Perfluorooctanoic Acid (PFOA) and its Direct Precursors: Human health tier II assessment

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Octanoic acid, pentadecafluoro-	335-67-1
Octanoic acid, pentadecafluoro-, ammonium salt	3825-26-1

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to

human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

Perfluorooctanoic acid (PFOA) and its salts are fully fluorinated organic compounds that can be produced synthetically or through the degradation or metabolism of other fluorochemical substances. PFOA is primarily used as a reactive intermediate, while its salts are used as processing aids to produce fluoropolymers and fluoroelastomers, and in other specialised surfactant uses.

The chemicals PFOA salts and PFOA rapidly dissociate to the perfluorooctonoate anion in the blood (Lundin et al., 2009) and are therefore considered direct precursors of PFOA. The PFOA derivative most widely used is the ammonium salt (ammonium perfluorooctanoate; APFO); this is the only salt of PFOA imported and used in Australia. The chemical PFOA and its salts are persistent in the environment and in humans with a half-life of years. Blood monitoring data suggested widespread exposure of the general population to PFOA and APFO, albeit at low levels (USEPA, 2005).

In this assessment, PFOA will be used as a group name for perfluorooctanoic acid and its ammonium salt (APFO); however, the perfluorooctanoate anion is of primary interest. The chemicals PFOA and APFO are sometimes used interchangeably as both the PFO-anion and PFOA (neutral species) exist in solution.

Import, Manufacture and Use

Australian

The chemicals PFOA and APFO are not manufactured in Australia or imported as base chemicals. The largest direct use of these chemicals is as processing aids in manufacturing of certain fluoropolymers.

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemicals have reported commercial uses including:

- as a primer for non-stick metal cookware;
- as fluoropolymer dispersion polymers in paints;
- in fire-fighting foams; and
- in textile and carpet protection

Following co-regulatory activity with NICNAS and industry, imports of polymers containing PFOA have virtually ceased, dropping from 27.5 tonnes in 2003 to approximately 20 kg in 2004, and only 25 g of the chemicals in this group have been used in the local manufacture of non-stick cookware.

APFO is used to produce most, but not all fluoropolymers (NICNAS).

International

The following international uses have been identified through:

- the Organisation for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS) International Assessment Report (OECD, 2006);
- Galleria Chemica.

The chemicals in this group have reported commercial and site limited uses, including as intermediates and in manufacturing polymer dispersants in paints, fire fighting foam, non stick layer on pans, rubber latex, surface cleaning products, lubricants, industrial coatings or inks, construction materials, metal treatment products, leather finishings and tyre treatments. They are also used as intermediates in manufacturing fluoropolymers.

Restrictions

Australian

Since July 2000, NICNAS has been actively involved in the OECD's international program on the scientific assessment and surveys of perfluorinated chemicals. In July 2006, NICNAS collected information on the manufacture, importation and uses of perfluorinated chemicals, including PFOA-related substances and products/mixtures containing these substances, for the calendar years 2004 and 2005. Information provided to NICNAS indicated that:

- No PFOA-related chemicals are manufactured in Australia.
- An antifoam product containing <10 % of a PFOA-related chemical was imported in 2005 for use in a dyeing process with sulfur dyes; the total quantity imported was approximately 10 kg.
- A de-dusting product for industrial use and a consumer paint product, both containing less than 100 ppm of a PFOA salt, were imported. The total volumes of PFOA salt in both products were 10 kg and 71 kg in 2004 and 2005, respectively. The concentrations of PFOA salts in these products were reduced to less than 10 ppm in 2006.

NICNAS continues to monitor imports and use of PFOA-related substances in Australia.

International

In December 2005, Health Canada and Environment Canada proposed temporary prohibitions on the introduction of four new polymers containing fluorinated carbon chains, based on the toxicological effects of their breakdown products, perfluorocarboxylic acids (PFCAs).

In February 2006, Environment Canada and Health Canada also published a position paper: *Perfluorinated carboxylic acid (PFCAs) and precursors: A proposed action plan for assessment and management*. A *Canada Gazette* notice was published in June 2006.

In January of the same year (2006), the United States Environmental Protection Agency (US EPA) launched a global PFOA stewardship program. The eight major companies that use or manufacture PFOA committed to reduce facility emissions and product content of PFOA and related chemicals by 95 % by no later than 2010, and to work toward eliminating emissions and product content by 2015.

The US EPA, in March 2006, also proposed to amend the polymer exemption rule of premanufacture notification (PMN) to exclude from eligibility polymers containing, as an integral part of their composition, certain perfluoroalkyl moieties consisting of a CF3- or longer chain length.

In October 2014, ECHA proposed the following restrictions on PFOA and its salts (ECHA, 2014 a):

'PFOA (CAS 335-67-1), including its salts and any other substance having linear or branched perfluoroheptyl derivatives with the formula C7F15- as a structural element, including its salts, except those derivatives with the formula C7F15-X, where X= F, Cl, Br, and any other substance having linear or branched perfluorooctyl derivatives with the formula C8F17- as a structural element, including its salts, except those derivatives with the formula C8F17-X, where X= F, Cl, Br or, C8F17-SO2X', C8F17-C(=O)OH or C8F17-CF2-X' (where X'=any group, including salts), shall not be manufactured, used or placed on the market as substances of their own, as constituents of other substances, in a mixture or in articles. The proposal is open for public consultation until 17 June, 2015'.

