Short chain perfluorocarboxylic acids and their direct precursors: Human health tier II assessment

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Hexanoic acid, undecafluoro-	307-24-4
Butanoic acid, heptafluoro-, anhydride	336-59-4
Butanoic acid, heptafluoro-	375-22-4
Pentanoic acid, nonafluoro-	2706-90-3
Hexanoic acid, undecafluoro-, ammonium salt	21615-47-4
Pentanoic acid, nonafluoro-, ammonium salt	68259-11-0

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 perfluorocarboxylic acids (PFCAs) and related chemicals containing three to five perfluorinated carbons, terminated with a carboxylate group. The chemicals have the potential to hydrolyse and/or dissociate into the perfluorobutanoate anion, perfluoropentanoate anion or perfluorohexanoate anions.

NICNAS has developed an action plan to assess and manage chemicals which may degrade to PFCAs, perfluoroalkyl sulfonates (PFASs) and similar chemicals, which can be found in Appendix G of the Handbook for Notifiers on the NICNAS website (NICNASa). Under this action plan, perfluorooctanoic acid (PFOA) hazard information is used to estimate the hazard of PFCA degradation products (with four or more perfluorinated carbons), 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 applies.

Shorter chain PFCAs have been developed and used by industry as alternatives to the long chain PFCAs (OECD, 2013). Data for perfluorohexanoic acid (PFHxA) and perfluorobutanoic acid (PFBA) are available, and therefore a toxicity profile that can be compared with that of PFOA can be developed for the members of this group.

This assessment will evaluate:

a) the relative hazard and risk of the chemicals in this group compared with PFOA; and

b) whether there are sufficient data to use in place of the default assumptions in the action plan.

It is noted that whilst the action plan does not apply to PFBA and its anhydride as they do not include a chain of four perfluorinated carbon atoms, PFBA could be formed by the degradation of indirect precursors of PFCAs (to be assessed separately (see below)) with four perfluorinated carbon atoms. In addition, toxicological data for PFBA can be used to help infer the properties of the intermediate perfluoropentanoic acid.

Perfluoroheptanoic acid (PFHpA) and its salts have not been included in this group. No toxicity information is available for PFHpA and it is not considered appropriate to extrapolate from PFHxA. The default position of using hazard information derived from PFOA therefore applies for PFHpA and it will be assessed separately.

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

The focus of this assessment will be bioaccumulation potential and systemic long-term effects. Data for acute and local effects have been included where available.

Import, Manufacture and Use

Australian

Information collected by NICNAS in 2006 indicated that PFHxA, perfluoropentanoic acid (PFPeA), and their derivatives are not currently imported or manufactured in Australia. However this information could be incomplete because the call for information did not specifically include the PFCAs group.

No specific Australian use, import, or manufacturing information was identified for PFBA and PFBA anhydride.

International

Limited specific international use, importation, or manufacturing information has been identified for the chemicals in this group. In general, the fluorochemical industry is developing short-chain PFOA replacement technology for fluoropolymer production (Ritter, 2010; OECD, 2013).

One chemical in this group (CAS No. 2706-90-3) is reported to be used as an intermediate (Galleria Chemica).

Available information indicates that PFHxA, perfluoropentanoic acid (PFPeA) and PFBA anhydride were in use between 1999 and 2002 in Nordic countries (SPIN). However, PFHxA is reported to not currently be manufactured for commercial use or used in fluoropolymer production (ENVIRON, 2014).

PFBA (CAS No. 375-22-4) and its anhydride (CAS No. 336-59-4) are used in the laboratory for acylation of alcohols, amino acids and other compounds. Derivatives are highly volatile and are used in gas chromatography separations.

Similarly, limited current data were identified for the salts in this group. The available information indicates that ammonium PFHxA could be used as a replacement for ammonium perfluorooctanoate in manufacturing fluorotelomers (Wang, et al., 2013).

All the chemicals in this group have been pre-registered under the Registration, Evaluation, Authorization and Restrictions of Chemicals (REACH) legislation. No chemicals in this group have undergone the full registration process for use in the European Union (EU) under the REACH legislation.

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.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

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 for any of the chemicals in this group.

International

No specific exposure standards are available for any of the chemicals in this group.

Health Hazard Information

While the focus of this assessment is to compare the toxicity of these chemicals with PFOA for certain endpoints (local effects and genotoxicity), where PFOA is inactive and there is no basis to suspect toxicological differences to exist, PFOA is used as an analogue for this assessment. Where data are not available for PFBA or PFPeA, PFHxA is considered a suitable analogue.

