisted of hunched posture, anorexia, bloody vaginal discharge, uterine stains, alopecia, rough haircoat, and bloody crust. Significant decreases in mean body weight gains during GD 6-8, 6-16, and 0-20 were also observed at the 5 and 10 mg/kg/day dose groups. These reductions were considered to be treatment-related since mean body weight gains were greater than controls during the post-exposure period (GD 16-20). Significant decreases in mean total food consumption were observed on GD 17-20 in the 10 mg/kg/day dose group, and on GD 7-16 and 0-20 in both the 5 and 10 mg/kg/day dose groups. The mean gravid uterine weight in the 10 mg/kg/day dose group was significantly lower when compared with controls. The mean terminal body weights minus the gravid uterine weights were lower in all treated groups, with significant decreases at 5 and 10 mg/kg/day. High-dose animals also exhibited an increased incidence in gastrointestinal lesions. No significant differences were observed in pregnancy rates, number of corpora lutea, and number and placement of implantation sites among treated and control groups. Two dams in the 10 mg/kg/day dose group were found dead on GD 17. Under the conditions of the study, a NOAEL of 1 mg/kg/day and a LOAEL of 5 mg/kg/day for maternal toxicity were indicated.

Signs of developmental toxicity included a dose-related trend toward an increased incidence of late resorptions, total resorptions, number of dead fetuses, and fetal loss, although, none of these effects were statistically significantly different from controls. Significant decreases in mean fetal weights for both males and females were observed in the 5 and 10 mg/kg/day dose groups. The percent of male fetuses was 52%, 54%, and 60% for 1, 5, and 10 mg/kg/day, respectively, compared to 44% in controls. Statistically significant increases in the incidences in the number of litters containing fetuses with visceral anomalies, delayed ossification, and skeletal variations were observed in the high dose group of 10 mg/kg/day. These included external and visceral anomalies of the cleft palate, subcutaneous edema, and cryptorchism as well as delays in skeletal ossification of the skull, pectoral girdle, rib cage, vertebral column, pelvic girdle, and limbs. Skeletal variations in the ribs and sternbrae were also observed. Under the conditions of the study, a NOAEL of 1 mg/kg/day and a LOAEL of 5 mg/kg/day for developmental toxicity were indicated.

The developmental eye abnormalities that were seen in the previous study (Gortner, 1980) were not observed in the 1983 developmental toxicity study even though the study design and doses were the same. Findings of abnormalities in eye development were initially thought to be treatment-related but then later suggested as being artifacts of sectioning. The Agency is aware of the controversy surrounding these findings and the matter is currently under review.

Christian et al. (1999a) administered pregnant New Zealand White rabbits, 22 per group, doses of 0, 0.1, 1.0, 2.5 or 3.75 mg/kg/day PFOS in 0.5% Tween-80 by gavage on gestation days 7-20. A dose volume of 5 mL/kg was administered, adjusted daily on the basis of individual body weights. The does were observed twice daily for viability, and clinical observations were recorded 1 hour prior to and after dosing during the treatment period and once daily during the post-treatment period (i.e. gestation days 20-29). Maternal body weights were recorded on gestation days 0 and 6-29; food consumption was recorded daily throughout the study. On gestation day 29, the does were euthanized; a gross necropsy of the thoracic, abdominal and pelvic viscera was conducted and the number of corpora lutea in each ovary was recorded. The uteri were examined for number and distribution of implantations, live and dead fetuses, and early and late resorptions. The fetuses were weighed, sexed and examined for external abnormalities. All fetuses were examined for visceral and skeletal abnormalities and the brain of one-half of the fetuses were free-hand cross-sectioned and examined *in situ*.

In addition, a satellite study was conducted in which pregnant New Zealand White rabbits were administered the same doses as in the main study. The number of does was 3, 5, 3, 3 and 5 in the control, 0.1, 1.0, 2.5 and 3.75 mg/kg/day groups, respectively. The does were euthanized on gestation day 21, blood samples were collected, and the liver was weighed and sectioned. The fetuses were removed and examined for external abnormalities. Fetuses and placentae were pooled per litter. All samples were sent to the Sponsor (3M) for analysis and final reports were not available at the time of OPPT's review of the data.