The OECD has been leading an international collaboration on the scientific assessment and surveys for perfluorinated chemicals.

Existing Worker Health and Safety Controls

Hazard Classification

PFOA is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

APFO is classified as hazardous in the HSIS; however, no risk phrases have been assigned (Safe Work Australia).

Exposure Standards

Australian

APFO has an exposure standard of 0.1 mg/m^3 time weighted average (TWA).

International

The following exposure standards are identified for PFOA (Galleria Chemica):

An occupational exposure limit of 0.005 mg/m^3 TWA in countries such as Japan and Switzerland.

The following exposure standards are identified for APFO (Galleria Chemica):

An exposure limit of 0.01 mg/m^3 TWA occupational exposure limit (OEL) in different countries such as the USA (American Conference of Industrial Hygienists; ACGIH), Canada (Alberta, British Columbia, Nova Scotia, Yukon), Denmark, Norway and 0.005 mg/m^3 in Switzerland.

Health Hazard Information

Toxicokinetics

Most toxicological studies were conducted using APFO. Since PFOA and APFO rapidly dissociate into the perfluorooctonoate anion in the blood, these studies are considered relevant for PFOA classification and risk assessment.

Studies in rats have shown that PFOA and APFO are well absorbed following oral, inhalation, and dermal exposure.

In an oral absorption study, Ophaug and Singer (1980) administered 2 mL of an aqueous solution of 2 mg PFOA to female Holtzman rats by gavage. The quantity of nonionic fluorine recovered in the urine was 61 %, 76 % and 89 % at 8, 24 and 96 hours after administration, respectively. Gibson and Johnson (1979) administered a single dose of ^{14}C-APFO averaging 11.4 mg/kg by gavage to three male 10-week-old CD rats. Twenty-four hours after administration, at least 93 % of the total ^{14}C was absorbed from the gastro-intestinal tract. The elimination half-life of ^{14}C from the plasma was calculated as 4.8 days in this study.

In an inhalation exposure study (Hinderliter, 2003), male and female Sprague Dawley (SD) rats (three/sex/group) were exposed to a single nose-only exposure of aerosols of 0, 1, 10, or 25 mg/m^3 PFOA for six hours. Blood samples were collected pre-exposure, at 0.5, 1, 3 and 6 hours during exposure, and at 1, 3, 6, 12, 18 and 24 hours after exposure. PFOA plasma concentrations were proportional to the inhalation exposure concentrations. The male maximum concentration (Cmax) values were approximately 2–3 times higher than those in the females. The female Cmax occurred approximately one hour after the exposure period, while the male Cmax occurred from the end of the exposure period up to six hours after exposure.

No specific dermal absorption studies have been conducted in rats. However, Kennedy (1985) treated rats dermally with a total of 10 applications of APFO at doses of 0, 20, 200 or 2,000 mg/kg. The treatment resulted in dose-related elevated blood organofluorine levels.

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.) injections. PFOA distributes primarily to the liver, plasma, and kidneys and, to a lesser extent, to other tissues of the body. It does not partition to the lipid fraction or adipose tissue. The distribution of PFOA is predominantly extracellular (OECD, 2006).

Several studies have examined the metabolism of PFOA; none showed clear evidence of metabolism. In one study, only the parent compound was present in rat tissues following i.p. of ^{14}C-PFOA (9.4 µmol/kg). No PFOA-containing hybrid lipids were detected. Fluoride concentrations in plasma and urine before and after PFOA treatment were unchanged, indicating that PFOA does not undergo defluorination (Vanden Heuvel et al., 1991).

The chemical PFOA is rapidly excreted following oral administration. There are gender differences in the elimination of PFOA in rats. In female rats, urine is the major route of excretion, while in male rats, PFOA is excreted through urine and faeces. There is also evidence of enterohepatic circulation of PFOA in rats. In an elimination study in SD rats (four rats/sex/group) using ^{14}C-PFOA (Kemper, 2003), urine was the primary route of excretion of ^{14}C in both sexes, accounting for 62–84 % of the administered dose. Cumulative recovery of ^{14}C in the urine increased gradually over the study's 28 days in male rats, but was essentially complete in female rats within the first 72 hours. No ^{14}C was eliminated as either $^{14}CO_2$ or volatile organic compounds. The rapid excretion of PFOA by female rats is believed to be due to hormonally controlled active renal tubular secretion (organic acid transport system) (OECD, 2006).

There are limited data on the half-life of PFOA in humans. The 3M company conducted a half-life study on 26 retired fluorochemical production workers from their Decatur (n = 24) and Cottage Grove (n = 3) plants. Serum samples were drawn from these workers every six months over a five-year period. Results indicated that the mean serum elimination half-life of PFOA in these workers was 3.8 years (Olsen et al., 2005). The range was 1.5–9.1 years.

In general, reported mean serum PFOA concentrations in the general population have been lower than those reported in workers occupationally exposed to PFOA. Additionally, data collected by the US EPA indicated substantially higher PFOA concentrations in residents living near a facility that uses PFOA than in those living far from the facility. The chemical PFOA has also been detected in presumably non-occupationally exposed subjects in Canada, Columbia, Poland, Belgium, India, Korea, Sri Lanka, Japan, and Sweden. The chemical PFOA has been detected in wildlife, air, water, soil, indoor dust, sludge, and food (OECD, 2006).

Acute Toxicity

Oral

The chemical PFOA has moderate acute oral toxicity.