Toxicokinetics

Based on the available information, the chemicals of this group are expected to be rapidly absorbed by the gastrointestinal tract and eliminated mainly in the urine. Elimination of these chemicals is substantially faster in humans than perfluoroalkyls with longer carbon chain lengths (ATSDR, 2009; Russell et al., 2013).

Toxicokinetics and metabolism studies using the sodium salt of PFHxA (NaPFHx—CAS No. 2923-26-4 (not listed on the AICS)) have been conducted in mice, rats and monkeys following oral and intravenous administration (Chengelis et al., 2009a). In both mice and rats, absorption of NaPFHx following oral administration was rapid (Gannon et al., 2011). Blood levels of the chemical were higher in males than in females in both mice and rats, probably due to a higher rate of clearance in females. Repeated oral exposure in rats demonstrated that uptake was proportional to dose, and there was no evidence of accumulation. Distribution of the chemical into tissues was examined in rats and mice. PFHxA was detected at low levels in a wide range of tissues and decreased significantly over 24 hours after administration.

In mice, rats and monkeys, NaPFHx was mainly excreted via the urine, with a small percentage (about 10 %) excreted in faeces. Excretion in both male and female rats and mice was rapid and virtually complete, indicating no bioaccumulation (Iwai, 2011). The half-life in male rats was 2–3 times longer than in females. PFHxA was excreted unchanged and no metabolites of PFHxA could be detected in the urine.

In human workers exposed to high concentrations of PFHxA, the apparent elimination half-life ranged between 14 and 49 days, with a geometric mean of 32 days (Russell et al., 2013). During seasonal use of ski wax, which contained an indirect precursor to PFHxA, levels of PFHxA in workers' blood increased during the ski season, then decreased to below the detection limit after exposure ceased. PFOA levels in blood were also monitored and were found at mostly stable concentrations before, during and after the ski season (elevated compared with the general population). These data suggest that PFHxA is cleared from blood more rapidly than PFOA and shortly after exposure ceases (Nilsson et al., 2010).

Overall, the available data indicate that PFHxA is rapidly and extensively absorbed, does not bioaccumulate, and is not metabolised, and is rapidly and completely excreted, mainly in the urine.

Studies with PFBA estimated its absorption, following oral administration, to be >95 % in rats. On average, the cumulative excretion of PFBA 24 hours after an oral dose was approximately 35 % in urine and 4–11 % in faeces in male mice; and 65–69 % in urine, and 5–7 % in faeces in female mice (Chang et al., 2008). Mean terminal serum PFBA elimination half-lives ranged from 1.03 hours (female) to 9.22 hours (male) in rats; 2.79 hours (female) to 16.25 hours (male) in mice; and approximately 40 hours in monkeys; and approximately 72 – 87 hours in humans (Chang et al. 2008). Similarly to PFHxA, all these data demonstrate that PFBA is cleared from blood much more rapidly than PFOA and it does not have any bioaccumulation potential in mammals.

Acute Toxicity

Oral

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

In an acute oral toxicity study in Crl:CD female rats, the median lethal dose (LD50) of NaPFHx was determined as 1750–5000 mg/kg bw, based on 1/4 rats dying in the 1750 mg/kg bw dose group and 3/3 rats dying in the 5000 mg/kg bw dose group (Loveless et al., 2009).

Female rats were used in this study. The serum clearance of PFHxA is reportedly faster in female rats than male rats. Subsequently systemic concentrations of PFHxA following oral administration were up to four-fold higher for males than females. Male rats might, therefore, be more sensitive to the effects of PFHxA than female rats and the LD50 for males could be lower.

Reactive chemicals in this group, such as the acids and anhydrides, are likely to have higher acute toxicity due to local effects, but data are not available.

Dermal

In an acute dermal toxicity study, conducted according to the Organisation for Economic Co-operation and Development (OECD) test guidelines (TG) for oral acute toxicity, single doses of 2000 mg/kg bw of the ammonium salt of PFHxA (ammonium PFHx; CAS No. 21615-47-4) was applied to the clipped skins of five male and five female Wistar rats. The test substance was held in contact with the skin with a surgical gauze patch dressing. No mortality occurred. Flat hunched postures were noted for the majority of animals.

