Perfluoroheptanoic acid and its direct precursors: Human health tier II assessment

21 April 2016

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Heptanoic acid, tridecafluoro-	375-85-9
Heptanoic acid, tridecafluoro-, ammonium salt	6130-43-4

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**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are perfluoroheptanoic acid (PFHpA, a perfluorocarboxylic acid) and its ammonium salt. The chemicals contain six perfluorinated carbons terminated with a carboxylate group. The chemicals are expected to dissociate to the perfluoroheptanoate anion in the blood and aquatic environment.

Structurally, these substances are intermediate to the long-chained perfluorinated carboxylates, containing seven or more perfluorinated carbon atoms (including perfluorooctanoic acid; PFOA), and the short-chained perfluorinated carboxylates (containing five or less perfluorinated carbon atoms). Available data indicate that the shorter-chain perfluorinated carboxylic acids (PFCAs) (containing five or less perfluorinated carbons) have potentially better human health outcomes and bioaccumulation profile than long-chain perfluoroalkyl substances. Chronic low-level effects on human health have not been identified (NICNASa). However,

it is not currently clear whether the hazards for the intermediate chain-length acids are comparable to the homologous long-chain or to the short-chain perfluorinated carboxylic acids in this series.

NICNAS has developed an action plan to assess and manage chemicals that could degrade to perfluorinated carboxylic acids, perfluoroalkyl sulfonates and similar chemicals, which can be found in Appendix G of the *Handbook for notifiers* on the NICNAS website (NICNASb). Under this action plan, PFOA hazard information is used to estimate the hazard of PFCA degradation products, unless sufficient toxicological data are available to demonstrate a lower toxicity profile. Data for the critical effects of bioaccumulation and hepatotoxicity, developmental toxicity and carcinogenicity need to be provided to demonstrate that a lower toxicity profile than PFOA applies to these chemicals.

This assessment will evaluate:

- the properties of the chemicals in this group and compare them with short- and long-chain homologues; and
- whether there are sufficient data to use in place of the default assumptions of the action plan.

Assessing these chemicals as a group provides additional relevant information for assessing the risk of more complex polyfluorinated substances (indirect precursors) containing six perfluorinated carbons that could degrade to perfluoroheptanoate in the environment. These more complex derivatives of PFHpA will be assessed separately under IMAP.

Import, Manufacture and Use

Australian

Information collected by NICNAS in 2006 indicated that these chemicals were not manufactured, imported or used in Australia at that time. However, this information could be incomplete because the call for information did not specifically include the chemicals in this group (NICNAS, 2013).

It is noted that these chemicals could be present in the environment due to historic use, or due to release from articles or using precursor chemicals not covered by this assessment.

International

Limited data are available for PFHpA. Available data suggest historic use of the chemical, with use reported in 1999 and 2000 in Sweden (SPIN). Similarly, limited current data were identified for ammonium PFHpA. Available information suggests that it could be used intentionally as a surfactant in manufacturing fluorocopolymers (Enokida, et al., 2000; Kanega, et al, 2008). The chemicals are pre-registered under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation, but have not been registered under the REACH legislation at the time of assessment. No evidence of the presence of these chemicals in consumer products was found in available North American databases (Household Products Database and Personal Care Council), indicating that the chemicals are not likely to be widely available for domestic or cosmetic uses.

Perfluoroheptanoic acid has been reported as a breakdown product or residual starting material in a number of products in a number of sources (DK EPA, 2008; US EPA, 2009; Hamilton and Hardy's Industrial Toxicology, 2015; Human Toxome Project, 2015; Galleria Chemica):

- impregnating products used by dry cleaners and for shoes;
- stain- and grease-proof coatings on food packaging;
- household textiles and textile care liquids;
- floor waxes and stone/tile/wood sealants;
- non-stick cookware;
- dental floss and plaque removers; and
- carpets.

Restrictions

Australian

No known mandatory restrictions have been identified for these chemicals.