In an oral acute toxicity study, 100, 215, 464, 1000 and 2150 mg/kg bw of APFO was administered to CD rats by gavage. Oral median lethal doses (LD50) of 680 mg/kg bw for male rats and 430 mg/kg bw for female rats were calculated (Dean&Jessup, 1978). The study was, however, not performed according to the OECD test guidelines (TG). Glaza (1997) reported an oral LD50 > 500 mg/kg in male rats and between 250 and 500 mg/kg in females.

In a guinea pig oral acute study, LD50s of 178 (male) and 217 (female) were reported. No details on doses or the mode of administration (dietary or gavage) are available (Du Pont, 1981).

Dermal

The chemical PFOA and its ammonium salt have low acute dermal toxicity. In an acute dermal study, one dose of 2000 mg/kg APFO (aqueous paste) was applied to clipped intact skin of New Zealand White rabbits (five/sex/group). Clinical observations and mortality checks were made at approximately 1, 2.5, and 4 hours after test material application, and twice daily thereafter for 14 days. All animals appeared normal and exhibited body weight gains throughout the study. The dermal LD50 was determined to be greater than 2000 mg/kg (Glaza, 1995). Dermal LD50s of 4300 mg/kg in rabbits, 7000 mg/kg in male rats and 7500 mg/kg in female rats have been reported (Kennedy, 1985).

Inhalation

The chemical APFO has moderate acute inhalation toxicity. In male CD rats the median lethal concentration (LC50) was 0.98 mg/L. Rats (six/sex/group) were exposed to APFO dust inhalation (head only) for four hours. The concentrations of APFO ranged from 0.38 to 5.7 mg/L. All deaths occurred within 48 hours (Kennedy et al., 1986). However, an earlier inhalation toxicity study (Rusch, 1979) reported no mortality in male or female SD rats following inhalation exposure to 18.6 mg/L of PFOA powder. Exposure in this study was only for one hour (full details of the two studies are not available).

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

The chemical PFOA is not a skin irritant. In an occluded skin irritation study, 0.5 g of APFO (aqueous paste) was applied to the shaved intact skin of six male White New Zealand rabbits for 24 hours. Signs of dermal irritation were observed for up to 24 hours after the patches were removed (48 hours after dose application). The chemical APFO caused mild erythema (colour

deep pink) in three rabbits and moderate erythema (redness deepened, dose-site outline sharp) in three rabbits. Of the six rabbits, four had evidence of mild oedema at 24 hours. At 48 hours, the reactions were still present although the degree and number of affected animals were reduced (erythema - 2 moderate, 3 mild and 1 slight; oedema – 1 mild, 2 slight and 3 not present) (Hazleton, 1990).

In another study (Griffith & Long, 1980), 0.5 mg/kg of APFO as powder was applied to the dry and moistened abraded skins of rabbits. The skin test sites were scored according to the Draize method, 24 hours and 48 hours after application. No irritation was observed. The primary skin irritation score was zero.

However, the data on APFO cannot be extrapolated to indicate that strongly acidic PFOA is a non-irritant.

Eye Irritation

APFO is a slight ocular irritant in rabbits. In an eye irritation study, not performed according to OECD test guidelines, 0.1 gram of APFO was applied to the eyes of six albino rabbits as a single dose. The eyes were examined 1, 24, 48 and 72 hours and five and seven days after installation. Installation of APFO caused moderate corneal opacity, iritis, and conjunctivitis. The effect was most pronounced at the one hour reading (mean score 14, highest possible score 110). The irritation was persistent for up to day seven (Griffith & Long, 1980).

In a subsequent washout study, the eyes of rabbits were washed five or 30 seconds after administering 0.1 g APFO into the corner of the eyes. The ocular effects were limited to conjunctival irritation. The eyes washed after five seconds had a maximum score of 5.3 noted at 72 hours and after five and seven days. The mild conjunctival effects were immediate and persistent (ECHA, 2010).

However, the data on APFO cannot be extrapolated to indicate that strongly acidic PFOA is a non-irritant.

Sensitisation

Skin Sensitisation

The chemical PFOA is not considered to be a skin sensitiser. In a dermal sensitisation test in guinea pigs (Buehler test), PFOA/APFO gave negative results (Moore, 2001). Details of the study are not available.

Repeated Dose Toxicity

Oral

Oral repeated-dose studies in rats and monkeys with APFO demonstrated that the liver is the primary target organ. Non-human primates were more sensitive to APFO than rodents. In rats, due to gender differences in elimination (see **Toxicokinetics**), adult male rats exhibited effects at lower doses than adult female rats (Griffith & Long, 1980).

In a 90-day oral repeated dose study, ChR-CD rats (five/sex/group) were fed 0, 10, 30, 100, 300 and 1000 ppm APFO, corresponding to 0, 0.6, 1.7, 5.6, 17.9 and 63.5 mg/kg bw/day in males and 0, 0.74, 2.3, 7.7, 22.4, 76.5 mg/kg bw/day in females. No treatment-related changes in behaviour and appearance, or in the haematologic, biochemical or urine parameters were reported. In males, a statistically significant decrease in body weight was reported at 1000 ppm. Absolute and relative liver weights were significantly increased in males from 30 ppm and in females only at 1000 ppm. Liver hypertrophy and hepatocellular necrosis were reported in the 30,100, 300 and 1000 ppm groups, respectively. A lowest observed adverse effect level (LOAEL) of 1.7 mg/kg bw/day and a no observed adverse effect level (NOAEL) 0.6 mg/kg bw/day were established based on liver effects (Goldenthal, 1978 a).