Maternal toxicity was evident at doses of 1.0 mg/kg/day and above. One doe in the 2.5 mg/kg/day group and nine does in the 3.75 mg/kg/day aborted. All abortions occurred on gestation days 22-28 and were considered treatment-related by the study authors. There was a significant increase in the incidence of scant feces in the 3.75 mg/kg/day group. Scant feces were also noted in one and three does in the 1.0 and 2.5 mg/kg/day groups, respectively. Mean maternal body weight gains were significantly reduced in the 3.75 mg/kg/day group on gestation days 10-13, 13-16, 16-19 and 21-24. Mean body weight gains were also calculated for the treatment period (days 7-21), post-treatment period (days 21-29) and duration of the study (days 7-29). There was a significant reduction in mean maternal body weight gain during the treatment period in the 1.0, 2.5 and 3.75 mg/kg/day groups. Mean body weight gain for the entire study period was also significantly reduced in the 2.5 mg/kg/day group. Mean food consumption (g/kg/day) was significantly reduced in the 2.5 mg/kg/day group on gestation days 16-19, 19-21 and 21-24, as well as for the entire study period (days 7-29). Mean food consumption was significantly reduced in the 3.75 mg/kg/day group on gestation days 13-16, 16-19, 19-21 and 21-24, as well as the entire treatment period. The LOAEL for maternal toxicity was 1.0 mg/kg/day and the NOAEL was 0.1 mg/kg/day.

Developmental toxicity was evident at doses of 2.5 mg/kg/day and above. The number of corpora lutea, resorptions, live/dead fetuses, litter size and sex ratio were comparable among treated and control groups. Mean fetal body weight (male, female and sexes combined) was significantly reduced in the 2.5 and 3.75 mg/kg/day groups. There was also a significant reduction in the ossification of the sternum (litter averages) in the 2.5 and 3.75 mg/kg/day groups, and a significant reduction in the ossification of the hyoid (litter averages), metacarpals (litter averages) and pubis (litter and fetal averages) in the 3.75 mg/kg/day group. The LOAEL for developmental toxicity was 2.5 mg/kg/day and the NOAEL was 1.0 mg/kg/day.

Reproductive Toxicity

A two-generation reproductive toxicity study, designed to test for the toxic effects of PFOS on reproductive function in adult animals and on developmental, learning, and reproductive effects in the offspring, was conducted in Sprague-Dawley rats (Christian et al., 1999b). Five groups of 35 rats per sex per dose group were administered PFOS by gavage at doses of 0, 0.1, 0.4, 1.6, and 3.2 mg/kg/day for six weeks prior to and during mating. Treatment in male rats continued until one day before sacrifice (approximately 22 days total); female rats were treated throughout gestation, parturition, and lactation.

F0 Generation:

Parental animals (F0) were observed twice daily for clinical signs. Body weights and food consumption values were recorded weekly during the treatment period in male rats; and weekly during mating and then daily during gestation, and on lactation days 1, 4, 7, 10, 14, and at sacrifice in female rats. Each

dosage group consisted of two sets of female rats. One set consisted of the first ten female rats with confirmation of mating; this group was dosed until gestation day (GD) 10 and delivered via Cesarean-sectioning. The remaining females comprised the second set which delivered naturally. During the 21-day lactation period, the dams were evaluated for clinical signs during parturition and length of gestation, and then each litter was evaluated at least twice daily for size and pup viability at birth. Pup observations during the 21-day lactation period included physical signs, body weights, nursing behavior, surface righting reflex, pinna unfolding, eye opening, acoustic startle response and air righting reflex. Pupil constriction was evaluated only on lactation day 21. On lactation day 4, litters were randomly culled to four male and four female pups. The remaining pups were sacrificed and necropsied. The F0 male rats were sacrificed and necropsied after the end of dosing at the time of parturition (lactation day 1). The testes, epididymides, prostate, and seminal vesicles were weighed. Evaluations of sperm number, motility, and morphology were not included in the protocol. The F0 generation females that delivered by Cesarean-section were sacrificed on GD 10 and necropsied. Pregnancy status was confirmed, the ovaries were examined for the number and distribution of corpora lutea, implantation sites were determined, and embryos were examined for viability. The F0 generation females that delivered naturally were sacrificed on lactation day (LD) 21 and necropsied. Ovaries were examined as above and the number and distribution of implantation sites was recorded. The liver from each parental rat was removed, weighed and analyzed. Blood samples were collected from 5 male rats that had mated and from 5 female rats on LD 21 for pharmacokinetic analysis; livers from the pups from the litters of these five dams were also collected for analysis. The final results of these analyses were not available at the time of this review.