Based on these results, the LD50 of ammonium PFHx (the ammonium salt of PFHxA) was established >2000 mg/kg bw (Teunissen, 2004a).

Inhalation

No data are available for the chemicals in this group.

Corrosion / Irritation

Respiratory Irritation

No data are available for the chemicals in this group.

Skin Irritation

In an acute dermal irritation study, conducted according to the OECD test guidelines, single doses of 0.5 mL of pure ammonium PFHx were applied to the clipped skins of New Zealand White rabbits as a semi-occlusive application (Teunissen, 2004b). Four hours' after application, the dressing was removed and the skin was cleaned of residual substance.

Four hours' exposure to 0.5 mL ammonium PFHx resulted in erythema and very slight oedema in the treated skin. However, these effects had resolved within seven days of the exposure. The chemical was considered to be a mild skin irritant. However, skin irritant/corrosive effects cannot be ruled out for PFBA anhydride (which is reactive and could hydrolyse to PFBA).

Eye Irritation

Ammonium PFHx was found to be a severe eye irritant in rabbits. In an eye irritation study conducted according to the OECD test guidelines, single doses of 0.1 mL ammonium PFHx was instilled into one eye of each of three rabbits. Observations were made one, 24, 48 and 72 hours and seven, 14, 21 and/or 28 days after instillation (Teunissen, 2004c).

Ammonium PFHx affected the cornea, iris and conjunctivae in all rabbits. The corneal injury consisted of opacity (maximum grade 2) and epithelial damage, which persisted until the study was terminated. Iridial irritation Grade 1 was observed in all animals, which had resolved within 48 hours in one animal and within seven days in the remaining animals. Conjunctival irritation included redness, chemosis and discharge. These completely resolved within 21 days in one animal and persisted until the study was terminated in the other two animals.

Ammonium PFHx was considered to be a severe eye irritant in rabbits. As a salt, it is considered to have lower irritation potential than the acids and anhydrides in the group; therefore, in the absence of additional information, classification is considered warranted for all chemicals in this group.

Sensitisation

Skin Sensitisation

No data are available for the chemicals in this group. Based on data for the analogues, PFOA and its ammonium salt (NICNAS), the chemicals in this group are not considered skin sensitisers.

Repeated Dose Toxicity

Oral

Based on the treatment-related effects reported in various repeated dose toxicity studies, repeated oral exposure to the chemicals is not considered to cause serious damage to health. The target organ for toxicity for PFOA is the liver (NICNASb). Effects observed in the liver in studies with PFHxA and PFBA were generally mild and reversible.

PFHxA showed low toxicity following repeated exposure. In two sub-chronic (90-day) studies in rats with PFHxA, the no observed adverse effect levels (NOAELs) of 20 and 50 mg/kg bw/day were based on mild effects observed at the 100 and 200 mg/kg bw/day doses, respectively, which were microscopic lesions in nasal tissue, changes in serum chemistry parameters and relative kidney weights.

In the first study (DuPont, 2007a, Loveless et al., 2009), Crl:CD rats were administered sodium salt of PFHxA by gavage for 90 days, at 0, 20, 100 or 500 mg/kg bw/day. No treatment-related clinical signs were observed. There was a mild but significant decrease in red blood mass parameters (red blood cell count, haemoglobin and haematocrit). Mild reversible increases in aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) activities were noted at the 100 and 500 mg/kg bw/day doses, which are likely to reflect an hepatic adaptive response. Relative liver weights were significantly increased at the 500 mg/kg bw/day dose. There was also pale discolouration of the liver at this dose, but no other treatment-related gross observations. Relative thyroid weight was also significantly increased in female rats at the 500 mg/kg bw/day dose. Mild reversible degeneration and atrophy of the olfactory epithelium (nose) was noted at the 100 and 500 mg/kg bw/day dose, as was minimal reversible hepatocellular hypertrophy. The hepatocellular hypertrophy was consistent with the increased liver weight and likely to be an adaptive response. Minimal hypertrophy of the thyroid follicular epithelium in the 500 mg/kg dose group was reversible and consistent with the induction of hepatic microsomal enzymes that led to increased biliary excretion of the thyroid hormone T4 (thyroxine), subsequent elevation of thyroid-stimulating hormone (TSH), and the consequent follicular hypertrophy.

Increased incidences of minimal to mild splenic extramedullary haematopoiesis and/or erythroid hyperplasia in bone marrow were present at the 500 mg/kg bw/day dose. These findings are consistent with the red blood cell changes observed. An NOAEL of 20 mg/kg bw/day was established based on the microscopic lesions in nasal tissue observed at the 100 mg/kg bw/day dose.