In a second 90-day study, ChR-CD male rats were fed APFO at 0, 0.06, 0.64, 1.94 and 6.50 mg/kg bw/day for 13 weeks. Significant increases in absolute and relative liver weights and hepatocellular hypertrophy were reported at weeks four, seven

and 13 in the 0.64, 1.94 and 6.50 mg/kg bw/day groups. There was no evidence of any degenerative changes or abnormalities associated with hypertrophy. Hepatic palmitoyl CoA oxidase activity (indicating peroxisome proliferation) was significantly increased at weeks four, seven and 13 in the 30 and 100 ppm groups. At 0.64 mg/kg bw/day, hepatic palmitoyl CoA oxidase activity was significantly increased at week 4 only. During the recovery period, in which a control diet was fed to the rats, none of the liver effects were reported, indicating that these treatment-related liver effects were reversible (Palazzolo, 1993). An LOAEL of 0.64 mg/kg bw/day and an NOAEL 0.06 mg/kg bw/day were established, based on increases in absolute and relative liver weights with hepatocellular hypertrophy.

In an oral repeated dose study in rhesus monkeys (two/sex/group), APFO was administered by gavage at doses of 0, 3, 10, 30 and 100 mg /kg bw/day for 90 days. All monkeys in the 100 mg/kg bw/day and three monkeys in the 30 mg/kg bw/day group died during the study. Clinical signs (anorexia, pale and swollen face, black stools, marked diarrhoea) were reported in the 3 and10 mg/kg bw/day groups, although no changes in body weights were reported in these animals. Changes in absolute and relative weights of the heart and brain were reported in female rats from 10 mg/kg bw/day upwards. In males, altered pituitary weights were reported at and above 3 mg/kg bw/day. However, no morphological changes were reported in these organs.

The males in the 30 mg/kg bw/day group that survived had slight to moderate hypocellularity of the bone marrow and moderate atrophy of lymphoid follicles in the spleen. Under the conditions of this study, the LOAEL was 3 mg/kg bw/day and no NOAEL was established (Goldenthal, 1978 b).

Dermal

The Crl:CD male rats were dermally exposed to 20–2000 mg/kg bw APFO, 6 hours/day, 5 days/week for two weeks (ten applications). Skin irritation and reversible reductions in body weight were observed at doses of 200 mg/kg bw and above. Increased liver weight, increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT), as well as hepatocellular hypertrophy and necrosis were observed at doses of 20 mg/kg bw/day and above. Affected livers contained one or more foci of coagulative necrosis. The Kupffer cells within the foci of hepatocellular necrosis contained large vesicular nuclei and were markedly increased in number. Inflammatory cells were occasionally present within, and at the periphery of, the necrotising lesions. All of the treatment related toxicity findings resolved during a 42-day recovery period. A NOAEL could not be established in this study as effects were seen at all doses (Kennedy, 1985).

Inhalation

In the only available inhalation repeated dose study (Kennedy et al., 1986), Crl:CD male rats were exposed to 0, 1, 8 or 84 mg/m^3 APFO (head only exposure) for 6 h/day, 5 days per week, for two weeks followed by a 28–84-day recovery period. Concentrations of organofluorine in the blood showed a dose relationship; with initial levels of 108 ppm in rats treated at 84 mg/m^3 and falling to 0.84 ppm after the 84-day recovery period (blood half-life of 5–7 days). Mortality was reported in the highest dose group. Reversible liver weight increases, reversible increases in serum enzyme activities and microscopic liver pathology, including necrosis, occurred at the two higher doses. No ocular changes were reported. The authors of the study considered the hepatocellular necrosis to be treatment related since hepatocellular necrosis is rarely encountered as a spontaneous lesion in young male rats. The NOAEL was established as 1 mg/m^3.

Observation in humans

Several epidemiological and medical surveillance studies have been conducted by 3M and Dupont on workers employed at their various APFO manufacturing sites in the United States of America (USA). Most of the studies were cross-sectional and focused primarily on males.

A retrospective cohort mortality study was performed on employees at the 3M Cottage Grove, Minnesota plant that produced APFO (Gilliland & Mandel, 1993). Standardised mortality ratios (SMRs), adjusted for age, sex, and race were calculated and compared with USA and Minnesota white death rates. The SMRs for males were stratified for three latency periods (10, 15, and 20 years) and three periods of employment duration (5, 10, and 20 years). For all female employees, the SMRs for death by all causes and for all cancers were less than one. In all male workers at the plant, the SMRs were close to one for most of the causes of death when compared with both the USA and Minnesota death rates.

Another retrospective cohort mortality study demonstrated a statistically significant association between prostate cancer mortality and employment duration in the chemical facility of a plant that manufactured 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. To investigate endocrine effects of PFOA, medical surveillance data, including hormone testing, from male employees only from the Cottage Grove, Minnesota plant, were analysed (Olsen et al., 1998). PFOA was not highly correlated with any hormones or with the covariates of age, alcohol consumption, body mass index (BMI) or cigarettes. Most of the employees had PFOA serum levels less than 10 ppm. The study reported an increase in oestradiol levels in workers with the highest PFOA serum levels; however, the difference was not statistically significant ($p < 0.05$) and the results were believed to have been confounded by body mass index.