F1 Generation:

Since F1 generation pup viability was significantly reduced in the 1.6 and 3.2 mg/kg/day dose groups, only the 0.1 and 0.4 mg/kg/day dose groups were carried into the second generation. Twenty-five F1 generation rats per sex per dose group were administered PFOS by gavage at doses of 0, 0.1, and 0.4 mg/kg/day beginning on LD 22 and continuing through the day before sacrifice. At 24 days of age, one rat per sex per litter in each dose group was tested in a passive avoidance paradigm. On LD 28, females were evaluated for the age of vaginal patency and on LD 34, male rats were evaluated for the age of preputial separation. One rat per sex per litter were evaluated in a water-filled M-maze on LD 70. Assignment to cohabitation within each dose group began on LD 90. Females with evidence of mating were considered to be at GD 0 and assigned to individual housing for the remainder of the dosing period.

The F1 generation male rats were sacrificed after mating, necropsied and evaluated as described in the F0 generation. All F1 generation females were allowed to deliver naturally. Dams that delivered litters were sacrificed and necropsied on LD 21. All F2 generation pups were sacrificed, necropsied, and examined on LD 21 as previously described for the F1 generation pups.

In the F0 generation male rats, there were no treatment-related clinical signs of toxicity, no mortality, and no effects on mating or on any of the fertility parameters evaluated in any dose group tested. Reported effects included reductions in both body weight gains and in absolute and relative food consumption at the 1.6 and 3.2 mg/kg/day dose groups during the pre-mating period. Following mating, food consumption was significantly reduced in the 0.4. and 1.6 mg/kg/day dose groups. Terminal body weights were also significantly reduced in the 1.6 and 3.2 mg/kg/day dose groups. Signs of reproductive toxicity in the F0 generation males were seen at the highest dose group of 3.2 mg/kg/day and included significant reductions in the absolute weights of the seminal vesicles (with fluid) and the prostate. A significant increase in the number of males with brown liver at 3.2 mg/kg/day dose group was also reported.

In the F0 generation female rats, no deaths were reported at any dose level. In dams sacrificed on GD 10 for Caesarean-sectioning, there did not appear to be any effects on estrous cycling, mating and fertility parameters, the numbers of corpora lutea and implantations, or in the number of viable or non-viable embryos. The only findings reported in the F0 dams occurred in the 0.4, 1.6, and 3.2 mg/kg/day dose groups and included localized alopecia during pre-mating, gestation, and lactation; and reductions in body weight and food consumption values observed during the pre-mating period and continuing throughout gestation and lactation.

Reversible delays in reflex and physical development were observed in the F1 generation offspring. The ability to surface right was significantly delayed in the 1.6 and 3.2 mg/kg/day dose groups on LDs 3-10 (delays in the 3.2 mg/kg/day dose group were observed on LD 1, after which there were no surviving pups remaining for further observation). By the end of the observation period, however, all surviving pups in the 1.6 mg/kg/day dose group had the ability to surface right. There were no delays observed in the ability to surface right in dose groups ≤ 0.4 mg/kg/day. Similar responses were seen for pinna unfolding and eye opening. Although there were transient delays seen with these signs of physical development across all dose groups, by the end of the observation period responses in pups were similar to controls. The time of development of the acoustic startle reflex and the ability to air right were both significantly reduced in the 1.6 mg/kg/day dose group. No effects on these reflexes were observed in the low dose group of 0.1 mg/kg/day and only a transient delay (on LD 16 only) in the ability to air right was seen in the 0.4 mg/kg/day group. At the end of lactation (LD 21), all live pups in all dose groups (0, 0.1, 0.4, and 1.6 mg/kg/day) had pupil constriction response.