However, in a subsequent study (unpublished data) the authors concluded that the morphology and distribution of the nasal lesions were consistent with a reflux mechanism (route (gavage) specific) and were not the result of systemic toxicity.

In the second study (Chengelis et al., 2009b), Crl:CD male and female rats were administered 0, 50 or 200 mg/kg bw/day of PFHxA by gavage for 90 days. There were no treatment-related clinical observations. A slight but significant decrease (<10 %) in mean red blood cell parameters (red blood cell count, haemoglobin and haematocrit) was noted at the 200 mg/kg bw/day dose, with a compensatory increase in reticulocytes in male rats. The observed changes were reversed during the recovery period. Significant increases in ALT and ALP at the 200 mg/kg bw/day dose, and lower cholesterol levels were also noted at the 50 and 200 mg/kg bw/day doses. Increases in relative liver weights at the 200 mg/kg bw/day dose and, in all treatment groups, increases in kidney weight were reported. Minimal centrilobular hepatocellular hypertrophy was observed in 7/10 animals. All of the observed effects related to treatment with PFHxA were mild, and many were reversible during the recovery period. The NOAEL of 50 mg/kg bw/day was established based on effects on bodyweight, serum chemistry parameters and relative kidney weights at the 200 mg/kg bw/day dose.

In a two-year oral chronic toxicity/carcinogenicity study (Klaunig et al., 2014), Crl:CD rats were administered PFHxA at 2.5, 15 or 100 mg/kg bw/day (males) and 5, 30 or 200 mg/kg bw/day (females) by gavage for up to 104 consecutive weeks. Several deaths occurred in rats in the highest dose groups, but histopathological evaluations concluded that these deaths were not related to exposure. Treatment-related effects consisted of changes in the specific gravity and pH of urine and slight histological changes such as kidney papillary necrosis and tubular degeneration. The NOAEL was established as 15 mg/kg bw/day for males and 30 mg/kg bw/day for females, based on the pathological effects in the kidney.

PFBA administered to rats by gavage at doses of up to 184 mg/kg/day for five days, or up to 150 mg/kg bw/day for 28 days, did not cause any morphological alterations in the respiratory tract, gastrointestinal tract or skeletal muscle. There were no significant gross or microscopic alterations in the spleen, thymus or mesenteric lymph nodes, or in haematological parameters (van Otterdijk, 2007a; van Otterdijk, 2007b).

In a 90-day repeated dose study, Crl:CD rats were administered PFBA at 6 or 30 mg/kg/day for 90 days (van Otterdijk, 2007b). Alterations in haematological parameters were noted in the high dose group rats, but these were not considered adverse effects by the study's authors, based on a lack of alteration in the bone marrow or spleen. At the highest dose tested, 30 mg/kg/day, increased absolute liver weight (23 %), increased serum ALP activity and reduced total serum protein were noted. PFBA also caused diffused panlobular hepatocyte hypertrophy. These effects were reversible during a 21-day recovery period; the NOAEL for the study was established as 6 mg/kg/day.

In a repeat dose study (Butenhoff et al., 2012), male and female rats were treated with ammonium perfluorobutyrate at doses up to 150 and 30 mg/kg bw/day for 28 and 90 days, respectively. Reduced serum thyroxine with no change in serum thyrotropin

was reported in female rats. In males, the effects were generally mild, reversible on cessation of treatment, and included: hepatic hypertrophy with minimal to slight hepatocellular hypertrophy, hypothyroxinaemia without evidence of a thyroid follicular response; reduced serum total cholesterol; mild reductions in red blood cell parameters without evidence of an effect on red blood cell turnover; and delayed bilateral pupillary light reflex.

According to the study authors, the hypothyroxinaemia likely resulted from a combination of competitive displacement of thyroxine as well as increased metabolism and elimination of thyroxine. Hypothyroxinaemia was not accompanied by an elevation of thyroxine stimulating hormone (TSH); nor was dosing with ammonium perfluorobutyrate accompanied by evidence of a hypertrophic or hyperplastic response of the thyroid follicles, based on morphometric endpoints.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available data, the chemicals are not considered to be genotoxic.