Cholesterol and triglyceride levels in workers were positively associated with PFOA exposures, which is inconsistent with the hypolipidaemic 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.

Genotoxicity

The chemical APFO is not mutagenic. It did not induce mutation in either *Salmonella typhimurium* or *Escherichia coli* when tested either with or without metabolic activation. The chemical APFO did not induce gene mutation when tested with or without metabolic activation in Chinese hamster ovary (CHO) cells (Murli, 1996 b, 1996 d); or chromosomal aberrations in human lymphocytes when tested with and without metabolic activation up to cytotoxic concentrations (Murli, 1996 c). The chemical APFO was tested twice for its ability to induce chromosomal aberrations in CHO cells. In the first assay, APFO induced 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 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 C3H 10T1/2 mouse embryo fibroblasts (Garry & Nelson, 1981) and in the mouse micronucleus assay (Murli, 1995, 1996 a).

Carcinogenicity

There is limited evidence of carcinogenic effects of PFOA in animals.

The carcinogenic potential of PFOA was investigated in two dietary studies in rats. In the first study (Sibinski, 1987), SD (Crl:CD BR) rats were fed diets containing 0, 30 or 300 ppm APFO for two years. Additional rats were fed 0 or 300 ppm APFO and evaluated at a one-year interim sacrifice.

There were no differences in mortality between the treated and untreated groups. Histological evaluations showed lesions in the liver, testis and ovary. In the liver, in the high-dose males, diffuse hepatomegalocytosis, portal mononuclear cell infiltration and hepatocellular necrosis were seen at the one year interim sacrifice and megalocytosis was observed in the high-dose euthanised males at the end of the study.

At the one-year evaluation sacrifice, testicular masses were found in 6/50 high-dose and 1/50 low-dose rats, but not in any of the controls. At the two-year evaluation, vascular mineralisation of the testes occurred in 18 % of the high-dosed males and 6 % of the low-dosed males, but was not seen in the controls. These testicular effects reached statistical significance in the high-dose group. At the termination of the study, there was a significant increase ($P < 0.05$) in the incidence of testicular (Leydig) cell adenomas in the high-dose male rats.

Dose-related increases in the incidence of ovarian tubular hyperplasia were found in female rats at the two-year evaluation. Using more recently published nomenclature, the ovarian lesions were diagnosed and graded as gonadal stromal hyperplasia and/or adenomas (Mann & Frame, 2004). There were also significant increases ($P < 0.05$) in the incidence of mammary fibroadenomas in both groups of female rats. However, this was not considered to be treatment-related on the basis of the historical control incidence (24%) from an earlier study.

The induction of Leydig cell tumours (LCT) was confirmed in a follow-up two-year mechanistic study of PFOA toxicity in male SD rats (Cook et al., 1994; Biegel et al., 2001). There was a significant increase in the incidence of LCT in the PFOA-treated rats (300 ppm) (11 %) compared with the controls. In addition, the treated group had significant increases of liver adenomas incidences (13 %) and pancreatic acinar cell tumours (PACT) (9 %).

A review of the pancreatic microscopic lesions in the two studies indicated that PFOA produced an increased incidence of proliferative acinar cell lesions in the rats at the dietary concentration of 300 ppm. The modes of carcinogenic action of PFOA-induced LCTs and PACT have not been fully elucidated (Klaunig et al., 2004). However, there is ample evidence that the liver tumours in rats are due to a peroxisome proliferator-activated receptor alpha (PPARa)-agonist mode of action (ECHA, 2010).

The induction of Leydig cell adenomas is considered to involve a hormonal mechanism, whereby PFOA either inhibits testosterone biosynthesis and/or increases serum oestradiol by inducing hepatic aromatase activity. The induction of pancreatic acinar cell tumours is considered to be related to an increased level of the growth factor, cholecystokinin (CCK) in serum, which appeared to be secondary to changes in the liver (ECHA, 2010).

The 3M company and Dupont have conducted several epidemiological and medical surveillance studies of the workers at their plants in various cities of the USA. No adverse health effects that can be directly attributed to PFOA exposure have been reported in fluorochemical production workers described in the studies above (**Repeated dose toxicity, oral**) (OECD, 2006).

Reproductive and Developmental Toxicity

PFOA did not have any effect on fertility parameters in rats. In an oral two-generation reproductive toxicity study conducted in rats (Butenhoff et al., 2004), five groups of SD rats (30/sex/dose group) were administered APFO by gavage at doses of 0, 1, 3, 10, and 30 mg/kg-day, six weeks before and during mating. Treatment of the parent (F0) male rats continued until mating was confirmed, and treatment of the F0 female rats continued throughout gestation, parturition, and lactation. The first generation (F1) rats were given the same dosage level of the test substance and in the same manner as their respective F0 sires and dams.

No effects on the reproductive parameters (fertility index, gestation index, number of implantation sites, litter size and viability, lactation index) were observed in F0 or F1 rats, although significant decreases in body weight and an increase in mortality were noted in F1 males and females, mainly during the first few days after weaning. Dosing with APFO resulted in a delayed onset of sexual maturation in both male and female F1 offspring. When the body weight was co-varied with the time to sexual maturation, the time to sexual maturation showed a statistically significant dose-related delay. No treatment-related adverse effects were observed in the second generation (F2) offspring at any doses.

