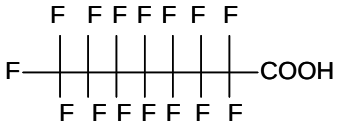
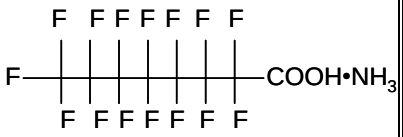
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	335-67-1	3825-26-1
Chemical Name	Perfluorooctanoic Acid (PFOA)	Ammonium Perfluorooctanoate (APFO)
Structural formula		

SUMMARY CONCLUSIONS OF THE SIAR

Chemical Identity

For the purposes of this document, the anion of PFO (perfluorooctanoate) is frequently referenced as PFOA or APFO. APFO and PFOA are sometimes used interchangeably. Perfluorooctanoic Acid (PFOA) is a fully fluorinated carboxylic acid. APFO is the ammonium salt of PFOA.

Human Health

APFO is the ammonium salt of PFOA and the two substances are metabolically equivalent. PFOA is a strong acid and it is expected to dissociate in biological media.

Several epidemiology and medical surveillance studies have been conducted on workers employed at various APFO manufacturing sites in the U.S. Most of the studies were cross-sectional and focused primarily on males. A retrospective cohort mortality study demonstrated a statistically significant association between prostate cancer mortality and employment duration in the chemical facility of a plant that manufactures PFOA. However, in an update to this study in which more specific exposure measures were used, a significant association for prostate cancer was not observed. Other mortality studies lacked adequate exposure data which could be linked to health outcomes. A study which examined hormone levels in workers reported an increase in estradiol levels in workers with the highest PFOA serum levels; however, these results may have been confounded by body mass index. Cholesterol and triglyceride levels in workers were positively associated with PFOA exposures, which is inconsistent with the hypolipidemic effects observed in rat studies. A statistically significant positive association was reported for PFOA and T3 levels in workers but not for any other thyroid hormones.

Little information is available concerning the pharmacokinetics of PFOA and its salts in humans. Preliminary results of a 5-year half-life study in 26 retired workers indicate that the mean serum elimination half-life of PFOA in these workers was 3.8 years (1378 days, 95% CI, 1131-1624 days) and the range was 1.5-9.1 years.

The pharmacokinetics of PFOA in non-human primates has been studied both in classical intravenous elimination studies using three male and three female cynomolgus monkeys and in a six-month, repeat-oral-dose toxicology study in male cynomolgus monkeys with recovery. These studies confirmed urinary elimination as the primary excretion mode. From the intravenous study, in which males and females were given a 10 mg/kg dose, mean elimination half-lives were 20.9 days for males and 32.6 days for females. In the six-month study, monkeys were dosed with 3, 10, or 30/20 mg/kg-d ammonium PFOA. Steady-state serum concentration was reached within four to six weeks, with steady state levels lower than those that would be predicted based on the elimination rates and not in linear proportion to dose. Males in the six-month toxicology study had elimination half-life rates approximating 20 days.

Studies in adult rats have shown that the ammonium salt of PFOA (APFO) is absorbed following oral and inhalation exposure; less absorption occurs following dermal exposure. Serum pharmacokinetic parameters and the distribution of PFOA has been examined in the tissues of adult rats following administration by gavage and by intravenous (i.v.) and intraperitoneal (i.p.) injection. PFOA distributes primarily to the liver, serum, and kidney, and to a lesser extent, other tissues of the body. It does not partition to the lipid fraction or adipose tissue. The distribution of PFOA is predominantly extracellular. PFOA is not metabolized and there is evidence of enterohepatic circulation of the compound. The urine is the major route of excretion of PFOA in the female

rat, while the urine and feces are both main routes of excretion in male rats.

There are gender differences in the elimination of PFOA in adult rats following administration by gavage and by i.v. and i.p.injection. In female rats, following oral administration, estimates of the serum half-life were dependent on dose and ranged from approximately 2.8-16 hours, while in male rats estimates of the serum half-life following oral administration were independent of dose and ranged from approximately 138-202 hours. In female rats, elimination of PFOA appears to be biphasic with a fast phase and a slow phase. The rapid excretion of PFOA by female rats is believed to be due to active renal tubular secretion (organic anion transporters); this renal tubular secretion is believed to be hormonally controlled. Hormonal changes during pregnancy do not appear to cause a change in the rate of elimination in rats.