NaPFHx was not mutagenic to bacteria or clastogenic in vitro to cultured human lymphocytes under the conditions of the tests (DuPont, 2006a; DuPont, 2006b). PFHxA did not induce oxidative DNA damage in human hepatoma Hep G2 cells, as measured by the formation of strand breaks, including alkali-labile sites and formamidopyrimidine-DNA-glycosylase-sensitive sites in DNA, using the Comet assay (Ricardo EAE Ltd, 2014), and produced only modest levels of reactive oxygen species (ROS), which were not concentration-dependent (Eriksen et al., 2001). A single intraperitoneal injection (i.p.) administration of PFBA to male Fischer 344 rats had no effect on either the liver or kidney DNA (ATSDR, 2009).

Based on the available data, the analogue chemical, PFOA, is not considered to be genotoxic (NICNASb).

Carcinogenicity

Carcinogenicity of PFHxAwas assessed as part of the two-year chronic toxicity/carcinogenicity study (Klaunig et al., 2014) (see **Repeat dose toxicity**). There was no evidence of carcinogenicity in either male or female rats treated daily with PFHxA for 104 weeks. When euthanised, there was no significant increase in tumour incidence in any organ. For the unscheduled deaths in the highest dose group (no further details), there was no indication that the death was related to increased tumour incidence in either male or female rats. Overall, there was no evidence of carcinogenicity associated with PFHxA treatment in rats.

Reproductive and Developmental Toxicity

Compared with results obtained using PFOA in mice, both PFBA and PFHxA had lower developmental toxicity (ATSDR, 2009). Foetotoxic effects were observed with PFHxA at relatively high doses (175 mg/kg bw) compared with 5 mg/kg bw/day for PFOA (NICNASb).

In a developmental and perinatal/postnatal reproduction study, conducted according to OECD guidelines (Iwai & Hoberman, 2014), Crl:CD1(ICR) pregnant mice were given 0, 7, 35 or 175 mg/kg bw/day ammonium PFHx from gestation day (GD) 6–18 (F0 generation mice). Male and female offspring (F1 generation) of these mice were administered the same doses from day 20–41 after birth.

There were no treatment-related deaths in the F0 generation and no treatment-related clinical changes seen during the gestation or lactation periods. No significant changes were seen at necropsy. At the 175 mg/kg bw/day dose, the number of

stillborn pups and pups dying on post natal day one (PND 1) was significantly increased and the mean pup weight/litter was reduced. Corneal opacity and microphthalmia were also observed in developing mice at the 175 mg/kg bw/day dose. Other reproductive parameters were unaffected by treatment.

In the F1 generation mice, no treatment-related clinical effects were observed. There was no effect on sexual maturity (preputial separation and vaginal patency) in males or females. The NOAEL for maternal toxicity (F0 generation) was therefore established as 175 mg/kg/day, the highest dose tested. The NOAEL for foetal toxicity in the F1 generation was 35 mg/kg/day, based on an increased number of stillborn pups and pups dying on PND 1 at the 175 mg/kg/day dose. The effects on stillbirth/perinatal mortality and effects on the eye occurred in the absense of maternal toxicity.

In a second developmental study (DuPont, 2007b), Crl:CD(SD) female rats were administered NaPFHx at 0, 20, 100 or 500 mg/kg bw/day by gavage from GD 6–20. There were no maternal deaths during the study. Treatment-related maternal effects observed only at the highest dose (500 mg/kg bw/day) included decreased food consumption, reduced body weight, nasal discharge, lung noise and stained skin/fur. No test-substance-related gross pathology findings were observed in dams at any dose. Reproductive parameters were similar across all groups. There were no test-substance-related foetal external alterations at any dosage. The NOAEL for maternal and foetal toxicity was established as 100 mg/kg bw/day, based on reduced maternal bodyweight and decreased foetal weight at the 500 mg/kg bw/day. There was no clear evidence of developmental toxicity.

Administering PFBA to rats by gavage at doses of up to 184 mg/kg bw/day for five days, 150 mg/kg bw/day for 28 days or 30 mg/kg bw/day for 90 days did not cause significant gross or microscopic alterations in primary and secondary reproductive organs (van Otterdijk, 2007b).