Due to the lack of effects on fertility parameters in the 2-generation study and lack of effects on the reproductive organs in experimental animal studies in males and females with durations up to 90 days (**Repeat dose toxicity**), no classification for fertility is proposed. However, in a chronic/carcinogenicity 2-year rat study (Sibinski, 1987), testicular and ovarian effects were noted and have been discussed in the **Carcinogenicity** section of this report.

Several prenatal developmental toxicity studies of PFOA have been conducted in mice, rats and rabbits. These studies indicated adverse effects of PFOA on the development of these animals.

In a developmental toxicity study that consisted of separate inhalation and oral exposure portions, each with two trials, SD rats were administered 0 and 100 mg/kg-day APFO in corn oil by gavage on gestation days (GD) 6–15 (oral exposure), or exposed to 0, 0.1, 1, 10, and 25 mg/m^3 APFO dust (whole-body) for 6 hours/day, on GD 6-15 (inhalation exposure). In the first trial of both oral and inhalation exposures, the dams were sacrificed on GD 21; while in the second trial, the dams were allowed to produce pup litters which were sacrificed on day 35 after birth (Staples et al., 1984).

In trial one of the inhalation portion of the study, significantly reduced food consumption and body weights were observed in rats exposed to APFO from inhalation exposure, at doses 10 and 25 mg/m^3. Three out of 12 dams died during treatment at 25 mg/m^3. Treatment-related clinical signs of maternal toxicity, such as a wet abdomens, chromodacryorrhoea, chromorhinorrhoea and lethargy occurred at these doses at the end of the exposure period. Statistically significant increases in mean liver weights were seen in the high-concentration group. Under the conditions of the study, the NOAEL and LOAEL for maternal toxicity of 1 and 10 mg/m^3, respectively, were indicated.

No effects were observed on the maintenance of pregnancy or the incidence of resorptions. Mean foetal body weights were significantly decreased in the 25 mg/m^3 groups. However, interpretation of the decreased foetal body weight is difficult given the high incidence of mortality in the dams. Under the conditions of the study, the NOAEL and LOAEL for developmental toxicity of 10 and 25 mg/m^3, respectively, were indicated.

In trial two of the inhalation study, clinical signs of maternal toxicity seen at 10 and 25 mg/m^3 were similar in type and incidence to those described for trial one. Signs of developmental toxicity in this group consisted of statistically significant reductions in pup body weight on the first day after birth. No significant effects were reported following external examination of the pups or with ophthalmoscopic examination of the eyes. Again, interpretation of these effects is problematic given the high incidence of maternal mortality. Under the conditions of the study, the NOAEL and LOAEL for developmental toxicity of 10 and 25 mg/m^3, respectively, were indicated.

In the oral exposure portion of the study, reduced food consumption and body weight were observed in treated dams in both the trials. Clinical signs of maternal toxicity in the dams were noted similar to those seen with inhalation exposure. No adverse signs of toxicity were noted for any of the reproductive parameters, such as maintenance of pregnancy or incidence of resorption. No significant adverse effects on offspring development were observed in either trial.

In a developmental toxicity study in New Zealand White rabbits (Gortner, 1982), administration of APFO (0, 1.5, 5 and 50 mg/kg/day) during gestation did not appear to affect the ovaries or reproductive tract contents of the does. No clinical signs were reported and no significant differences were noted between controls and treated groups for the number of male and female foetuses, dead or live foetuses, or foetal weights. There were no differences reported for the number of resorption and implantation sites, corpora lutea, the conception incidence, abortion rate, or the 24-hour mortality incidence of the foetuses. Gross necropsy and skeletal/visceral examinations were unremarkable. The only sign of developmental toxicity consisted of a dose-related increase in a skeletal variation, extra ribs or 13th rib, with statistical significance in the high-and mid-dose groups (38 % at 50 mg/kg/day, 30 % at 5 mg/kg/day). Therefore, under the conditions of the study, an LOAEL for developmental toxicity of 5 mg/kg/day was indicated.

In a developmental toxicity study in mice (Lau et al., 2005), groups of pregnant CD-1 mice were given 0, 1, 3, 5, 10, 20, or 40 mg/kg APFO daily by oral gavage on GD 1–17. Statistically significant reductions in bodyweight gain occurred in the two highest dose groups. No changes in the number of implantations were reported. However, statistically significant increases in the incidence of full litter resorption from 5 mg/kg bw/day upwards were reported. The number of live foetuses per litter was significantly reduced at 20 mg/kg bw/day. Foetal body weights were significantly decreased at 20 mg/kg bw/day and reduced ossification of sternebrae, caudal vertebrae, metacarpals, metatarsals, phalanges, calvaria, supraoccipital and hyoid as well as an enlarged fontanelle were reported in the 10 and 20 mg/kg bw/day dose groups.

The incidences of stillbirth and neonatal mortality were markedly increased in the 10 and 20 mg/kg bw/day dose groups. Most pups from these groups did not survive the first day of life. In the two lowest dose groups, postnatal survival was comparable to controls; however, among the survivors, a trend towards growth retardation was noted leading to 25–30 % lower bodyweights in pups in the 3 mg/kg bw/day group, at weaning. Significant delays in eye opening, by as much as three days, was noted in pups from 5 mg/kg bw/day upwards. The onset of puberty of male pups was markedly advanced. The preputial separation in the 1 mg/kg bw/day dose group was almost four days earlier than in control pups, and this accelerated pubertal onset took place despite a body weight reduction of 25–30 %. No acceleration in female pubertal onset was reported. The LOAEL of 1 mg/kg bw/day is based on increases in the onset of sexual maturation in males. No NOAEL for developmental effects could be determined.