Several recent studies have been conducted to examine the kinetics of PFOA in the developing rat. These studies have shown that PFOA readily crosses the placenta and is present in the breast milk of rats. The gender difference in elimination is developmentally regulated; between 4-5 weeks of age, elimination assumes the adult pattern and the gender difference becomes readily apparent. Distribution studies in the postweaning rat have shown that PFOA is distributed primarily to the serum, liver, and kidney.

In acute toxicity studies in animals using APFO, the oral LD_{50} values for CD rats were >500 mg/kg for males and 250-500 mg/kg for females, and <1000 mg/kg for male and female Wistar rats. There was no mortality following inhalation exposure of 18.6 mg/l APFO for one hour in rats. The dermal LD_{50} in rabbits was determined to be greater than 2000 mg/kg. APFO is a primary ocular irritant in rabbits, while the data regarding potential skin irritancy are conflicting.

APFO did not induce mutation in either S. typhimurium or E. coli when tested either with or without mammalian activation. APFO did not induce gene mutation when tested with or without metabolic activation in the K-1 line of Chinese hamster ovary (CHO) cells in culture. APFO did not induce chromosomal aberrations in human lymphocytes when tested with and without metabolic activation up to cytotoxic concentrations. APFO was tested twice for its ability to induce chromosomal aberrations in CHO cells. In the first assay, APFO induced both chromosomal aberrations and polyploidy in both the presence and absence of metabolic activation. In the second assay, no significant increases in chromosomal aberrations were observed without metabolic activation. However, when tested with metabolic activation, APFO induced significant increases in chromosomal aberrations and in polyploidy. APFO was negative in a cell transformation assay in mouse embryo fibroblasts and in the mouse micronucleus assay.

Repeat-dose studies have been conducted in non-human primates. In a 13-week study with Rhesus monkeys, exposure to doses of 30 mg/kg-day or higher resulted in death. Clinical signs of toxicity were noted at doses as low as 3 mg/kg-day. Unlike rodent studies, analyses of the serum and liver levels did not reveal a gender difference in monkeys, but the sample size was very small. In a 6-month study of male cynomolgus monkeys, there was a steep dose response curve for mortality. Increases in liver weight were noted at doses as low as 3 mg/kg-day, but there was no evidence of peroxisome proliferator-activated receptor alpha activity (PPARα). The LOAEL for the study was 3 mg/kg-day, and a NOAEL was not identified.

Repeat-dose studies in rats and mice demonstrated that the liver is the primary target organ. Due to gender differences in elimination, adult male rats exhibit effects at lower administered doses than adult female rats. Dietary exposure to APFO for 90 days resulted in significant increases in liver weight and hepatocellular hypertrophy in female rats at 1000 ppm (76.5 mg/kg-day) and in male rats at doses as low as 100 ppm (5 mg/kg-day). Chronic dietary exposure of rats to 300 ppm (males, 14.2 mg/kg-day; females, 16.1 mg/kg-day) APFO for 2 years resulted in increased liver weight, hepatocellular hypertrophy, hematological effects, and testicular masses in males; and reductions in body weight and hematological effects in females.

The carcinogenic potential of PFOA has been investigated in two dietary carcinogenicity studies in rats. Under the conditions of these studies, there is some evidence that PFOA is carcinogenic, inducing liver tumors, Leydig cell tumors (LCT), and pancreatic acinar cell tumors (PACT) in male rats. The evidence for mammary fibroadenomas in the female rats is equivocal since the incidences were comparable to some historical background incidences. There is sufficient evidence to indicate that PFOA is a PPARα-agonist and that the liver carcinogenicity (and toxicity) of PFOA is mediated by PPARα in the liver.

PFOA appears to be immunotoxic in mice. Feeding mice a diet containing 0.02% PFOA resulted in adverse effects to both the thymus and spleen. In addition, this feeding regimen resulted in suppression of the specific humoral immune response to horse red blood cells, and suppression of splenic lymphocyte proliferation. The suppressed mice recovered their ability to generate a humoral immune response when they were fed a diet devoid of PFOA. Studies using transgenic mice showed that the PPARα was involved in causing the adverse effects to the immune system.

