Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Heptene, tridecafluoromethoxy-

Assessment statement

13 July 2022

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AICIS assessment statement

Chemical in this assessment

Name	CAS registry number
Heptene, tridecafluoromethoxy-	1452389-83-1

Reason for the assessment

An application for an assessment certificate under section 31 of the Industrial Chemicals Act 2019 (the Act)

Certificate Application Type

Health and environment focus

The assessed chemical is a perfluorinated chemical that contains a sequence of greater than or equal to 4, but no more than 20, fully fluorinated carbon atoms, meeting the criteria for a specified class of introduction under subsection 7(3)(e) of the Industrial Chemicals (General) Rules 2019 (the Rules). In accordance with table item 1 section 28 and table item 1 section 29 of the Rules, the indicative human health and environment risk for the proposed introduction is medium to high respectively.

Defined scope of assessment

The chemical has been assessed:

- as imported at 10 tonnes/year or less with reformulation and repackaging occurring in Australia;
- for end use:
  - as a cleaning solvent, carrier fluid or heat transfer fluid;
  - in aerosol spray;
- for use only in industrial or commercial settings by professional workers that does not result in direct release to natural water ways, municipal water supplies, or municipal sewerage systems.

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will be imported into Australia in neat form for reformulation or in end-use products. The applicant indicated that the assessed chemical will be a replacement for 1,1,1,2,2,3,4,5,5,5- decafluoropentane (CAS No. 138495-42-8) which is being phased down globally under the Kigali Amendment to the Montreal Protocol.

The assessed chemical will only be used under industrial or commercial settings by professional workers as a cleaning solvent, carrier fluid, heat transfer fluid or in aerosol spray to a maximum use concentration of 100%.

Human health

Summary of health hazards

Based on the available information, the assessed chemical:

- is likely to be of low acute oral, dermal and inhalation toxicity;
- is likely to be non-irritating to skin and slightly irritating to eyes;
- is not considered as a skin sensitiser; and
- is not considered genotoxic.

Based on the available repeated dose oral and inhalation toxicity studies in rats (see **Supporting information** below), the assessed chemical caused statistically significant liver weight increases (up to 40% when compared to non-treated animals) at or above the treatment level of 100 mg/kg bw/day. Increased liver weights persisted after the recovery period of 4 weeks in the animals exposed at 1000 mg/kg bw/day for 90 days, indicating that the liver weights were unable to recover to normal level following the termination of the treatment. However, as there were no adverse histopathological or biochemical effects associated with the liver weight changes, the chemical could not be considered for hazard classification based on the GHS criteria.

The assessed chemical is expected to degrade to form persistent short- and very-short chain perfluorinated acids (PFCAs) in the environment. Available data indicate that chronic low-level effects of these potential degradants on human health have not been identified. Further evaluation of the degradants may be required if hazard information becomes available (NICNAS 2016).

Hazard classification relevant to worker health and safety

Based on the available data, the assessed chemical does not satisfy the criteria for classification according to the Globally Harmonised System of Classification and Labelling of Chemicals (UNECE 2017), for hazard classes relevant for worker health and safety as adopted for industrial chemicals in Australia.

Summary of health risk

Public

When introduced and used in the proposed manner, it is unlikely that the public will be exposed to the chemical. No risks are identified for public health during this assessment that require specific risk management measures if the assessed chemical is introduced and used in accordance with the terms of the assessment certificate.

The assessed chemical and some of its degradants are considered persistent in the environment. Secondary human exposure to the persistent chemicals may occur through the environment, however, available data indicate that short-chain PFCAs have lower toxicity and are more rapidly eliminated from human bodies than the long-chain perfluoroalkyl substances (PFAS). Human health effects with chronic low-level exposure have not been identified.

However, further evaluation of the long-term effects may be required if relevant data becomes available.

Workers

Potential exposure of workers to the assessed chemical at concentration up to 100% may occur during reformulation, repackaging and end use activities. Workers may experience certain health effects if repeatedly exposed to the assessed chemical at high concentrations. Control measures (see **means for managing risks** section) are required to manage the risk to workers.

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data the chemical is:

- Persistent (P)
- Not bioaccumulative (not B)
- Not toxic (not T)

Environmental hazard classification

The assessed chemical is not toxic to aquatic life up to its limit of solubility. The assessed chemical satisfies the criteria for classification as Chronic Category 4 (H413) under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) with consideration given to degradation and bioaccumulation factors.

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (long-term)	Aquatic Chronic 4	H413: May cause long lasting harmful effects to aquatic life

Summary of environmental risk

The assessed chemical will be introduced for use as a cleaning agent, heat transfer fluid, carrier fluid. The chemical also will be used in aerosol spray products. These uses will result in the release of the assessed chemical to air. No direct releases of the assessed chemical to wastewaters or surface waters are expected. The assessed chemical is expected to stay in air until it degrades.

The assessed chemical is not readily biodegradable and is persistent in the air. The assessed chemical is hydrophobic (log Kow ≥ 4) and has the potential to bioconcentrate in fish under experimental laboratory conditions including continuous exposure. However, the assessed chemical is highly volatile from water and the laboratory conditions are not considered to be environmentally relevant. As such, the assessed chemical is not considered to be bioaccumulative.

The assessed chemical has potential to contribute to global warming. However, this potential is lower than the synthetic greenhouse gases that are controlled under the Ozone Protection and Synthetic Greenhouse Gas Management Act 1989.