International

No known mandatory restrictions have been identified for these chemicals.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Limited toxicological data are available. The toxicity of the chemicals in this group is expected to be intermediate between PFHxA and PFOA. Whilst toxicokinetic data (see **Toxicokinetics** section) indicate similar mechanisms of elimination to shorter-chain PFCAs, total clearance in animals and humans decreases with increasing chain length, and longer bioelimination half-lives in humans compared with shorter-chain PFCAs have been reported (although the extent of the increase is uncertain). Data for the critical effects of hepatotoxicity, developmental toxicity and carcinogenicity are not available for the chemicals. In the absence of data,to meet the requirements of the NICNAS action plan, data from PFOA and its ammonium salt (APFO) have been used to estimate the hazard of these chemicals (see **Grouping rationale** section). In addition, data for perfluorohexanoic acid (PFHxA) and ammonium perfluorohexanoate (PFHx) has been used to infer acute toxicity and local toxicity.

Toxicokinetics

Based on the available information, the chemicals of this group are expected to be rapidly absorbed and mainly eliminated in the urine in animals and humans. The renal elimination process for PFCAs is sex-, species- and chain-length- dependent.

In studies in mice and rats, PFHpA was shown to be rapidly eliminated in the urine. Total clearance in animals and humans decreases with increasing chain length, with the clearance rate for PFHpA higher than PFOA, but lower than PFHxA (Han et al., 2012; Fujii et al. 2015). Following intraperitoneal (i.p.) injection in Wistar rats, 92 % of a PFHpA dose was rapidly eliminated in urine within 120 hours after dosing (Kudo et al., 2001). Similar results were seen in NJcl mice administered PFHpA intravenously (i.v.) or by gavage. When administered intravenously, the chemical was rapidly and almost completely eliminated in the urine after 24 hours (99 % for males and 66 % for females) and only a small amount was excreted in faeces (3 % for males and 13 % for females). Gavage-administered animals showed similar clearance patterns to i.v. administered animals (Fujii et al., 2015).

Whilst dose-dependent accumulation was observed with PFHpA in the liver of male and female mice (Kudo et al, 2006), levels detected in the liver in this and other studies (Fujii, 2015), were significantly lower than those observed with PFOA. In Wistar rats, PFHpA was found to be below the detection limit (3 nmol/g liver) at doses up to 30 mg/kg body weight in both male and female rats (Kudo & Kawashima, 2003).

The half-life for PFHpA in female and male rats was reported as 1.2 and 2.4 hours, respectively, compared with 5.63 and 0.08 days for PFOA (Ohmori et al., 2003). The estimated half-life in humans has ranged from 70 days (in ski wax technicians) (Russell et. al. 2015) to 1.2 to 1.5 years (based on blood and urine samples from China) (Zhang, et al., 2013). Comparatively, the mean serum elimination half-life of PFOA in workers was 3.8 years (NICNASc), while the half life of PFHxA ranged between 14 and 49 days, with a geometric mean of 32 days (NICNASb). In various biomonitoring studies in humans, detection of PFHpA was typically below 0.1 ng/mL in the blood (Dong et al., 2013; Yeung et al., 2013; Zhang et al., 2013). A mean concentration of 4 ng/L was reported in the blood from ski wax technicians (Nilsson et al., 2013). In one study, PFHpA was not detected in

maternal sera, cord sera or human milk with the limit of detection (LOD) <0.26 ng/mL, <0.13 ng/mL and <4.45 pg/mL for maternal sera, cord sera or human milk, respectively (Kim et al., 2011). A geometric mean for serum concentrations for the American population from the National Health and Nutrition Examination Survey (2011–12) was not calculated, due to the significant portion of results below the limit of detection (0.1 ng/mL). The 95th percentile value in this survey was reported as 0.22 ng/mL (CDC, 2015).

Acute Toxicity

Oral

Based on the available data, the chemicals in this group are expected to have moderate toxicity following acute oral exposure.

An acute lethal dose of 670 mg/kg bw has been reported for PFHpA. Rats were administered the undiluted liquid in doses ranging from 300 to 3375 mg/kg. Necrosis of the stomach was observed in animals which died (unpublished study provided by Dupont Co.).