The most significant finding reported in the offspring was that of reduced pup viability at the two highest dose groups. The reductions in pup viability began to appear on LD 4 postculling in the 1.6 mg/kg/day dose group, with over 26% of the pups found dead between LD 2-4. In the 3.2 mg/kg/day dose group 45% of the pups were found dead on LD1; no pups survived beyond LD 1. As a result, the viability index was greatly reduced in these dose groups (0% at 3.2 mg/kg/day and 66% at 1.6 mg/kg/day). The lactation index was also significantly reduced (94.6%) in the 1.6 dose group. In addition, gestation length was significantly reduced in the high-dose group and there also was a significant reduction in the

number of implantation sites followed by a concomitant reduction in litter size. Statistically significant reductions in pup body weights were also observed at the two highest dose groups. Other adverse signs in the 3.2 mg/kg/day dose level associated with reductions in pup viability and maternal care included litters with pups that were not nursing or who had no evidence of milk in the stomach, as well as maternal cannibalization of pups that were stillborn or found dead.

Since F1 generation pup viability was significantly reduced in the 1.6 and 3.2 mg/kg/day dose groups, only the 0.1 and 0.4 mg/kg/day dose groups were carried into the second generation.

Clinical observations in the F1 generation male rats appeared unremarkable. No treatment-related deaths were reported and no statistically significant differences were reported for any of the following parameters: body weights/body weight gains, average day of preputial separation; values for learning, short-term retention, long-term retention or response inhibition as evaluated by performance in a passive avoidance or watermaze performance paradigm; mating or fertility parameters; necroscopic examinations; absolute or relative weights for the right or left testis, seminal vesicles, right epididymis, or prostate; and terminal body weights. The only reported effects were significant reductions in absolute food consumption on postweaning days 1-8 occurring at the 0.1 and 0.4 mg/kg/day dose levels.

Clinical observations for the F1 generation females were likewise unremarkable. Observations at the 0.4 mg/kg/day dose group included, reductions in body weights on day 1 postweaning, significant losses in body weight on LDs 1-4, and significant reductions in food consumption on days 1-8 postweaning and during lactation. There were no statistically significant differences reported for any of the following parameters: values for learning, short-term retention, long-term retention or response inhibition as evaluated by performance in a passive avoidance or watermaze performance paradigm; mating and fertility parameters; gestation index; pregnancy rates; and necroscopic examinations.

Evidence of treatment-related effects in the F2 generation pups consisted of reductions in mean pup body weights (on a per litter basis) observed at 0.1 mg/kg/day on LD 4 and 7. Body weights were comparable to control levels by LD 14. At 0.4 mg/kg/day, statistically significant reductions in mean pup body weights were observed on LDs 7-14. Mean body weights on LD21 continued to remain lower than controls, although the difference was not statistically significant (46.5 g in 0.4 mg/kg/day dose group vs. 50 g in controls). Clinical and necroscopic observations of the F2 generation pups were unremarkable. No other toxicologically significant effects were reported.

Under the conditions of the study, the NOAEL and LOAEL for both the F0 and F1 generation male and female parents are 0.1 mg/kg/day and 0.4 mg/kg/day, respectively, based on reductions in body weight gain and food consumption. The NOAEL and LOAEL for the F1 generation offspring are 0.4 mg/kg/day and 1.6 mg/kg/day, respectively, based on significant reductions in the number of

implantation sites, litter size, pup viability, growth and survival. The NOAEL and LOAEL for the F2 generation offspring are 0.1 mg/kg/day and 0.4 mg/kg/day, respectively, based on significant reductions in pup growth.

III. Human Data

For many years, PFOS has been measured in the serum of workers occupationally exposed to PFOS. It was also recently detected in the serum of the general population, but at much lower levels. The results of the most recent analyses of blood samples are described below and summarized in Table 1.

Occupational exposures

PFOS serum levels have been measured in workers involved in both the manufacturing of perfluorochemicals and the processing of these compounds into products, such as fire protection and surface protection products. Biomonitoring data are available from manufacturing plants in Alabama and Belgium, and a processing facility in Japan.

Fluorochemical Manufacturing

Two 3M plants, located in Decatur, Alabama and Antwerp, Belgium, produce certain fluorochemicals that may transform metabolically to PFOS. Serum PFOS levels were measured in manufacturing plant employees in 1995 (n = 178) and 1997 (n = 149) using high performance liquid chromatography/mass spectrometry (3M Report, 1999). The PFOS levels in workers across both plants in 1995 ranged from 0.10 ppm to 12.83 ppm. The serum levels were slightly lower at the Antwerp plant across both sampling periods. The range of PFOS levels of workers in 1997 was 0.10 - 9.93 ppm. Most of the employees at both facilities and during both sampling periods had PFOS serum levels that were <6 ppm.