In an oral prenatal developmental toxicity study in rats, the LOAEL and NOAEL for maternal toxicity were 150 mg/kg-day and 5 mg/kg-day, respectively. There was no evidence of developmental toxicity after exposure to

doses as high as 150 mg/kg-day. In a rat inhalation developmental toxicity study, the NOAEL and LOAEL for maternal toxicity were 1 and 10 mg/m^3, respectively. The NOAEL and LOAEL for developmental toxicity were 10 and 25 mg/m^3, respectively. In a rabbit oral prenatal developmental toxicity study there was a significant increase in skeletal variations after exposure to 5 mg/kg-day APFO, and the NOAEL was 1.5 mg/kg-day. There was no evidence of maternal toxicity at 50 mg/kg-day, the highest dose tested. In a mouse oral developmental toxicity study, there was evidence of maternal toxicity and developmental toxicity and the authors calculated benchmark doses for a variety of endpoints. Decreased weight gain and increased liver weight was observed in adult females; the BMD5 and BMDL5 estimates for decreases in maternal weight gain were 6.76 and 3.58 mg/kg, respectively, and the BMD5 and BMDL5 estimates for increases in maternal liver weight were 0.20 mg/kg and 0.17 mg/kg, respectively. The BMD5 and BMDL5 estimates for the incidence of full-litter resorptions and neonatal mortality (determined by survival to weaning) observed at the 5 mg/kg/day dose group were 2.84 and 1.09 mg/kg, respectively. Significant alterations in postnatal growth and development were observed at 1 and 3 mg/kg/day, with BMD5 and BMDL5 estimates of 1.07 and 0.86 mg/kg, respectively, for decreased pup weight at weaning; and 2.64 and 2.10 mg/kg, respectively, for delays in eye opening. The BMD5 and BMDL5 estimates for reduced phalangeal ossification were <1 mg/kg. BMD5 and BMDL5 estimates for reduced fetal weight at term were estimated to be 10.3 and 4.3 mg/kg, respectively.

A variety of endpoints were evaluated throughout different lifestages in a two-generation reproductive toxicity study in rats exposed to 0, 1, 3, 10, or 30 mg/kg/day APFO. In that study, a reduction in F1 pup mean body weight on a litter basis was observed during lactation (sexes combined) in the 30 mg/kg-day group. F1 male pups in the 10 and 30 mg/kg-day groups exhibited a significant reduction in body weight gain during days 8-50 postweaning, and body weights were significantly reduced in the 10 mg/kg-day group beginning on postweaning day 36, and in the 30 mg/kg-day group beginning on postweaning day 8. F1 female pups in the 30 mg/kg-day group exhibited a significant reduction in body weight gain on days 1-15 postweaning, and in body weights beginning on day 8 postweaning. Reproductive indices were not affected in the F1 animals. There was a significant increase in mortality mainly during the first few days after weaning, and a significant delay in the timing of sexual maturation for F1 male and female pups in the 30 mg/kg-day group. No effects were observed in the F2 pups. However, it should be noted that the F2 pups were sacrificed at weaning, and thus it was not possible to ascertain the potential post-weaning effects that were noted in the F1 generation. Adult systemic toxicity consisted of reductions in body weight in both the F0 and F1 animals.

Environment

Both PFOA and APFO are solid at environmental relevant temperatures. The melting point for PFOA is 54.3°C and the boiling point is 190°C at 1013 hPa. APFO starts to decompose above 105°C. At 20°C, the water solubility of PFOA is 9.5 g/l and of APFO >500 g/l. When dissolved in water, the strong acid PFOA (pKa 2.5) dissociates.

Pure PFOA at room temperature has moderate vapor pressure (2.3 Pa). The vapor pressure of APFO is much lower with 0.008 Pa. APFO or PFOA dissolved in water dissociate to ions. Although the dissociated fraction is not subject to volatilization, depending on the pH, pure PFOA might volatilize from water to a certain degree.