Both PFOA and PFHxA and their salts are also considered to have moderate toxicity following oral exposure, based on data for APFO and sodium PFHxA (NICNASa, NICNASc).

Dermal

Based on data for PFOA and APFO (NICNASc) and the ammonium PFHx (NICNASa), the chemicals in this group are expected to have low acute toxicity following dermal exposure.

Inhalation

Based on data for APFO (NICNASc), the chemicals in this group are expected to have moderate acute toxicity following inhalation exposure. In the absence of information, classification aligned with PFOA and APFO is considered warranted (see **Recommendation** section).

Corrosion / Irritation

Skin Irritation

Based on data for APFO (NICNASc) and ammonium PFHx (NICNASa), ammonium PFHp is likely to be, at most, mildly irritating to the skin. However, skin irritant and/or corrosive effects cannot be ruled out for PFHpA.

Eye Irritation

Ammonium PFHx is considered to be a severe eye irritant in rabbits (NICNASa). In the absence of information, hazard classification aligned with PFHxA and ammonium PFHx is considered warranted (see **Recommendation** section).

Sensitisation

Skin Sensitisation

Based on data for PFOA and APFO (NICNASc), the chemicals in this group are not considered to be skin sensitisers.

Repeated Dose Toxicity

Oral

Based on the available data on the analogue chemical APFO, the chemicals in this group are considered to have the potential to cause serious damage following repeated oral toxicity. Increased mortality and liver toxicity were reported in mice, rats and monkeys following repeated oral exposure to APFO. 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 (NICNASc). Although, based on toxicokinetic data, it is anticipated that effects in the liver would occur at higher doses for PFHpA and its salt compared with PFOA, in the absence of further information, classification aligned with PFOA and APFO is considered warranted (see **Recommendation** section).

Various studies have investigated the effects of PFHpA on liver enzymes. The maximum induction of peroxisomal beta-oxidation was assessed in Wistar rats (Kudo et al., 2000). A slight, but significant increase in liver beta-oxidation was induced by treatment with 160 mg/kg PFHpA, while a significant increase in liver beta-oxidation was detected following 10 mg/kg PFOA. The potency of induction of hepatomegaly, peroxisomal beta-oxidation and microsomal 1-acylglycerophosphocholine acyltransferase in the liver was investgated in mice (Kudo et al., 2006). Similarly to all PFCAs tested, PFHpA induced hepatomegaly and peroxisomal beta-oxidation. The potency of these effects is reported to increase with increasing chain length. The doses required to induce an approximately 1.7-fold increase in liver weight relative to body weight in male mice were >150, 50, 5, and 5 mg/kg for PFHxA, PFHpA, PFOA and perfluorononanoic acid (PFNA), respectively. Fischer-344 (F344) rats treated with PFHpA (150 mg/kg) showed no increase in hepatic peroxisomal fatty acyl CoA-oxidase (FAO) activity (an indicator of peroxisome induction) on days three or five post-treatment (Goecke-Flora & Reo, 1996). In Wistar rats, the activity of peroxisomal beta-oxidation was not affected at doses up to 30 mg/kg body weight in either male or female rats (Kudo & Kawashima, 2003). Peroxisomal beta-oxidation induction is considered to depend only on the number of PFCA molecules in hepatocytes, rather than the difference in their chemical structures (Kudo & Kawashima, 2003; Kudo et al., 2006).

Dermal

Limited data are available. Based on data for APFO (NICNASc), classification for repeated dose toxicity following dermal exposure is not considered warranted.

Inhalation

Liver toxicity, including hepatocellular necrosis, was observed, at low concentrations, in a repeated dose inhalation toxicity study with APFO (NICNASc). Although, based on toxicokinetic data, it is anticpated that effects in the liver would occur at higher doses for PFHpA and its salt compared with PFOA, in the absence of information, classification aligned with PFOA and APFO is considered warranted (see **Recommendation** section).

Genotoxicity

Based on the weight of evidence from the available data for shorter and longer chain PFCAs (NICNASa; NICNASc), the chemicals in this group are not considered to be genotoxic.