The participation rate of the total number of potentially exposed employees in the medical monitoring program from which these data were derived was not provided. It was expressed that the employees were offered a medical monitoring program, but it is not clear how many of them actually participated. In addition, age of the employees and duration of employment were not reported, and it is unclear how many of the total number of employees worked at each plant. Therefore, it should be noted that these data only provide a snapshot of the serum levels of participating workers during each sampling period.

In order to address the voluntary nature of the monitoring program at the 3M plants, a random sample of employees from the Decatur plant was chosen to measure seven different fluorochemicals in employees blood (Olsen et. Al., 1999). Limited job information, years worked, and building location were collected to provide a better understanding of the distribution of fluorochemical serum levels in employees. The random sample consisted of 187 chemical plant workers (126 randomly chosen

workers and 61 volunteers) and 76 film plant workers (60 randomly chosen and 16 volunteers). The levels in these employees, who were sampled in late 1998, were similar to those reported above. Mean PFOS levels were 1.505 ppm (range, 0.091-10.600) for the random sample, 1.259 ppm for the volunteers, and 1.424 ppm for all participants. Since the PFOS levels appeared to be log normally distributed, geometric means were also calculated. They were 0.944 ppm (95% CI 0.787-1.126) for chemical plant employees and 0.136 ppm (95% CI 0.114-0.161) for film plant employees. When compared by job description, workers in the chemical plant had higher PFOS levels than workers in the film plant. PFOS levels in males were positively, although modestly, associated with number of years worked in the chemical plant. Although this cross-sectional study tried to address the volunteer bias associated with the previous study, there are still many limitations regarding exposures and worker participation.

Fluorochemical Processing

Biomonitoring data were submitted on workers in Japan processing perfluorinated chemicals into fire protection products and surface products (Burris et. Al., 1999). In 1999, PFOS, PFOA and PFHS (perfluorohexanesulfonate) were measured in employees' serum at the Sagamihara plant. Serum was drawn from both production employees (n = 32) who regularly handle fluorochemicals and management employees (n = 32) who are not regularly exposed. Serum was also drawn from management employees (n = 30) at the Head Office in Tokyo. The highest PFOS level in 32 production employees was 0.628 ppm, with an arithmetic mean of 0.135 ppm. The highest PFOS level in either of the management groups was 0.0967 ppm, while the average level was approximately 0.04 ppm. The results of the biomonitoring performed at the Sagamihara plant indicate lower levels of PFOS than at either of the manufacturing facilities cited above.

Although the exposures would not necessarily be considered "occupational" for either group, PFOS levels in corporate staff/managers at a 3M plant in St. Paul, Minnesota were similar to those reported in the corporate managers in Japan (3M Report, 1999). Thirty-one employees, none of whom had worked in fluorochemical production or research and development, were sampled in 1998. All of the participating employees had measurable levels of PFOS in their serum. The mean PFOS level was 0.047 ppm, with a range of 0.028 to 0.096 ppm. In this group of 3M employees, age was significantly associated with increased serum PFOS. No other data on these workers were provided.

Non-occupational exposures

PFOS has been measured in the serum of the general U.S. population and in small numbers of historical samples (dating as far back as 1957) from sources throughout the world.

In 1998, PFOS levels in pooled serum from 2 commercial sources in the U.S. ranged from 43- 45 ppb and 26 - 45 ppb (3M Report, 1999). There were approximately 500 donors in the first source and an

estimated 200 donors in the second. No other data, such as geographic location or age of the donors, were provided. 3M also analyzed thirty-five lots of individual or pooled human sera samples from U.S. chemical or biological supply companies in 1999 (3M Letter, 1999). These samples yielded an average of 35 ppb PFOS, ranging from 5 to 85 ppb.

Sera pooled from 18 regional blood banks in various geographic regions of the U.S. were analyzed for PFOS in 1998 (3M Report, 1999). There were 68 pools and an estimated 340-680 donors. The overall mean PFOS serum level across the pools was 29.7 ppb. The PFOS levels varied quite a bit depending on the geographic location of the blood bank. The range of the levels across geographic regions was 9 to 56 ppb, while the range of the averages was 14 to 52 ppb.