The assessed chemical will degrade in the air to eventually form short and very-short chain perfluorinated carboxylic acids (PFCAs). These PFCAs are extremely persistent but are not currently known to cause short-term adverse effects to the environment. The long-term environmental effects of short and very-short chain PFCAs are still uncertain. Therefore, further evaluation may be required when relevant data becomes available.

The assessed chemical and its degradants are expected to undergo long range transport, either through atmospheric transport or transport through surface waters and ocean currents.

Based on the assessed use pattern and the available information on the hazards of the assessed chemical and its degradants, it is expected that the risks from the introduction and use of the assessed chemical can be managed if the assessed chemical is introduced and used in accordance with the terms of the assessment certificate.

Means for managing risk

Workers

Information relating to safe introduction and use

The information in this statement should be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

The following control measures could be implemented to manage the risk arising from exposure to the assessed chemical during reformulation and end use activities:

- Use of engineering controls such as
  - Enclosed and automated processes where possible
  - Adequate workplace ventilation to avoid accumulation of vapours, mists or aerosols
- Use of safe work practices to
  - Avoid areas where vapours, mists or aerosols may be present
  - Avoid contact with eyes
- Use of personal protective equipment (PPE)
  - Impervious gloves
  - Respiratory protection
  - Protective clothing

A copy of the Safety Data Sheet (SDS) should be easily accessible to employees.

Specific requirements to provide information

Introducers of the assessed chemical, assessment certificate holders or persons covered by an assessment certificate must provide information in writing to the Executive Director within 20 working days:

- for the degradants of the assessed chemical, specifically but not limited to short and very-short chain perfluorinated carboxylic acids, if additional information becomes available that indicates the presence of higher hazards than the hazards described in this assessment.

Conclusions

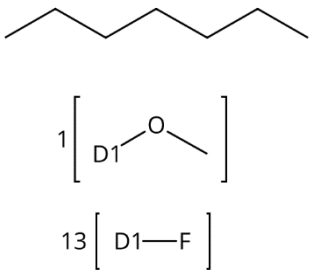
The conclusions of this assessment are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director is satisfied that when the assessed chemical is introduced and used in accordance with the terms of the assessment certificate the human health and environment risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory and the proposed means for managing the risks identified during this assessment are implemented.

Note: Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* (the Act) apply.

Supporting information

Chemical identity

Synonyms	Tridecafluoromethoxyheptene HFX-110 (trade name)
Structural formula	
Molecular formula	$C_8H_3F_{13}O$
Molecular weight (g/mol)	< 500
Chemical description	Unknown variable composition or biological (UVCB) substance

Relevant physical and chemical properties

Physical form	Colourless liquid
Freezing point	< -85 °C
Boiling point	110.5 °C
Kinematic Viscosity	0.74 mm^2/s
Vapour pressure	2.15 kPa at 20 °C and 2.88 kPa at 25 °C
Relative density	1.59 at 25 °C
Water solubility	0.15 mg/L
Henry's law constant	6.95 x 10^6 $Pa.m^3/mol$
Ionisable in the environment?	No
log K_{ow}	4.5 – 4.9
log K_{oc}	4.5
Autoignition	348 – 351 °C

Introduction and use

Approximately 5 tonnes/year of the chemical will be imported into Australia in neat form in containers with various sizes up to 200 L that will be locally reformulated and repackaged into end-use products. Another 5 tonnes/year of the chemical will be imported in finished end use products with no re-packaging.

The chemical will be used in cleaning solvents and heat transfer fluids at up to 100% concentration, in carrier fluids at up to 99% concentration and in aerosol spray products at up to 95% concentration.

Reformulation

At the reformulation site, the chemical will be typically blended into end-use products using liquid processes. The chemical will be pumped from the containers or manually poured from pails into a mixing tank and blended with other ingredients for a period of 30 minutes to a few hours. The reformulated products will then be packaged into suitable end use containers for distribution to industrial or commercial sites. Typically, multiple batches of reformulation will be processed without intermediate cleaning of equipment. For aerosol spray products, the assessed chemical will be mixed with propellants and filled into end use containers using an aerosol filling line.

End Use

Cleaning solvent

The assessed chemical will be used as a vapour cleaning agent from 1% to 100% concentration under industrial settings. The processes will be carried out using dedicated vapour degreasers. The vapour degreasers range in sizes from portable 4 - 100 L to non-portable 2000 L which are typically under robotic control. The cleaning units will be filled with the chemical by workers using pumps. Substrates to be cleaned will be put in the equipment basket. The cleaning processes will be carried out in closed systems with provisions for the chemical to be distilled and recycled with heat-cold cycles.

Carrier fluid

The assessed chemical will be used as a carrier fluid for lubricants, ink, polymers, and adhesives under industrial settings only. The chemical from 1% to 99% concentration will be mixed with other coating ingredients in a closed system. This blend will then be transferred into a coating tank where substrates to be coated will be immersed into the mixture and withdrawn at a slow and constant rate. Once the coated substrates are removed from the liquid, the assessed chemical will evaporate and its vapour will be recaptured by condensing coils and return to the tank. The coating units are expected to be fully automated and enclosed. Small number of workers may fill the tank with the coating solution and dip the substrates manually.

Heat transfer agent

The assessed chemical will be used as a heat transfer agent at industrial sites. Formulated end use products containing 1% to 100% concentration of the chemical will be pumped from the packaging drums into the target equipment and be sealed in a closed system. The fluid containing the chemical will be periodically topped up and typically be replaced every five years by trained technicians. The chemical in the drained fluid will be recovered via filtration and

distillation by a third-party facility. It is expected that at least 90% of the chemical will be recovered and re-used.