Administering PFBA (35–350 mg/kg bw/day) to pregnant mice on GD 1–17 had no significant effect on a wide range of developmental parameters, including neonate weight gain and viability. Significant delays were seen in vaginal opening (two days) at maternal doses of 175 mg/kg bw/day and in preputial separation at 350 mg/kg bw/day (two days) (Das et al., 2008). PFBA did not significantly affect gene expression in the foetal liver. On GD 18, maternal serum PFBA was 2000–4000 ng/mL with no apparent dose–response relationship. In pups, serum PFBA was 400–600 ng/mL on PND 1 and 110–150 ng/mL on PND 10. The milder response of PFBA compared with PFOA is attributed to PFBA's faster elimination as well as its lower biochemical potency (ATSDR, 2009).

In conclusion, based on still births and increased postnatal pup mortality and decreased pup body weight and corneal opacity and microphthalmia observed in mice with ammonium salt of PFHxA, a classification for developmental effects is proposed for of short-chain PFCAs, except for substances with three or less perfluorinated carbons (e.g. PFBA) that did not show any developmental toxicity effects.

Risk Characterisation

Critical Health Effects

The data available indicate that the toxicological profile for short-chain PFCAs (C4–C6) have potentially better human health outcomes and bioaccumulation than long-chain perfluoroalkyl substances. Chronic low-level effects on human health have not been identified. There is no evidence of significant hepatotoxicity or carcinogenicity in repeated dose toxicity studies. Compared with PFOA, the chemicals in the short-chain PFCA group (ammonium PFHx, PFBA) showed developmental effects in mice (stillborn and postnatal deaths, late maturation) at much higher doses (175 mg/kg bw/day). The other known critical health effects of the well-evaluated chemicals in this group for risk characterisation include acute toxicity from oral exposure and eye irritation.

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 to short-chain PFCAs in the environment

Public exposure to short-chain PFCAs could occur through secondary exposure in the environment. Significant industrial use of the remaining chemicals in this group is considered unlikely. However, it is noted that the common perfluorinated components of the chemicals in this group could be present in the environment due to their release from articles or due to release from related chemicals not covered by this assessment. These perfluorinated components are highly persistent and environmental levels can continue to increase over time due to indirect release pathways (NICNAS).

The available data indicate that short-chain PFCAs have lower toxicity and are more rapidly eliminated than the long-chain perfluoroalkyl substances. Chronic low-level effects on human health have not been identified. The chemicals in the short-chain PFCA group are persistent in the environment, but have a short half-life in humans. Further assessment of the chemicals in this group may be necessary to assess the risk of secondary exposure to these chemicals, if hazard data become available indicating adverse health effects.

Occupational Risk Characterisation

Based on the available use information, the chemicals in this group are not likely to be used in significant quantities in Australia. The relevance to humans of the developmental effects seen in mice is not known. However, workers are not expected to be exposed to the high doses of the chemicals (PFHxA and PFBA) at which developmental effects were noted in mice. Therefore, the chemicals are not considered to pose an unreasonable risk to workers' health.

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.

However, should hazard data become available indicating adverse health effects, further assessment of the chemicals in this group may be necessary to assess the risk of secondary exposure to short-chain PFCAs.

Sufficient toxicological data are available to demonstrate a lower toxicity profile for short-chain PFCAs (containing 3,4, and 5 perfluorinated carbons) compared with PFOA. It is therefore recommended that this assessment be included in the action plan currently contained in Appendix G of the Handbook for Notifiers (NICNASa), as an additional source of toxicity data for chemicals that degrade to short-chain PFCAs containing three to five perfluorinated carbons. Any changes to the assessment outcomes under the action plan, for chemicals that degrade to short-chain PFCAs, will be considered as part of the IMAP assessment for indirect precursors of short-chain PFCAs.

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. Developmental toxicity classification does not apply to PFBA.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)	Suspected of damaging the unborn child - Cat. 2 (H361d)