Very limited data have recently become available on PFOS levels in U.S. children. In a 1999 pilot study meant to verify the analytic technique used on small volumes of serum, blood samples of children 6-12 years old were analyzed for PFOS (3M Report, 1999). Ten samples were analyzed using high-pressure liquid chromatography/electrospray tandem mass spectrometry (limit of detection is 3 ppb). PFOS was detected in all of the samples. The average level of PFOS in these samples was 54 ppb, with a range of 31-115 ppb. These individual levels are higher than those reported in pooled samples in adults in the general population; however, given the small number of samples, few inferences can be made about the results of these data. A study analyzing over 600 pediatric serum samples is ongoing.

These data are useful in providing preliminary levels of PFOS in the general U.S. population, but they must be interpreted carefully. It cannot be assumed that the reported PFOS levels are representative of the U.S. population. Many of the blood banks originally contacted for possible inclusion in the study declined to participate, thus introducing possible non-response bias. Only a small number of samples have actually been analyzed for PFOS, and some of the levels varied quite a bit depending on geographic location of the blood bank. Also, no other data, such as age, sex, or other demographic variables, are available on the donors. Blood donors as a group cannot be considered representative of the U.S. population as a whole.

A summary of the occupational and general population exposure data are presented below in Table 1.

TABLE 1

MEAN PFOS SERUM LEVELS IN HUMAN POPULATIONS

Occupational Exposures		
Plant Location	Mean (ppm)	Range (ppm)
Decatur, Alabama		
1995	2.44	0.25 - 12.83
1997 (n = 84)	1.96	0.10 - 9.93
Antwerp, Belgium		
1995	1.93	0.10 - 9.93
1997 (n = 65)	1.48	0.1 - 4.8
Sagamihara, Japan (1999) (processing PFOS) n = 32	0.135	0.0475 - 0.628
General Population Exposures		
Source	Mean (ppb)	Range (ppb)
Non-occupational (n = 31) (corporate staff or managers) St. Paul, Minnesota (1998)	47	28 - 96
Non-occupational (1999) (plant management, Japan) Sagamihara n = 32	40.3	31.9 - 56.6
Tokyo n=30	52.3	33 - 96.7
Commercial		
Intergen n = ~500 donors	44	43 - 44
Sigma n = ~ 200 donors	33	26 - 45
Other Commercial Sources n = 35 lots	35	5 - 85
Blood Banks n = ~340-680 donors	29.7	9 - 56
Samples in children n = 10	54	31 - 115

Human Hazard Data

Epidemiologic data on the health effects associated with fluorochemical exposure are limited. There are two studies that specifically analyzed possible effects of PFOS on workers.

The same group of employees (males only) who had been monitored for PFOS serum levels in 1995 and 1997 at the Decatur, Alabama plant were studied to determine if there were any associations between PFOS levels and hematology, clinical chemistries, and hormonal parameters (Olsen et. Al., 1998, 1999). Animal studies had reported that PFOS is a peroxisome proliferator in rats and that it reduces cholesterol in rhesus monkeys. When the data from both plants were combined, there were no consistent associations between PFOS levels in the workers and the hematology and other clinical chemistry parameters for either time period. Mean serum cholesterol levels remained constant or increased with increasing PFOS serum levels depending on the year; however, those employees with the highest PFOS levels had lower HDL mean values. It should be noted that age was significantly associated with higher PFOS levels. In addition, there were no associations between clinical hepatic enzyme tests and serum PFOS levels in workers.

Eleven hormone values were collected from 88 of the employees who participated in the study in 1995. The employees who participated in the hormone portion of the study were significantly different from the non-participants at both locations (younger, higher PFOS levels, smokers, and higher WBC). After adjusting for confounders, there were no significant associations between PFOS and the hormones analyzed, except estradiol; however, it seems that one employee with high PFOS measurements (12.83 ppm) and a large BMI may have influenced these results. Removal of this employee from the analyses resulted in no significant associations with estradiol.

There were several differences between the employees at the two plants, such as body mass index, alcohol consumption, and age. In addition, there were only 61 employees common to both the 1995 and 1997 cohort due to a high rate of turnover at both plants from 1996-1997. Some of the findings were not consistent over the 2 time periods. The participation rate in this voluntary biomonitoring was very low at the Decatur plant (35-40%). In addition, the employees at both sites used PFOA as a surfactant (mean PFOA serum levels in 1995 were 1.46 ppm and in 1997 were 1.57 ppm). The number of years that each group worked at the 2 plants (exposure) were not provided in the analyses, although the youngest employees had the lowest levels of serum PFOS. Also, ninety-five percent of the employees across both plants and both time periods had serum PFOS levels less than 6 ppm. There is also the concern that serum PFOS may not accurately reflect body burden because PFOS primarily concentrates in the rat liver. These limitations indicate that the results of this study should be interpreted carefully.