Aerosol

Approximately 25% of the total import volume of the assessed chemical (maximum 2.5 tonnes/year) will be reformulated and packaged with propellants and other substances including inks, adhesive, polymers, and lubricants into aerosol cans. These aerosol spray cans will be used by workers mainly for cleaning small parts and/or coating substrates. The final use concentration of the chemical in the spray cans range from 20% to 95%.

Human exposure

Workers

Reformulation

Dermal and ocular exposure of workers to the assessed chemical at up to 100% concentration may occur when handling and transferring the chemical or products containing the chemical during blending, sampling and repackaging processes. Inhalation of vapours, mists or aerosols of the chemical may also occur if the containers or equipment are opened and respiratory protection is inadequate.

The reformulation and packaging will be carried out under closed systems with local exhaust ventilation. Filling of the chemical or products containing it in aerosol cans will also be performed in closed systems under pressure.

According to the applicant, workers will be trained and are expected to wear PPE including respiratory protection to reduce potential exposure.

End Use

There is potential for dermal and ocular exposure of workers to the chemical at a maximum concentration of 100% during end uses. Inhalation of vapours, mists or aerosols of the chemical may also occur if respiratory protection is inadequate. Exposure mainly will occur when the closed systems or containers are opened to process the liquids containing the chemical, to treat the substrates or to clean and maintain the equipment. Spray operations using the aerosols cans containing the chemical will likely generate significant amount of vapours, mists and aerosols of the chemical and increase the potential for inhalation.

According to the applicant, all operations using the assessed chemical are proposed to be conducted in closed systems or under local exhaust ventilation. Workers are expected to wear PPE including respiratory protection during all operations.

Public

The chemical is proposed for use in industrial or commercial settings only. The risk of direct public exposure to the assessed chemical through release from industrial use is not expected.

However, the assessed chemical may be released to the air from mainly the spray applications. In the air, degradation of the assessed chemical is expected to occur to form fluorinated esters,

fluorinated carbonyls, and short- to very-short chain perfluorinated acids (PFCAs) (Jubb et al. 2014), which may lead to unquantifiable secondary human exposure.

Health hazard information

Toxicokinetics

In a toxicokinetic study, groups of male Sprague Dawley rats (6 animals/dose/route) were exposed to the chemical:

- via single intravenous injection at 10 mg/kg bw; or
- via single oral administration of 1500 or 3000 mg/kg bw; or
- via repeated oral administration of 1500 mg/kg bw/day for 14 days.

Following the intravenous injection, blood samples were collected at 1, 5, 15 and 30 minutes intervals followed by 1, 2, 4, 6, 10 and 24 hours. For oral administrations, blood samples were collected at 0.5, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 36 hours after the last exposure.

Results showed that blood concentrations of the chemical decreased rapidly after the intravenous injection, with less than half of the initial blood concentration measured between 1 and 5 minutes, and measurements were below the detection limit of 20 ng/mL after 10 hours. After the single oral administration, blood concentrations of the chemical peaked approximately in 2 to 5 hours. Blood concentrations were below the detection limit after 36 hours. A similar pattern was observed after the repeated oral administration. Blood concentrations peaked in 5 to 6 hours, and however were still above the detection limit after 36 hours.

The study concluded that the chemical may have limited cumulative effects in rats. However, there was no data provided about the distribution to other tissues and excretion of the chemical.

Acute toxicity

Oral

An acute oral toxicity study was conducted on the assessed chemical following OECD TG 420 (fixed dose procedure). An initial limit dose of 5000 mg/kg bw was administered to one female rat (Sprague Dawley derived albino) by oral gavage. In the absence of mortality, 4 additional females received a dose level of 5000 mg/kg bw simultaneously. No mortality was observed till the end of observation period of 14 days. All animals appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behaviour. The assessed chemical is likely to be of low acute toxicity to rats via the oral route with an LD50 > 5000 mg/kg bw.

Dermal

An acute dermal toxicity study was conducted on the assessed chemical following OECD TG 402 (limit test). A single dose of 5000 mg/kg bw was applied to shaved, intact skin of 5 male and 5 female rats (Crl:CD(SD)). The sites were covered with a semi-occlusive dressing for 24 hours. After removal of the patch, the test animals were observed for a period of 14 days. No mortality, dermal irritation, body weight effects or clinical signs of toxicity were observed during the study. No gross lesions were recorded at necropsy. The assessed chemical is likely to be of low acute toxicity to rats via the dermal route with an LD50 > 5000 mg/kg bw.

Inhalation

An acute inhalation toxicity study was conducted on the assessed chemical following OECD TG 403. Groups of rats (Crl:CD(SD)) with 5 animals/sex/group were exposed (whole body) to the assessed chemical in the form of vapour for 4 hours at concentrations of 2000, 5000, 9700 and 15 000 parts per million (ppm). The test animals were observed for a period of 14 days. During the exposure, test animals from 9700 ppm group displayed decreased activity in approximately 10 minutes and became motionless in 45 minutes with only startle response when checked. Rats exposed to 15 000 ppm displayed periodically rapid head bobbing, rapid ear twitching, excessive grooming, chewing motions and an increased startle response during the first 45 minutes, and became motionless throughout the remainder of the exposure. Test animals exposed to 9700 and 15 000 ppm displayed body weight loss on the day after the exposure. No test substance related gross pathological and histopathological changes were observed during necropsy at the end of the study.