In two studies by White et al. (2007, 2009), the effects of PFOA on the development of the mammary gland following gestational exposure was reported. A significant reduction in mammary gland differentiation among dams exposed to PFOA during GD 1–17 or 8–17 was evident on post-natal day (PND) 10. On PND 20, delays in normal epithelial involution and alterations in milk protein gene expression were observed. All exposed female pups displayed stunted mammary epithelial branching and growth at PND 10 and 20, while control litters had average mammary gland development at these time points. Intrauterine exposure during the final days of pregnancy caused adverse mammary gland developmental effects similar to those of extended gestational exposures (ECHA, 2014).

In conclusion, based on the increased postnatal pup mortality, decreased pup body weight and delayed sexual maturation observed in several mouse studies, as well as pup skeletal variations in the rabbit study, in the absence of marked maternal toxicity, a classification of APFO for developmental effects is proposed.

Other Health Effects

Endocrine Disruption

Human epidemiological findings, together with animal studies, indicate a PFOA-mediated effect on the endocrine system (ECHA, 2014 b). There are several studies suggesting that PFOA can alter steroid hormone production (Zhao et al., 2012) or act indirectly, via ovarian effects, as a means of endocrine disruption (Dixon et al., 2012). Oestrogen or progesterone supplements reversed the PFOA-inhibitory effect on mammary glands in one study (Zhao et al., 2012). The low dose effect on uterine weight and histopathological changes to the uterus, cervix and vagina have been shown in immature CD-1 mice (Dixon et al., 2012). PFOA can thus act as a so-called obesogene similar to other endocrine disruptive compounds (EDCs) that can act directly on ligands for nuclear hormone receptors or affect components in metabolic signalling pathways (ECHA, 2014 b).

Risk Characterisation

Critical Health Effects

The chemicals PFOA and APFO have moderate acute toxicity from oral exposure and low to moderate toxicity from inhalation exposure. They are moderately irritating to the eyes and non-irritating to the skin of rabbits.

Increased mortality and liver toxicity were reported in mice, rats and monkeys following repeated oral exposure to APFO, and in rats following inhalation exposure. Hepatocellular hypertrophy, degeneration and focal to multifocal necrosis were reported with increasing severity between oral doses of 1.5–15 mg/kg bw/day in rats and mice.

In two carcinogenicity studies, APFO induced liver adenomas, Leydig cell adenomas and pancreatic acinar cell tumours in SD rats. The evidence indicates that APFO is a PPARa agonist and that the liver carcinogenicity (and toxicity) of APFO is mediated by binding to the PPARa in the liver in rodents. However, the available data are insufficient to characterise the mode of action for APFO-induced Leydig cell adenomas and pancreatic acinar cell tumours.

Several epidemiological and medical surveillance studies of the workers at 3M plants in various cities of the USA could not establish a link to PFOA exposure and cancer incidence. The evidence of PFOA carcinogenicity is therefore regarded as limited.

The chemicals PFOA or APFO did not have any effect on fertility parameters in rats. In several mouse studies, as well as in the rat two-generation study, increased postnatal pup mortality, decreased pup body weight and delayed sexual maturation was observed in the absence of marked maternal toxicity. Studies in mice suggested that the postnatal developmental toxicity of APFO was mainly due to gestational exposure and that exposure earlier in gestation produces stronger responses. However, there are questions relating to the human relevance of some of these findings. It is possible that the developmental effects of PFOA observed in mice may be, at least partly, mediated via mechanisms not relevant for humans, for instance through the peroxisome proliferator-activated receptor (PPAR). Mechanistic studies have shown that some of the effects of PFOA were either absent or attenuated in PPAR-knockout mice when compared to the wild-type (Abbott et al., 2007; Albrecht et al., 2013), raising the possibility that these effects are mediated through the PPAR pathway, not present in humans. However, currently there is no experimental evidence that the developmental effects observed in experimental animals are mediated via the PPAR pathway. In the absence of such evidence, the harmonised classification for developmental toxicity of PFOA is considered appropriate. However, there are questions relating to the human relevance of some of these findings. It is possible that the developmental effects of PFOA observed in mice may be, at least partly, mediated via mechanisms not relevant for humans, for instance through the peroxisome proliferator-activated receptor (PPAR). Mechanistic studies have shown that some of the effects of PFOA were either absent or attenuated in PPAR-knockout mice when compared to the wild-type (Abbott et al., 2007; Albrecht et al., 2013), raising the possibility that these effects are mediated through the PPAR pathway, not present in humans. However, currently there is no experimental evidence that the developmental effects observed in experimental animals are mediated via the PPAR pathway. In the absence of such evidence, the harmonised classification for developmental toxicity of PFOA is considered appropriate.

Public Risk Characterisation

Given the uses identified for these chemicals, it is unlikely that the public will be exposed. Hence, the public risk from these chemicals is not considered to be unreasonable. While long-term studies in animals show adverse effects, epidemiological studies in workers exposed to these chemicals do not provide clear evidence of effects in humans, and exposure of the general public to similar levels is not expected.