Carcinogenicity

In the absence of information, classification aligned with PFOA and APFO is considered warranted (see **Recommendation** section).

In two carcinogenicity studies, APFO induced liver adenomas, Leydig cell adenomas and pancreatic acinar cell tumours in Sprague Dawley (SD) rats. The chemical is a peroxisome proliferator-activated receptor-alpha (PPARa) agonist and the liver

carcinogenicity (and toxicity) could be mediated by binding to the PPARa in the liver in rodents. However, the available data are insufficient to characterise the mode of action for Leydig cell adenomas and pancreatic acinar cell tumours. Several epidemiological and medical surveillance studies of the workers at plants in various cities of the USA could not establish a link between PFOA exposure and cancer incidence. The evidence for PFOA carcinogenicity is therefore regarded as limited.

Wolf et al. (2012) showed an increase in activity of human and mouse PPARa, in vitro with PFHpA.

Reproductive and Developmental Toxicity

In the absence of information about effects on the reproductive system, classification aligned with PFOA and APFO is considered warranted (see **Recommendation** section).

In several mouse studies with APFO, as well as in a rat two-generation study, increased postnatal pup mortality, decreased pup body weight and delayed sexual maturation were observed in the absence of marked maternal toxicity. Studies in mice suggested that the postnatal developmental toxicity was mainly due to gestational exposure and that exposure earlier in gestation produces stronger responses. PFOA did not have any effect on fertility parameters in rats (NICNASc). Similar effects were observed with shorter-chain PFCAs, albeit at higher concentrations (NICNASa).

Other Health Effects

Endocrine Disruption

Human epidemiological findings, together with animal studies, indicate a PFOA-mediated effect on the endocrine system. There are several studies suggesting that PFOA can alter steroid hormone production or act indirectly, via ovarian effects (NICNASc). Similar effects cannot be ruled out for the chemicals in this group.

Risk Characterisation

Critical Health Effects

The toxicity profile of the chemicals in this group is expected to be intermediate to between those of PFHxA and PFOA. Data for the critical effects of hepatotoxicity following repeated exposure, developmental toxicity and carcinogenicity are not available for the chemicals. Therefore, there are insufficient data to use in place of toxicity data for PFOA. Based on toxicokinetic data, it is anticpated that long-term effects would occur at higher doses for PFHpA and its salt, compared with PFOA. However, a separate no-observed adverse effect level (NOAEL) cannot be established.

The critical health effects for risk characterisation include systemic long-term effects (hepatotoxicity and developmental toxicity) and acute effects (acute toxicity from oral and inhalation exposure). The chemicals can also cause eye irritation. Skin irritation and/or corrosive effects cannot be ruled out for PFHpA. The evidence for carcinogenicity is regarded as limited.

Public Risk Characterisation

Based on the available use information, the chemicals are not likely to be available for domestic or cosmetic uses. Hence, the public risk from direct use of these chemicals is not considered to be unreasonable.

Secondary exposure via the environment

Public exposure to the chemicals in this group could occur through secondary exposure via the environment. Currently reported blood levels are similar to levels found for PFHxA, which is more rapidly eliminated compared with PFHpA. This indicates that current exposure to PFHpA is generally low.

However, it is noted that these chemicals are persistent and potentially bioaccumulative. Chemicals which are persistent and bioaccumulative remain in the environment and accumulate in biota over an extended period of time, even if new emissions of the chemicals cease (NICNASd). In the absence of data which demonstrate a lower toxicity profile for PFHpA compared to PFOA, the chemicals in this group should be assumed to be of equivalent concern to PFOA in accordance with the action plan. However, the action plan outlines the type of information that would be required to make a more definitive conclusion as to the toxicity of the chemicals relative to PFOA. If such information becomes available, this would be assessed as part of a Tier III assessment.

The chemicals in this group have been assessed as having the potential to give rise to adverse outcomes for the environment and have been recommended for further risk management as part of the IMAP Tier II Environment assessment report for these chemicals (NICNASd). The risk from release of the chemicals from indirect precursors of PFHpA will be determined as part of a separate IMAP assessment.