The 4 hour approximate lethal concentration (ALC) of the assessed chemical was considered to be greater than 15 000 ppm, the highest vapour concentration practically achievable for the assessed chemical in the study. The no observed adverse effect concentration (NOAEC) for histopathological changes of the respiratory tract, liver and kidneys was reported by the study author to be 15 000 ppm. The assessed chemical is unlikely to be toxic to rats via inhalation at or below the vapour concentration achievable under the study conditions.

Irritation

Skin irritation

A skin irritation study was conducted on the assessed chemical following OECD TG 404. The test was conducted in a stepwise manner using a single semi-occlusive patch (6 cm^2) with 200 µL of the chemical applied initially to one New Zealand albino rabbit for 4 hours. The site was evaluated for irritation upon the patch removal, at 30 and 60 minutes followed by 24, 48 and 72 hours using Draize method. With no dermal irritation observed in the first animal, 2 additional rabbits were exposed to the chemical in the same manner. No skin irritation was seen in the test animals with erythema and oedema scores of zero for all time points. Based on the results, the assessed chemical is considered non-irritating to the skin.

Eye irritation

An eye irritation study was conducted on the assessed chemical following OECD TG 405. The test was conducted in a stepwise manner in New Zealand albino rabbits. A volume of 100 µL of the chemical was instilled into the conjunctival sac of the right eye of one rabbit. The left untreated eye served as control. Ocular irritation was evaluated at 1, 24, 48 and 72 hours after exposure by Draize method. With no significant eye irritation observed in the first test animal, 2 additional rabbits were exposed to the chemical in the same manner. No corneal opacity was observed in any of the test animals. One hour after the exposure, all treated eyes exhibited iritis and conjunctivitis (score = 1). Conjunctival redness and discharge (score = 1) was seen at 24 hours reading in one test animal. All animals recovered by 48 hours. Based on the results, the assessed chemical is considered slightly irritating to the eyes.

Sensitisation

Skin sensitisation

A local lymph node assay (LLNA) was conducted on the assessed chemical following OECD TG 429. Groups of female CBA/JHsd mice (5 animals/group) were treated at 5%, 25%, 50%, or 100% concentration on both ears for 3 consecutive days. Negative and positive controls were performed in parallel. No clinical signs of toxicity and changes in body weight were observed. After 5 days of the initial exposure, the mice received ^{3}H-thymidine by tail vein injection and were sacrificed approximately 5 hours later. The cell proliferation in the draining auricular lymph nodes of the ears was measured. Stimulation indices of 1.15, 1.02, 0.91 and 0.80 were obtained for 5%, 25%, 50% and 100% test concentrations, respectively. Based on the results, the assessed chemical is not considered a skin sensitiser.

Repeat dose toxicity

Oral

Three repeated dose oral toxicity studies conducted on the assessed chemical were provided.

28-day study (similar to OECD TG 407)

In a repeated dose toxicity study, the assessed chemical was administered through the diet to Crl:CD(SD) rats (5/sex/dose) for 28 days at 100, 250 and 1000 mg/kg bw/day. Additional 5 males and 5 females were included in the control and high dose groups for a recovery period of 14 days after the end of the dosing period. The study was performed as per Japanese 'Testing Methods New Chemicals Substance' (Notification No. 1121003, PFSB, MHLW; No. 2 of November 2003, MIB, METI; No. 031121002, EPB, MOE; dated November 21, 2003).

There were no deaths of animals reported. There were also no treatment related changes in clinical observations, functional performance tests, food consumption, body weight, urinalysis, haematology, and necropsy.

Absolute liver weight was statistically significantly increased in males treated at 1000 mg/kg bw/day. The increased liver weights were approximately 16%, 16%, and 41% compared to the control group in the 100, 250 and 1000 mg/kg bw/day treatment groups respectively, and were still present at the end of the recovery period in the 1000 mg/kg bw/day group above 10% to the control group. Hepatocellular hypertrophy was noted in both sexes treated at 250 mg/kg bw/day or higher. The liver weight increase might be toxicologically relevant to the treatment. However, the study authors considered the effects as non-adverse since no morphological evidence of liver damage was noted. The study authors reported a NOAEL of 1000 mg /kg bw/day in the study.

28-day study (OECD TG 407)

In another 28-day repeated dose toxicity study conducted according to OECD TG 407, Crl:CD(SD) rats (10/sex/dose) were administered the assessed chemical by gavage at doses of 250, 500 or 1000 mg/kg bw/day. No recovery period was included in the study. No test substance related mortality, body weight effects and food consumption changes were observed.

Treatment related increase in liver weight was observed in all dose groups. In males, liver weight increased by 23%, 36%, and 32% above the control group in low, mid and high dose

groups, respectively. The increased liver weight in some males in the high dose group correlated with an increase in microscopic centrilobular hepatocellular hypertrophy. However, there were no correlated changes in hepatocyte morphology or related hepatocellular enzyme activities including aspartate or alanine aminotransferase. In females, liver weight relative to the body weight increased by 6%, 8%, and 10% in low, mid and high dose groups, respectively. No microscopic changes in the liver were noted in the treated females.

In males, kidney weight increases were observed in a similar trend. All such increases were statistically significant. However, no correlated gross, clinical pathology or microscopic findings were observed. There was no kidney weight increase in treated females.