A retrospective cohort mortality study was also performed on Decatur employees to determine whether plant employees had significantly different death experiences from the general population (Mandel and Johnson, 1995). There were 1957 employees who had worked at least one year at the Decatur plant between 1961 and 1991. Seventy-four deaths were recorded, and there were no significantly elevated SMRs for all major causes of death regardless of the comparison population used (Alabama state, US, or Alabama counties). When the data were analyzed by job description (chemical department vs. film plant employees), there was a statistically significant deficit for all causes of death in both job categories.

This study had almost complete follow-up of the cohort and ascertainment of causes of death. However, since the workforce was relatively young, only 74 deaths were reported for 1,951 employees. Also, PFOS serum levels were not examined in relation to mortality. In addition, the number of women in the study was very small (4 deaths). Therefore, the cohort needs to be followed for many additional years to provide a meaningful picture of the mortality experience of these workers.

IV. References

3M Reports: "The Science of Organic Fluorochemistry" and "Perfluorooctane Sulfonate: Current Summary of Human Sera, Health, and Toxicology Data", dated February 5, 1999. (8EHQ-0299-373).

Biesemeier, J.A. and Harris, D.L. 1974. Eye and Skin Irritation Report on Sample T-1117. Report. Project No. 4102871, WARF Institute Inc.

Burris J, Olsen G.W., Mandel J.H., Schumpert, J.C. 1999. Determination of Serum Fluorochemical Levels in Sumitomo 3M employees. Final Report. 3M Company, 3M Medical Department, Epidemiology, 220-3W-05. FYI-0500-01378.

Christian, M.S., Hoberman, A.M., and York, R.G. 1999a. Oral (Stomach Tube) Developmental Toxicity Study of PFOS in Rabbits. Argus Research Laboratories, Inc. Protocol Number: 418-012, January 1999. FYI-0500-01378. 04/21/00 Submission.

Christian, M.S., Hoberman, A.M., and York, R.G. 1999b. Combined Oral (Gavage) Fertility, Developmental and Perinatal/Postnatal Reproduction Toxicity Study of PFOS in Rats. Argus Research Laboratories, Inc. Protocol Number: 418-008, Sponsor Study Number: 6295.9, June 10, 1999.(8EHQ-0200-00374).

Cifone, M.A. 1999. Unscheduled DNA Synthesis in Rat Liver Primary Cell Cultures with PFOS. Final Report. Covance Study No. 207840447. Covance Laboratories Inc., Vienna, Virginia 22182.

Dean, W.P., Jessup, D.C., Thompson G., Romig, G., and Powell, D. 1978. Fluorad Fluorochemical Surfactant FC-95 Acute Oral Toxicity (LD₅₀) Study in Rats. Study No. 137-083, International Research and Development Corporation. (Includes Acute Oral Toxicity Study in Rats with T-2297 CoC . Project No. 78-1433A, Biosearch, Inc.)

Goldenthal, E.I., Jessup, D.C., Geil, R.G. and Mehring, J.S. 1978a. Ninety-day Subacute Rhesus Monkey Toxicity Study. Study No. 137-092, International Research and Development Corporation, Mattawan, MI. FYI-0500-1378. 05/04/00 Submission. Repeated-Dose Toxicity #1.

Goldenthal, E.I., Jessup, D.C., Geil, R.G., Jefferson, N.D. and Arceo, R.J. 1978b. Ninety-day Subacute Rat Study. Study No. 137-085, International Research and Development Corporation, Mattawan, MI. FYI-0500-1378. 05/04/00 Submission. Repeated-Dose Toxicity #2.

Goldenthal, E.I., Jessup, D.C., Geil, R.G. and Mehring, J.S. 1979. Ninety-day Subacute Rhesus Monkey Toxicity Study. Study No. 137-087, International Research and Development Corporation, Mattawan, MI. FYI-0500-1378. 05/04/00 Submission. Repeated-Dose Toxicity #1b.