Occupational Risk Characterisation

During product formulation, exposure to the chemicals may 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 systemic long-term and systemic acute health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalational 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.

A Tier III assessment may be required if sufficient health hazard information as outlined in the action plan becomes available.

The chemicals in this group have been assessed as having the potential to give rise to adverse outcomes for the environment and have been recommended for further risk management as part of the IMAP Tier II Environment assessment report for these chemicals (NICNASd).

Regulatory Control

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. If data on the individual group members becomes available, these should be used to determine individual classifications.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]

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Acute Toxicity	Harmful if swallowed (Xn; R22) Harmful by inhalation (Xn; R20)	Harmful if swallowed - Cat. 4 (H302) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)
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 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 industry

Control measures

Control measures to minimise the risk from 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;
- 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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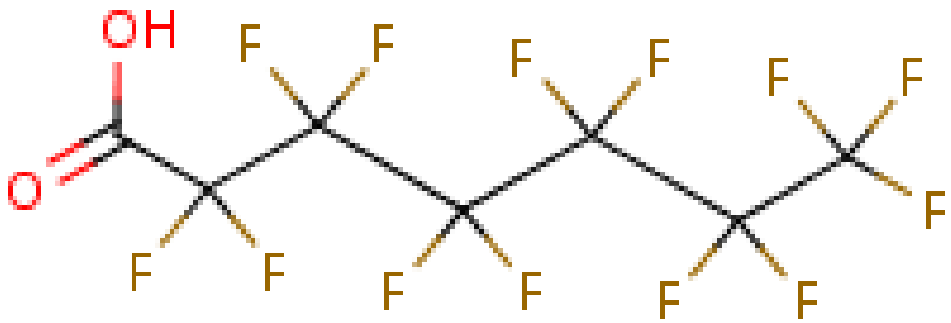
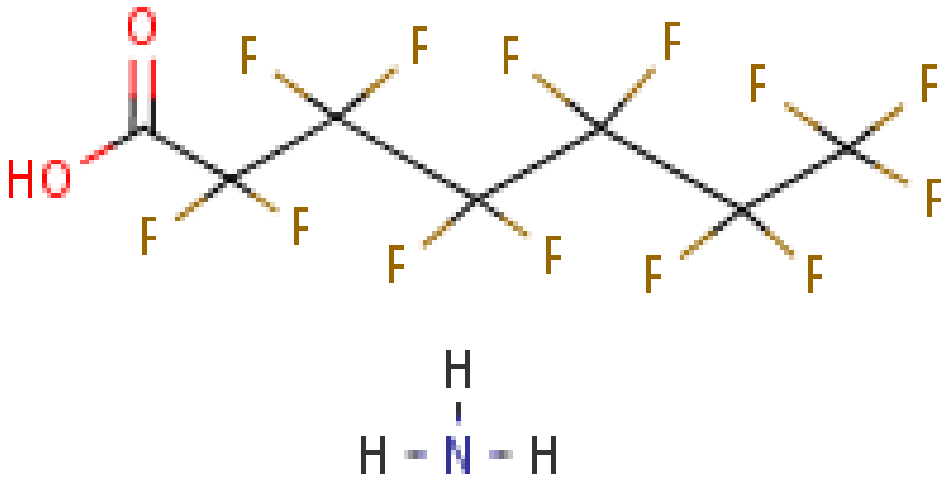
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Heptanoic acid, tridecafluoro-** tridecafluoro-1-heptanoic acid perfluoroheptanoate PFHpA IPC-PFFA-7 C7-PFA
CAS Number	375-85-9
Structural Formula	
Molecular Formula	C7HF13O2
Molecular Weight	364

Chemical Name in the Inventory and Synonyms	**Heptanoic acid, tridecafluoro-, ammonium salt** Tridecafluoroheptanoic acid, ammonium salt Perfluoro-n-heptanoic acid ammonium salt Ammonium perfluoroheptanoate
CAS Number	6130-43-4

Structural Formula	
Molecular Formula	C7HF13O2.H3N
Molecular Weight	381

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