Statistically significant clinical biochemistry changes were observed in the treated animals when compared to the untreated animals:

- Sorbitol dehydrogenase levels decreased in the mid and high dose groups to 73% and 79% respectively;
- Creatinine levels decreased in males of the high dose group to 86%;
- Blood glucose increased in females of the mid and high dose groups to 112% and 119% respectively;
- Globulin levels increased in females of the mid and high dose groups to both 106%;
- Aspartate aminotransferase (AST) decreased in females in the mid dose group to 80%.

The organ weight and clinical biochemistry changes observed above were considered by the study authors as adaptive, and the NOAEL was reported as greater than 1000 mg/kg bw/day. As no recovery period was included in the study, it was not possible to determine whether the above effects in liver and kidney weights were reversible after the termination of the treatment.

90-day study (OECD TG 408)

In a sub-chronic repeated dose toxicity study (OECD TG 408), the assessed chemical was administered to groups of male and female Crl:CD(SD) rats by oral gavage for approximately 90 days, at doses of 250, 500 and 1000 mg/kg bw/day. A recovery period of 1 month was included in the study for the control and high dose groups.

There were no deaths and no treatment related changes observed in food consumption, body weight, behaviours, clinical signs, ophthalmological parameters, neurobehavioural evaluations and hematology parameters in the animals at any dose level.

Treatment related increases in cholesterol levels were observed in males in the 500 and 1000 mg/kg bw/day groups. The increased cholesterol levels were reversible following the recovery period.

A statistically significant increase (11%) in the mean testes weight was observed in males of the 1000 mg/kg bw/day group. An increase in mean testes weight of 6% and 4% in the 250 and 500 mg/kg bw/day dose groups respectively was observed. However, it was not statistically significant when compared to the untreated control group. The increase was not considered test substance related by the study authors since there was no microscopic findings correlated and organ weight values did not demonstrate a dose response.

At the end of the treatment period, increased liver weights were observed in both sexes at all doses and correlated with hepatocellular hypertrophy except for females treated at 250 mg/kg bw/day. In males, mean liver weight significantly increased by 22%, 29%, and 45% above the control group mean in low, mid and high dose groups, respectively. In females, mean liver

weight significantly increased by 25%, 17%, and 21% above the control group mean in low, mid and high dose groups, respectively. After the recovery period, increased mean liver weight in the 1000 mg/kg bw/day dose group in both sexes was persistent but not statistically different from the control group.

The NOAEL for the assessed chemical was not determined for male rats based on the increase in severity of chronic progressive nephropathy (CPN) and associated clinical pathology changes at all dose levels. However, CPN is a known common age related renal disease often occurring in male rats of the strain and may not be relevant to human (Hard et al. 2013). The study authors considered the NOAEL for female rats to be 1000 mg/kg bw/day based on the lack of adverse effects observed in the study. However, statistically significant liver weight increases were observed in both sexes of the treated rats at doses of 250 mg/kg bw/day and above.

Inhalation

A repeated dose inhalation toxicity study was conducted on the assessed chemical in Crl:CD(SD) rats (OECD TG 412). Potential of the chemical to induce micronuclei in bone marrow was also examined by analysing peripheral blood reticulocytes of the treated rats (see **Genotoxicity** below).

Treatment groups were formed in 20 animals/sex/group and were exposed (whole body) for 6 hours per day and 5 days per week to 1000, 2500 or 5100 ppm vapour of the chemical over a 4 week period for a total of 21 exposures. At the end of the exposure 10 animals/sex/group were sacrificed and the remaining animals were subject to a 14 day recovery. There were no treatment related deaths and clinical changes observed in the study, including food consumption, clinical signs, ophthalmological observations and neurobehavioral parameters.

Plasma and urine fluoride levels increased in treated animals as expected. Increased urine volume, decreased urine specific gravity, increased serum proteins and decreased body weight were observed in male rats exposed to 5100 ppm. These observations were considered to be indicative of an adverse effect of dehydration, likely occurring secondary to fluoride diuresis. Changes in urinalysis and serum protein were reversible following the recovery period.

A treatment related increase in liver weights occurred in all treated males and in females at 5100 ppm. In males, liver weight relative to body weight when compared to the control group increased significantly by 16.9%, 36.3% and 62.7% at 1000, 2500 and 5100 ppm, respectively, showing dose response. In females, liver weight relative to body weight increased significantly by 36.3% at the dose level of 5100 ppm. The relative liver weight increases were associated with hepatocellular hypertrophy. After the recovery period, the relative (to body) liver weights in the males were still significantly above the control group by 12% and 26% in the 2500 ppm and 5100 ppm dose groups, respectively, and in the females by 16.7% in the 5100 ppm dose group. No morphological evidence of liver damage was noted in the study.

Hyperplasia/squamous metaplasia of the larynx occurred in all treated animals and was persistent in some animals after the recovery period. Goblet cell hypertrophy/hyperplasia also occurred. These changes were considered by the study authors an adaptive response to irritation and were expected to be recoverable over time. Microscopic evidence of fluoride exposure was noted in the incisor teeth of males treated at 2500 and 5100 ppm with degeneration/atrophy of ameloblastic epithelium noted in a single male at 5100 ppm, which was considered adverse.

Based on the above results, the study authors concluded the no observed adverse effect concentration (NOAEC) for male rats to be 2500 ppm and for female rats to be 5100 ppm.

Other related information

The Agency for Toxic Substances and Disease Registry (ATSDR) and the US Environmental Protection Agency (US EPA) indicated that long-term exposure to high levels of PFAS can have adverse effects on human health including the liver damage and gastrointestinal tract disorders (The State of Alaska 2019). Research involving humans suggest that high levels of exposure of certain PFAS may lead to increased cholesterol levels, changes in liver enzymes and increased risk of kidney and testicular cancer (ATSDR 2020).