[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 oral and ocular 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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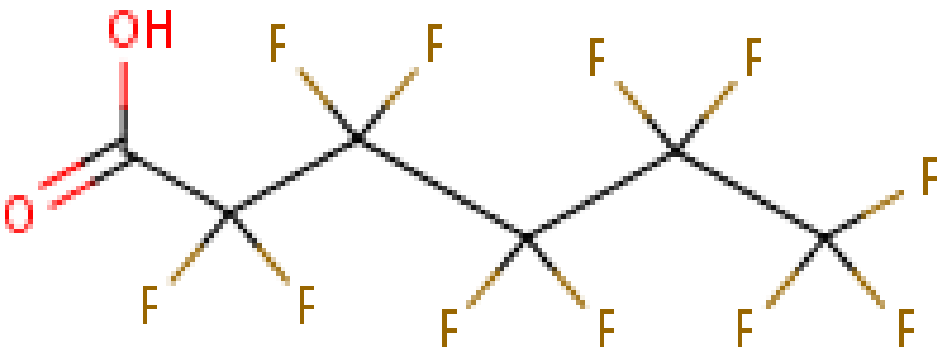
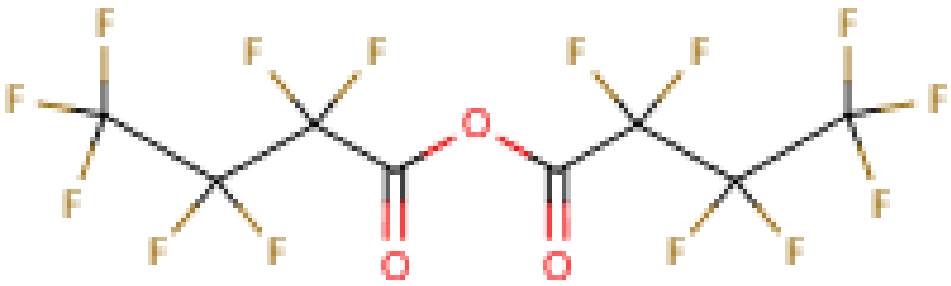
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Hexanoic acid, undecafluoro-** perfluorohexanoic acid undecafluoro-1-hexanoic acid undecafluorocaproic acid
CAS Number	307-24-4
Structural Formula	
Molecular Formula	C6HF11O2
Molecular Weight	314

Chemical Name in the Inventory and Synonyms	**Butanoic acid, heptafluoro-, anhydride** Heptafluorobutyric anhydride
CAS Number	336-59-4

Structural Formula	
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Molecular Weight	410.06

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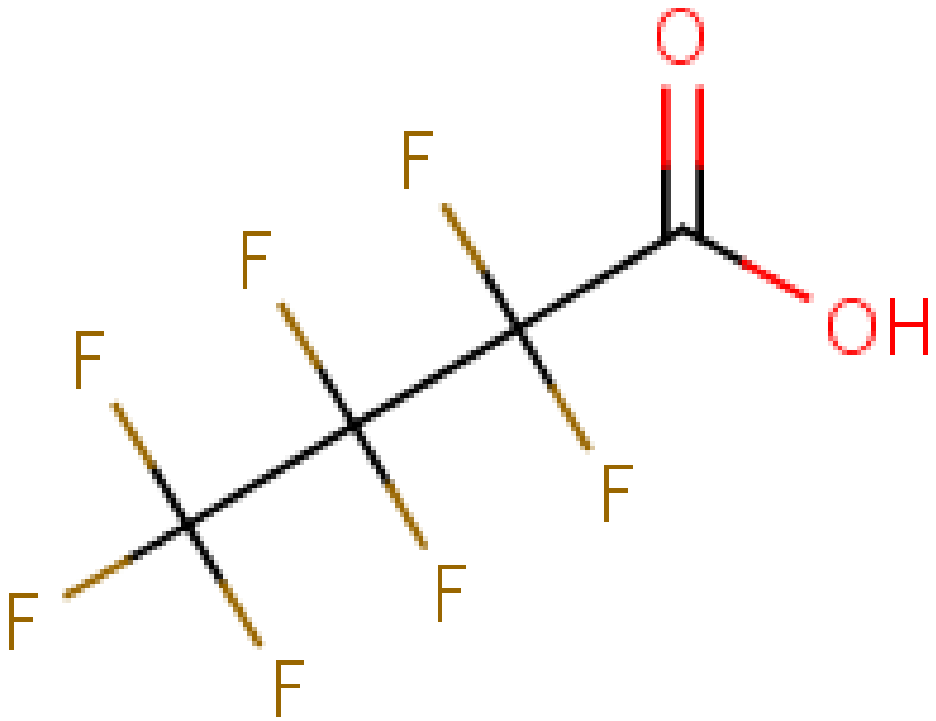
Structural Formula	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Molecular Weight	214.04