Due to emissions for more than 50 years, PFOA is distributed worldwide in the marine environment, and hence may be transported to remote areas via the aqueous phase and the atmospheric phase. However, the significance of these sources are not currently known. Both atmospheric and aquatic transport mechanisms are actively being investigated.

Possible substances subject to atmospheric long-range transport are PFOA precursors rather than PFOA itself. Potential precursors are fluorotelomer alcohols, -olefins and perfluoroalkyl sulfonyl derivates. These substances are degraded by OH radicals via gas-phase reactions to result partially in PFOA. The relative environmental significance of these sources is not known at this time.

Due to the stability of the C-F bond, PFOA is persistent in the environment. No degradation could be observed in the studies on abiotic or biological degradability in water. Also the examinations on photolytic and photochemical degradation in air indicate high stability under environmentally relevant conditions. The half-life of the reaction with OH-radicals in the atmosphere is 130 days.

According to the low adsorption potential and the water-solubility, PFOA is mobile in soil.

The available ecotoxicological studies using APFO indicate a low acute toxicity for aquatic organisms. In the short term tests using fish, invertebrates, and algae, effective concentrations were as follows:

Oncorhynchus mykiss	LC_{50} (96 h)	= 707 mg/l	(nominal)
Daphnia magna	EC_{50} (48 h)	= 480 mg/l	(measured)
Pseudokirchneriella subcapitata	$EC_{50\text{growth rate/biomass}}$ (72 h)	> 400 mg/l	(nominal)

The NOEC values determined in the chronic tests using fish and daphniae, were 40 mg/l (*O. mykiss*, NOEC, 85 d, measured) and 20 mg/l (*D. magna*, NOEC, 21 d, measured). In a 10 day study using *Chironomus tentans* no effects were observed up to a nominal concentration of 100 mg/l. In addition to that, the following information about effects on community level (indoor and outdoor microcosm studies) is available:

Zooplankton community	35 d-$LOEC_{species\ richness}$	= 10 mg/l	(nominal)
Myriophyllum spicatum	35 d-EC_{10}	= 5.7 mg/l	(measured)
Myriophyllum spp.	35 d-NOEC	= 23.9 mg/l	(measured)

In several tests on effects using activated sludge, no inhibition of microbial activity was measured up to a nominal concentration of 1000 mg/l.

Concerning the effects on terrestrial organisms, in a test using *Caenorhabditis elegans* without analytical verification, an EC_{50} (48 h) of 973 mg/l (nominal) was calculated. In a chronic study using the same species, a reduction of abundance and egg production was observed at the 4th generation at a concentration of $4.1x10^{-3}$ mg/l (nominal). The NOEC for this endpoints was $4.1x10^{-4}$ mg/l.

In tests with the rainbow trout *Oncorhynchus mykiss* a bioconcentration factor (BCF) of 0.038 and bioaccumulation factors (BAF) for organs of 27 (blood), 8.0 (liver) and 4.0 (carcass) were obtained. These laboratory studies indicate a low bioaccumulation potential in fish. Some monitoring data suggest a low biomagnification potential in aquatic food webs, while in some marine and Canadian Arctic mammalian food web studies a potential for biomagnification has been suggested. Further elucidation of the mechanisms leading to uptake and accumulation in biota is required.

Exposure

APFO is used as a processing aid in the production of fluoropolymers. In 2002, its world-wide production was about 200-300 metric tons. Entry into the environment occurs during production and use of PFOA / APFO. Other sources for releases to the environment are residual contents of PFOA in fluoropolymer and fluoroelastomer products, PFOA as a byproduct in end products and fire-fighting foams containing perfluorocarboxylates, PFOA contaminations in perfluorooctyl sulfonyl (PFOS) based products, and PFOA contamination in fluorotelomer products. An indirect source for PFOA in the environment is the degradation (biotic and abiotic) of some fluorotelomer-based products.

The global distribution of PFOA was demonstrated by several monitoring studies. Elevated PFOA concentrations were measured near industrialized and urbanized regions. PFOA could be detected in air in concentrations in the range of pg/m³, ng/g dw in soil, in sediment, suspended matter, and sewage sludge.