Genotoxicity

The chemical was found negative in a bacterial reverse mutation assay (OECD TG 471) when tested at up to 5000 µg/plate and in an in vitro mammalian cell gene mutation assay (OECD TG 476) when tested up to 2000 µg/mL. Negative results were also observed in a mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus in Chinese hamster ovary (CHO) cells with or without metabolic activation at concentrations up to 2000 µg/plate.

In a study following OECD TG 473, CHO cells were exposed to the chemical at concentrations of 250, 750, 1250, 2500 or 3621 µg/mL with or without metabolic activation. The chemical was found negative. However, the results showed that, after 4 hours exposure with metabolic activation, a statistically significant increase in structural aberrations was observed at 2500 µg/mL. Statistically significant increases in numerical aberrations were also observed at 2500 and 3621 µg/mL. These increases were within the negative historical control range and not considered by the study authors as biologically relevant.

In a mammalian erythrocyte micronucleus test (OECD TG 474), single doses of 500, 1000, or 2000 mg/kg bw of the assessed chemical were administered to male and female Crl:CD(SD) rats by oral gavage with concurrent negative and positive controls. No clinical signs of toxicity or mortality were observed at any dose levels tested. Under the conditions of this study, the chemical did not induce biologically relevant increases in micronucleated reticulocytes in peripheral blood cells. Therefore, the chemical was concluded to be negative for genotoxicity in vivo via oral route in rats.

In another mammalian erythrocyte micronucleus test (OECD TG 474), conducted as part of a 28-day inhalation study (see **Repeat dose toxicity** above), rats were exposed to the vapour of the chemical via inhalation at concentrations of 1000, 2500 or 5100 ppm. The incidence of micronucleated reticulocytes did not increase with biological relevance in any of the treatment groups. Therefore, under the conditions of the study, the chemical was not considered by the study authors to be genotoxic in vivo via inhalation in rats.

Reproductive and development toxicity

In a prenatal development toxicity study (OECD TG 414), the assessed chemical was administered to mated Crl:CD(SD) female rats at 250, 500 and 1000 mg/kg bw/day by oral gavage from gestation days 6 to 20. Dams were then euthanized and underwent a gross external and internal examination. No treatment related effects were observed on mortality, clinical observations, maternal body weight and food consumption, maternal gross post-mortem observations, reproductive outcome and quantitative litter size, and foetal malformations or variations in the study. Based on the results, the NOAEL for maternal and

developmental toxicity was established for the study as 1000 mg/kg bw/day, the highest dose tested.

Other

Hazards of potential degradants

The assessed chemical is expected to degrade in the air to form persistent short- and very-short chain perfluorinated acids (PFCAs) such as heptafluorobutanoic acid, trifluoroacetic acid, and pentafluoropropanoic acid (see **Environmental fate** below). Secondary human exposure to these degradants at low level may be possible.

Available data indicated that short-chain PFCAs generally have lower toxicity and are more rapidly eliminated from the body than long-chain perfluoroalkyl substances. Human health effects with chronic low level exposure have not been identified. There was no evidence of significant hepatotoxicity or carcinogenicity in relevant repeated dose toxicity studies available at the evaluation of short-chain PFCAs. No developmental toxicity effects were observed in studies on heptafluorobutanoic acid (NICNAS 2016).

Further evaluation of health hazards of the degradants may be required if hazard data become available indicating adverse health effects.

Other hazards

Based on the SDS provided by the applicant, vapours of the assessed chemical are heavier than air and can cause suffocation by reducing oxygen available for breathing. Rapid evaporation of the chemical may cause frostbite.

Environmental exposure

The assessed chemical will be imported into Australia in finished products or as a raw material for reformulation. Reformulation and repackaging will occur in sealed equipment through closed processes. Reformulation processes will be isolated from wastewater streams. No releases to the environment are expected to occur through these processes.

The assessed chemical will have use in aerosol products used for cleaning and spray adhesives for professional use. During the use of these products, the entirety of the assessed chemical will be released to the air.

Use of the assessed chemical for cleaning and degreasing will occur within closed systems. The assessed chemical will be pumped from containers into the cleaning units through closed lines. Items to be cleaned will be loaded into baskets and then lowered into the unit. Incidental releases to air may occur through the loading process but is expected to be minimised through user training provided by the introducer. Cleaning units will be isolated from wastewater streams and no release to water will occur. Waste liquid will be collected via a sump and distilled for re-use or disposed of in accordance with the respective state and local legislation.

For carrier fluid uses, the assessed chemical will be blended with the substance it is “carrying” (e.g. lubricant, ink, water proofing chemicals) and pumped into a tank connected to the line process. During the line process the assessed chemical will evaporate. Capture of the assessed chemical using local exhaust will reduce releases of the assessed chemical to air.

Recovery systems are expected to be used to recondense the assessed chemical for re-use or disposal.

For use as a heat transfer fluid, the assessed chemical will be pumped through closed lines into equipment at industrial sites. The equipment will be filled and then typically sealed for 5-year periods. After 5 years, the assessed chemical will be pumped out of the equipment, collected and sent to a third-party facility for recovery and re-distillation. The assessed chemical may have some release through pressure-relief vents when the equipment is not in use. However, these releases of the assessed chemical to the air are expected to be minor.