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CAS Number	2706-90-3
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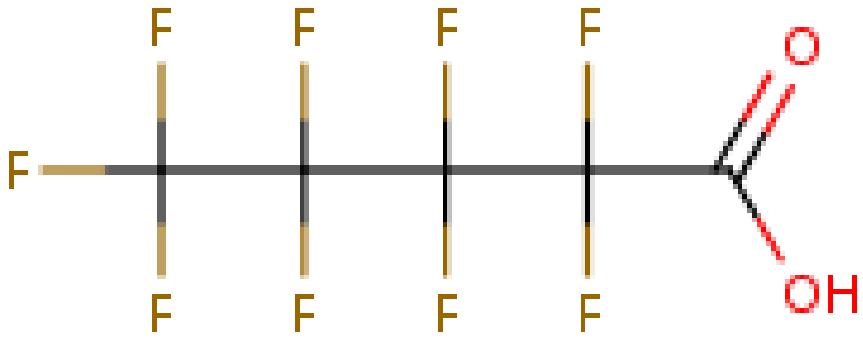
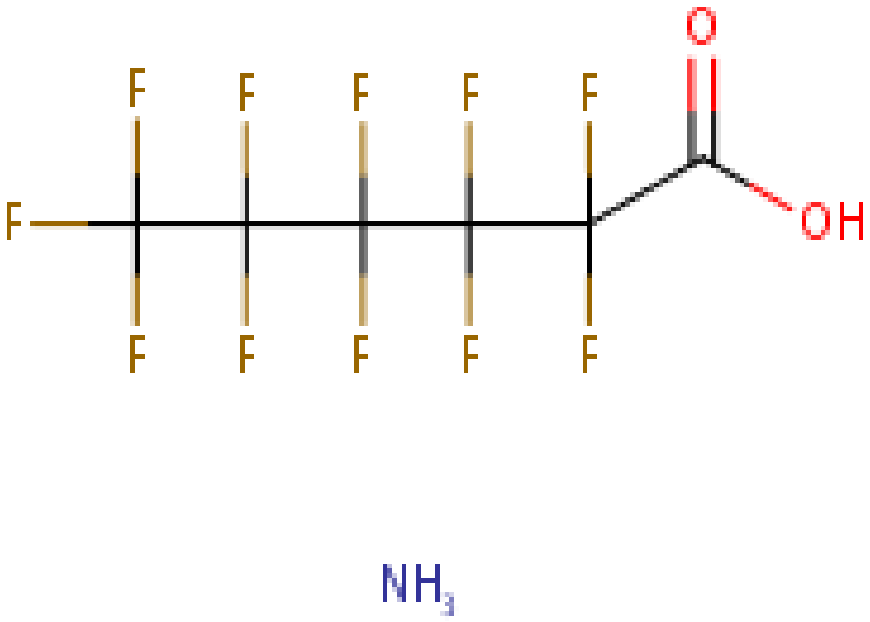
	
Molecular Formula	C5HF9O2
Molecular Weight	264.05

Chemical Name in the Inventory and Synonyms	**Hexanoic acid, undecafluoro-, ammonium salt** undecafluorohexanoic acid, ammonium salt ammoniun perfluorohexanoate ammonium undecafluorohexanoate
CAS Number	21615-47-4
Structural Formula	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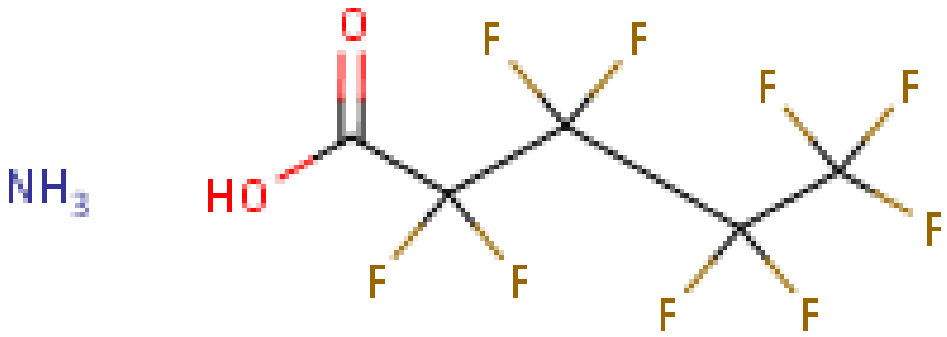
Molecular Weight	331

Chemical Name in the Inventory and Synonyms	**Pentanoic acid, nonafluoro-, ammonium salt** nonafluoropentanoic acid, ammonium salt ammonium perfluorovalerate pentanoic acid nonafluoro-, ammonium salt
CAS Number	68259-11-0
Structural Formula	

	
Molecular Formula	C5HF9O2.H3N
Molecular Weight	289

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