PFOA concentrations up to 67,000 ng/l and 3,200,000 ng/l were analysed in sewage effluent and landfill effluent. Sporadically, PFOA was determined in ground water samples (up to 3,400,000 ng/l). In fresh water samples (rivers, lakes, rain water) PFOA was regularily measured. The maximum concentration determined was 11,300 ng/l. Elevated concentrations of PFOA were also detected in coastal waters near industrialized and urbanized areas; the maximum concentration was 15,300 ng/l.

In freshwater and salt water fish PFOA was detected occasionally. The maximum concentration (91 ng/g ww) was found in common shiner (liver samples) after a spill of fire retardant foam. The highest PFOA concentration in birds was determined in liver samples of cormorants (450 ng/g ww). However, it should be noted that for this colony of cormorants the highest value (450 $\mu g.kg^{-1}$ ww) appeared to be an outlier as the concentration was 4.5 times greater than the standard deviation of the mean The occurrence of PFOA even in remote areas, was demonstrated by analysis of polar bear liver samples (highest concentration: 55.8 ng/g ww). Liver samples of other mammals (e.g. seals, whales, walrus, dolphin) contained PFOA; concentrations up to 62 ng/g ww.

In addition to the environmental measurements, PFOA was regularly analysed in human blood samples. While the pathways of human exposure to PFOA and its salts are unknown, there are limited data on PFOA blood serum levels in both occupationally- and non-occupationally-exposed populations. It has been detected in samples of human blood (plasma, serum and whole blood), liver, seminal plasma, and breast milk from several countries throughout the world, including the US, Canada, Columbia, Poland, Belgium, India, Korea, Sri Lanka, Japan, Sweden and Germany. Preliminary US reports indicate that individuals living near a facility that uses PFOA have much higher PFOA serum concentrations than the levels previously reported for US populations.

The routine finding of PFOA in human blood initiated research on the sources of human exposure. Fluoropolymers and fluoroelastomers are typically manufactured through telomerization. As APFO is an essential processing aid in this process, trace amounts of PFOA may be generated as an unintended by-product.

Fluorotelomer-based products have numerous uses in many industrial and consumer products, including soil-,

stain-, grease-, and water-resistant coatings on textiles and carpet, personal care products, and nonstick coatings on cookware, and uses in the automotive, mechanical, aerospace, chemical, electrical, medical, and building and construction industries. Consumer exposure to PFOA due to impurities in the finished products can not be excluded. However, based on analysis of consumer articles and using a simple compartmental model estimation, an explanation for the PFOA concentrations found in humans can not be given.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemical is a candidate for further work. The chemicals possess properties indicating a hazard for human health (eye irritation; subchronic toxicity; potential carcinogenicity; developmental toxicity). In the US, data collected in the National Health and Nutrition Examination Survey (NHANES) will provide data on exposure profiles of individuals across the U.S. Epidemiologic studies have not shown conclusively an association of PFOA exposure and health outcomes but most of the studies were cross-sectional; further work is needed to understand any potential associations. Further work on the species differences in toxicokinetics and mode of action to enhance our ability to predict risk in humans is currently underway. Member countries are invited to perform an exposure assessment and then if indicated, a risk assessment.

Environment:

The chemical is a candidate for further work. PFOA is persistent in the environment. The primary environmental sink is the aqueous phase. PFOA tends to be dissipated into organisms and is eliminated from the body very slowly. Laboratory studies and monitoring data in some aquatic food webs indicate a low bioaccumulation potential in fish, but other data suggest a potential for biomagnification, e.g. in marine mammals and Canadian Arctic food webs. Hence, for substances like PFOA, bioconcentration values in fish may not be the most relevant endpoint to consider. For PFOA, biomagnification may occur in air-breathing species (e.g., terrestrial mammals, birds and marine mammals). Further elucidation of the mechanisms leading to uptake and accumulation in biota is required.

The main industrial sources of environmental emissions appear to have been identified. Further research is needed to quantify the sources leading to the ubiquitous environmental distribution and human exposure. In conclusion, member countries are invited to perform an exposure assessment (consideration should be given to precursors to PFOA) and, if indicated, a risk assessment. Member countries are invited to consider risk management measures, e.g. environmental emission reductions.