Recovery of the used assessed chemical typically will involve the pumping of the assessed chemical into distillation units. The assessed chemical will be pumped through closed lines and the distillation unit will operate as a closed loop. Releases of the assessed chemical to air are expected to be minimal and no release to water will occur. The wastes remaining from the distillation process will be collected for appropriate disposal.

Environmental fate

Partitioning

The assessed chemical is slightly soluble in water, is highly volatile and has a high Henry's law constant. Correspondingly, it will rapidly evaporate from its neat form, and from water and moist soils. When released directly to the air through its uses, the assessed chemical is expected to remain entirely in the air compartment until it degrades.

The potential degradants of the assessed chemical (see **Degradation** below) are expected to be significantly more water soluble and less volatile than the assessed chemical (Neale et al. 2021; NICNAS 2015; Russell et al. 2012; Solomon et al. 2016). Therefore, the degradants may be removed from the atmosphere through deposition and eventually partition to the water compartment.

Degradation

The assessed chemical is persistent in the air according to domestic threshold values. The assessed chemical has demonstrated primary biodegradation in water. However, the assessed chemical is expected to form persistent degradants in air and in water.

A supplied inherent biodegradation study performed according to OECD TG 302C showed 39.5% degradation after 28 days according to oxygen demand. This indicates that the assessed chemical will undergo primary degradation. A supplied ready biodegradation study performed according to OECD TG 301D demonstrated 0% degradation after 28 days.

The assessed chemical is not expected to undergo hydrolysis in waters under environmental conditions.

In the air, degradation of the assessed chemical is expected to occur through reactions with atmospheric hydroxyl (-OH) radicals and nitric oxide (NO). The reaction constants of various isomers of methyl-perfluoroheptene-ethers (MPHE) with hydroxyl radicals have been previously measured (Jubb et al. 2014). The studied MPHE isomers are consistent with the potential components of the assessed chemical. Isomer structure and stereochemistry are major factors that influence the rate of the initial hydroxyl group addition reaction. Correspondingly, the expected atmospheric lifetimes of the various isomers of MPHE range from 4 to 111 days.

The proposed atmospheric degradation pathway for the assessed chemical indicates that the isomers of the assessed chemical will form fluorinated esters, fluorinated carbonyls, and short- and very-short chain perfluorinated acids (PFCAs) in air (Jubb et al. 2014). Fluorinated esters and carbonyls may then undergo hydrolysis in the atmosphere to produce additional PFCAs. Short-chain PFCAs (heptafluorobutanoic acid) and very-short chain PFCAs (trifluoroacetic acid, pentafluoropropanoic acid) are expected to be recalcitrant in the environment (Ateia et al. 2019; NICNAS 2015; Solomon et al. 2016).

Bioaccumulation

The assessed chemical is not expected to bioaccumulate in aquatic organisms under environmentally relevant exposure conditions.

A supplied bioaccumulation study fulfilling OECD TG 305 criteria investigated the bioaccumulation of the assessed chemical in carp (*Cyprinus carpio*). The determined whole body steady state bioconcentration factor (BCF) values for the isomers in the assessed chemical ranged from 1100 to 2210 L/kg for the high exposure dose, and 1560 to 2850 L/kg for the low exposure dose. Specific body part BCF values indicated that more accumulation occurred within the head and viscera of the carp compared to the muscle, bones, skin, scale and intestines. The results of this test are indicative of the potential for the assessed chemical to bioconcentrate in fish under laboratory conditions where the fish are continuously exposed to the assessed chemical. For the purpose of this assessment, the results are not considered to be relevant, given the assessed chemical is highly volatile from water and is not expected to reach comparable exposure conditions and concentrations under environmentally relevant conditions.

Short chain PFCAs, such as heptafluorobutanoic acid, have been detected in wildlife in Australia and internationally (Du et al. 2021; Gao et al. 2020; Li et al. 2021; NICNAS 2015; Sharp et al. 2021; Szabo et al. 2022). However, there is no current indication that the levels of these short-chain PFCAs magnify through trophic levels.

Environmental transport

The isomers of the assessed chemical are expected to have atmospheric lifetimes ranging from 4 to 111 days. As such, the assessed chemical is expected to be transported significant distances from sites of release.

Additionally, the degradants of the assessed chemical are expected to be very mobile in waters and extremely resistant to further degradation. Once formed in the environment, these degradants are expected to undergo long-range transport, either through atmospheric transport or transport through surface waters and ocean currents (NICNAS 2015; Solomon et al. 2016).

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) has not been calculated for the assessed chemical.

Short and very-short chain PFCAs have been detected globally in the environment at various concentrations (Ateia et al. 2019; Neale et al. 2021; Sharp et al. 2021; Solomon et al. 2016; Szabo et al. 2022). While the degradation of the assessed chemical in air will contribute to the environmental load of short and very-short chain PFCAs, it is not possible to calculate the PFCA concentrations arising from the use of assessed chemical, as many different

atmospheric contaminants may be expected to form PFCAs through pathways similar to the assessed chemical.

Environmental effects

As the assessed chemical will form persistent degradants, the hazards of the assessed chemical and its degradants are both considered for environmental effects.

Information on the acute ecotoxicity of short and very-short chain PFCAs is available in previous assessments under NICNAS (National Industrial Chemicals Notification and Assessment Scheme) or in the public domain (Neale et al. 2021; NICNAS 2015; Russell et al. 2012; Solomon et al. 2016). However, limited information is currently available on the long-term ecotoxic effects of short and very-short chain PFCAs.