Secondary exposure via the environment

Public exposure to PFOA or APFO could occur through secondary exposure via the environment. It is noted that these chemicals can be present in the environment due to historic use, or due to release from articles or using chemicals not covered by this assessment. The chemical PFOA and its salts are persistent in the environment and in humans with a half-life of years. Blood monitoring data suggested widespread exposure of the general population to PFOA and APFO, albeit at low levels (US EPA, 2005).

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also

occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical acute and systemic long-term health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise ocular and inhalation exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation.

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Harmful by inhalation (Xn; R20)	Toxic if swallowed - Cat. 3 (H301) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)	Causes serious eye irritation - Cat. 2A (H319)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23) Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372) Causes damage to organs through prolonged or repeated exposure if swallowed - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)	May damage fertility or the unborn child - Cat. 1B (H360D)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical[s], if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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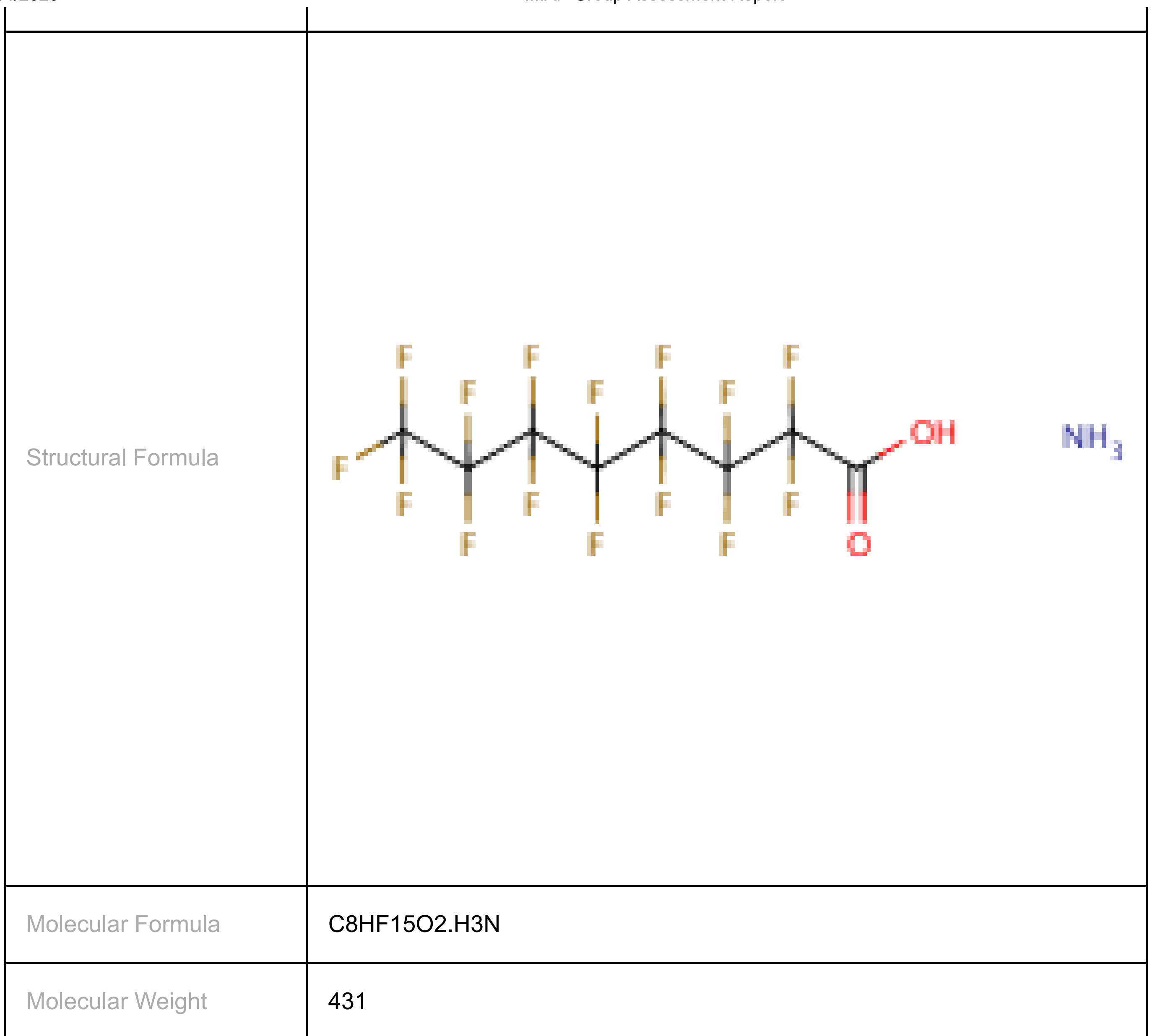
Last Update 13 February 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Octanoic acid, pentadecafluoro-** pentadecafluoro-1-octanoic acid pentadecafluorooctanoic acid perfluorooctanoic acid PFOA
CAS Number	335-67-1
Structural Formula	F F F F F F F O / F / F F F F F F F OH
Molecular Formula	C8HF15O2
Molecular Weight	414

Chemical Name in the Inventory and Synonyms	**Octanoic acid, pentadecafluoro-, ammonium salt** ammonium pentadecafluorooctanoate pentadecafluoro-1-octanoic acid, ammonium salt perfluorooctanoic acid, ammonium salt ammonium PFOA APFO
CAS Number	3825-26-1

Structural Formula	
Molecular Formula	C8HF15O2.H3N
Molecular Weight	431

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