Gortner, E.G. 1980. Oral Teratology Study of FC-95 in Rats. Safety Evaluation Laboratory and Riker Laboratories, Inc. Experiment Number: 0680TR0008, December, 1980. FYI-0500-01378. 04/21/00 Submission.

Johnson, J.D., Gibson, S.J. and Ober, R.F. 1979a. Absorption of FC-95-14C in Rats after a Single Oral Dose. Riker Laboratories, Inc., Subsidiary of 3M, St. Paul, MN. Project No. 890310200.

Johnson, J.D., Gibson, S.J., and Ober, R.E. , 1979b. Extent and Route of Excretion and Tissue Distribution of Total Carbon-14 in Rats after a Single Intravenous Dose of FC-95-14C. Riker Laboratories, Inc., Subsidiary of 3M, St. Paul, MN.

Johnson, J. D., Gibson, S.J., and Ober, R.E. (1984). Cholestyramine-Enhanced Fecal Elimination of Carbon-14 in Rats after Administration of Ammonium [14C]Perfluorooctanoate or Potassium [14C]Perfluorooctanesulfonate. *Fundamental and Applied Toxicology* 4: 972-976.

Litton Bionetics, Inc., 1979. Mutagenicity Evaluation of T-2014 CoC in the Ames Salmonella/Microsome Plate Test. Final Report. LBI Project No. 20838.

Mecchi, M.S. 1999. *Salmonella – Escherichia coli*/-Mammalian-Microsome Reverse Mutation Assay with PFOS. Final Report. Covance Study No.: 20784-0-409. Covance Laboratories, Vienna, Virginia 22182.

Murli, H. 1996. Mutagenicity Test on T-6295 in an *In Vivo* Mouse Micronucleus Assay. Final Report.

CHV Study No.: 17403-0-455. Corning Hazleton Inc. (CHV) Vienna, Virginia 22182.

Murli, H. 1999. Chromosomal Aberrations in Human Whole Blood Lymphocytes with PFOS. Final Report. Covance Study No.: 2784-0-449. Final Report. Covance Laboratories Inc., Vienna, Virginia 22182.

Olsen G.W., Logan, P.W., Simpson, C.A., Hansen, Burris J.M., Burlew M.M., Schumpert JC, Mandel JH. August 11, 1999. Fluorochemical Exposure Assessment of Decatur Chemical and Film Plant Employees. Final Report, 3M Medical Department. FYI-0500-01378.

Rusch, G.M., Rinehart, W.E. and Bozak, C.A. 1979. An Acute Inhalation Toxicity Study of T-2306 CoC in the Rat. Project No. 78-7185, Bio/dynamics Inc.

Simmon, V. F. 1978. In Vitro Microbiological Mutagenicity Assays of 3M company Compounds T-2247 CoC and T-2248 CoC. Final Report. SRI Project: LSC-4442-016. SRI International Menlo Park, California 94025.

Thomford, P.J. 1998. 4-Week Capsule Toxicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T-6295) in Cynomolgus Monkeys. Unaudited Draft. Study No. 6329-222 for 3M, St. Paul, MN, by Covance Laboratories Inc., Madison, WI. 8EHQ-RDT-4. FYI-0500-1378. 05/04/00 Submission. Repeated-Dose Toxicity #4.

Thomford, P.J. 2000. 26-Week Capsule Toxicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T6295) in Cynomolgus Monkeys. Unaudited Draft Final Report Prepared for 3M, St Paul, Minnesota by Covance Laboratories, Inc., Madison Wisconsin 53704- 2595. Study Number 6329-223. April 12, 2000. 502 pp. FYI-0500-1378. 05/04/00 Submission. Repeated-Dose Toxicity #5.

Wetzel, L.T. 1983. Rat Teratology Study, T-3351, Final Report. Hazleton Laboratories America, Inc. Project Number: 154-160, December 19, 1983. (TSCA Section 8(e) submission 8EHQ-0399-374. 04/21/00 Submission.

York, RG, Hansen, K, and Clemen, L., 1999. Analytical Laboratory Report on the Determination of the Presence and Concentration of Potassium Perfluorooctanesulfonate (CAS Number: 2795-39-3) in the Serum and Liver of Sprague-Dawley Rats Exposed to PFOS via Gavage. Argus Research Laboratories, Inc., Horsham, PA. Laboratory Report No. U2006, Requestor Project No. 3M TOX 6295.9, 3M Environmental Laboratory Report No. FACT Tox-012.