Effects on the atmosphere

The 100-year global warming potential (GWP) values for the isomers of the assessed chemical have been calculated and are expected to range from 1 to 30 (Jubb et al. 2014). Therefore, releases of the assessed chemical are expected to have an effect on global warming that is greater than or similar to releases of carbon dioxide of the same volume.

The assessed chemical does not contain ozone depleting elements (chlorine, bromine, iodine) and is not expected to affect atmospheric ozone.

Effects on Aquatic Life

The assessed chemical is difficult to test using standard ecotoxicity testing methods due to its very high volatility from water and slight water solubility (OECD 2019). Measured concentrations during toxicity testing were often observed to be below the water solubility of the assessed chemical, despite use of high loading rates and use of solvents.

Acute toxicity

The following measured median lethal concentration (LC50) and median effective concentration (EC50) values for the assessed chemical for model organisms were supplied by the applicant:

Taxon	Endpoint	Method
Fish	96 h LC50 > 0.096 mg/L	*Oryzias latipes* (Japanese medaka) OECD TG 203 Semi-static conditions Measured concentration
	14 d NOEC ≥ 0.089 mg/L	*Danio rerio* (zebrafish) OECD TG 204 Semi-static conditions Measured concentration

Taxon	Endpoint	Method
Invertebrate	48 h EC50 > 0.157 mg/L	*Daphnia magna* (water flea) Immobility OECD TG 202 Semi-static conditions Measured concentration
Algae	72 h EC50 > 0.000447 mg/L	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Measured concentration
	72 h EC50 > 120 mg/L	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Nominal concentration

No effects due to the assessed chemical were observed for fish or invertebrates. In one supplied algae toxicity study, the measured concentration of the chemical was below the limit of detection (< 0.0001 mg/L) after 3 hours. In another supplied algae toxicity study, 33% growth inhibition was observed at the highest nominal concentration of 120 mg/L after 72 hours.

Chronic toxicity

The following measured no-observed-effect concentration (NOEC) value for model organisms was supplied by the applicant:

Taxon	Endpoint	Method
Invertebrates	21 d NOEC ≥ 0.107 mg/L	*Daphnia magna* (water flea) Mortality, body size, number of offspring OECD TG 211 Semi-static conditions Measured concentration

Effects on terrestrial life

The following measured LC50 value for model organisms was supplied by the applicant:

Taxon	Endpoint	Method
Earthworms	14 d LC50 > 1011 mg/kg	*Eisenia fetida* OECD TG 207 Nominal concentration

Predicted no-effect concentration (PNEC)

A predicted no-effect concentration (PNEC) was not calculated for the assessed chemical.

Exposure to the assessed chemical is not anticipated to occur as air is the only compartment where release of the assessed chemical will occur. Additionally, the assessed chemical has very high volatility and is expected to predominately remain in the air until it degrades.

Any effects caused by the assessed chemical will likely be through its long-lived short and very-short chain PFCA degradants. The available information indicates that short and very-short chain PFCAs are not toxic to most aquatic species in the short-term (Neale et al. 2021; Russell et al. 2012; Solomon et al. 2016). However, short and very-short chain PFCAs are extremely persistent in the environment and their long-term effects are uncertain. Therefore, no PNEC could be calculated for the assessed chemical.

Environmental hazard categorisation

The categorisation of the environmental hazards of the assessed chemical according to domestic environmental hazard thresholds is presented below:

Persistence

Persistent (P). Based on estimated lifetime in air and the expected formation of persistent degradants, the assessed chemical is categorised as Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). The assessed chemical is not expected to bioaccumulate in aquatic organisms under environmentally relevant exposure conditions.

Toxicity

Not Toxic (Not T). Based on supplied ecotoxicity information, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

The assessed chemical will be released directly to air through its assessed uses, where it will be persistent and undergo long-range transport. The assessed chemical will be degraded in the air and eventually produce short and very-short chain per-fluorinated degradants (PFCAs). These degradants will be mobile and long-lived in the environment (Ateia et al. 2019; NICNAS 2015; Solomon et al. 2016).

While the isomers of the assessed chemical are expected to have GWP values greater than or equal to 1, the magnitude of these potentials is lower than the GWPs of the greenhouse gas chemicals controlled under the Ozone Protection and Synthetic Greenhouse Gas Management Act 1989.

As the assessed chemical is highly volatile and directly released to air, exposure of aquatic organisms to the assessed chemical is not expected to occur. Rather, environmental exposure will occur through the degradants of the assessed chemical. The current evidence suggests

that short and very-short chain PFCAs, such as trifluoroacetic acid and heptafluorobutanoic acid, are not acutely toxic to most organisms. However, the long-term effects of short and very-short chain PFCAs are still uncertain and are the subject of ongoing research.

Current concentrations of short and very-short chain PFCAs, in the ocean and in precipitation, are below known acute ecotoxicity endpoints (Neale et al. 2021; Solomon et al. 2016). These degradants are extremely persistent and removal from environmental waters is extremely slow. However, while increased use of PFCA precursors is expected to cause further increases in environmental concentrations of short-chain PFCAs, the predicted concentration increases over the next few decades are currently expected to be minor (Neale et al. 2021; Solomon et al. 2016).

Therefore, although the assessed chemical and its degradants are persistent, have global warming potential, and have potential to undergo long-range transport, the introduction is not currently expected to pose risks to the environment.

As the environmental and toxic effects of short and very-short chain PFCAs is an area of ongoing research, re-assessment/evaluation may be required if information becomes available that indicates the assessed chemical or its degradants have greater hazards than those considered in this assessment.

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