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

5-Cyclotetradecen-1-one, 3-methyl-

Assessment statement (CA09517)

20 February 2024

Table of contents

AICIS assessment statement (CA09517) 3

Chemical in this assessment 3

Reason for the assessment 3

Defined scope of assessment 3

Summary of assessment 3

Means for managing risk 6

Conclusions 7

Supporting information 8

Chemical identity 8

Relevant physical and chemical properties 8

Human exposure 9

Health hazard information 12

Environmental exposure 15

Environmental effects 18

Categorisation of environmental hazard 19

Environmental risk characterisation 19

References 20

AICIS assessment statement (CA09517)

Chemical in this assessment

Name	CAS registry number
5-Cyclotetradecen-1-one, 3-methyl-	1117765-92-0

Reason for the assessment

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

Certificate Application type

AICIS received the application in a Health Focus type.

Defined scope of assessment

The chemical has been assessed as:

- a fragrance component imported into Australia at up to 1 tonne per year
- imported at up to 100% concentration for local reformulation into finished cosmetic and household products
- imported or reformulated as a component of finished end-use cosmetic and household products at less than 1% concentration for consumers and professional use

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia. It will be imported into Australia at up to 1 tonne per year, in high density polyethylene or steel lacquer lined drums of varying sizes up to 180 kg and will be delivered by road directly to customers for further processing.

The assessed chemical will be imported either in the neat form for local reformulation into finished cosmetic and household products, or as a fragrance component in finished end-use cosmetic and household products and fine fragrances. The end-use concentration of the assessed chemical will be less than 1% in finished cosmetic and household products, perfumes/fine fragrances, air care products, and up to 0.5% in candles. The assessed chemical will also be available at up to 0.1% for the consumer use of polishes and wax blends and at up to 0.16% in washing/cleaning products.

The assessed chemical at less than 1% concentration in washing/cleaning products and polishes/wax blends will be available for professionals and industrial use. Finished products containing the assessed chemical at various concentrations will be packaged in suitable containers and transported to industrial customers or retail outlets.

Human health

Summary of health hazards

The identified health hazards are based on available data for the assessed chemical. For further details of the health hazard information, see **Supporting information**.

Based on the data provided, the assessed chemical is sensitising to the skin, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section). In local lymph node assay (LLNA) studies, the reported concentration producing a 3-fold increase in lymphocyte proliferation (EC3) was 16.4% (see **Supporting Information**). Based on its physicochemical properties, the assessed chemical is not expected to be readily absorbed following oral, dermal or inhalation exposure.

The data provided indicate that the assessed chemical is:

- likely to be of low acute oral, dermal and inhalation toxicity
- slightly irritating to the skin and eyes
- unlikely to be genotoxic
- not likely to cause systemic toxicity following repeated oral exposure (up to 923 and 864 mg/kg bw/day for male and female rats, respectively)

Hazard classifications relevant for worker health and safety

Based on the data provided, the assessed chemical satisfies the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017), as adopted for industrial chemicals in Australia.

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin sens. 1B	H317: May cause an allergic skin reaction

Summary of health risk

Public

When introduced and used in the proposed manner, there will be widespread and repeated exposure of the public to the assessed chemical at less than 1% concentration through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposures are also possible, particularly from air care products and from products applied by spray.

The assessed chemical is a skin sensitiser (Category 1B). Given the proposed low use concentrations of the assessed chemical (less than 1% concentration) in cosmetics and household products skin sensitisation effects are not expected. Similarly, skin sensitisation effects are also not expected when the assessed chemical is used in air care products. The assessed chemical is not persistent in the environment and, therefore, not expected to cause inhalation risk when used at less than 1% concentration in continuous action, electrical air fresheners.

The repeated dose toxicity potential of the assessed chemical was estimated by calculating the margin of exposure (MoE), using the worst-case exposure scenario from the use of multiple cosmetic and domestic products simultaneously by an individual. The total daily systemic

exposure was estimated as 4.45 mg/kg bw/day (see Human exposure section under **Supporting information**). Using No Observed Adverse Effect Levels (NOAELs) of 923 and 864 mg/kg bw/day for the assessed chemical for males and females, respectively (derived from a repeated dose oral toxicity study in rats), a MoE of 208 for males and 194 for females was calculated. A MoE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

This assessment does not identify any risks to public health that would require specific risk management measures when the assessed chemical is introduced in accordance with the terms of the assessment certificate.

Workers

Workers may experience exposure to the assessed chemical in its neat form during reformulation processes such as weighing and transfer stages, blending, quality control analysis, filling and repackaging processes, and cleaning and maintenance of equipment, particularly where manual or open processes are used.

Exposure to the assessed chemical in end-use products (at less than 1% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g., hairdressers and workers in beauty salons). Exposure to the assessed chemical in end-use products (at less than 1% concentration) may also occur in the professional cleaning industry, through the use of products containing the assessed chemical as a fragrance ingredient, such as in cleaning products, and polishes and wax blends.

Workers may experience allergic skin reactions if exposed to the assessed chemical during compounding and end-use product formulation activities at concentrations above 1%. Specific risk management measures are required to manage the risks to workers (see **Means for managing risk** section).

The frequency and extent of exposure of workers applying cosmetic products to clients is similar to public exposure, or lower if personal protective equipment (PPE) is used. No specific controls are required for workers applying end-use products to clients.

Environment

Summary of environmental hazard characteristics

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

- Not persistent (not P)
- Bioaccumulative (B)
- Toxic (T)

Environmental hazard classification

The assessed chemical is formally classified under the GHS (UNECE 2017) as Acute Category 1 (H400) and Chronic Category 1 (H410) based on the toxicity to aquatic invertebrates. Considerations were also made for the rapid biodegradation and bioaccumulation potential of the assessed chemical.

Environmental Hazard	Hazard Category	Hazard Statement
Acute Aquatic	Acute aq. – Cat. 1	H400: Very toxic to aquatic life
Chronic Aquatic	Chronic aq. – Cat. 1	H410: Very toxic to aquatic life with long lasting effects

Summary of environmental risk

The assessed chemical will be introduced as a fragrance ingredient for use in a variety of products. These uses may result in the release of the assessed chemical to sewers and to air.

The assessed chemical is readily degradable and is not persistent. The assessed chemical has a potential to bioaccumulate and is toxic to aquatic organisms according to domestic threshold values.

As the assessed chemical does not meet all three PBT criteria, it is unlikely to have unpredictable long-term effects and its risk may be estimated by the risk quotient method (RQ = PEC ÷ PNEC). Based on calculated RQ values < 1 for the river and ocean compartments, it is expected that the environmental risk from the introduction of the assessed chemical can be managed.

Means for managing risk

Workers

Recommendation to Safe Work Australia

- It is recommended that Safe Work Australia (SWA) update the *Hazardous Chemical Information System* (HCIS) to include classifications relevant to work health and safety (see **Hazard classifications relevant for worker health and safety**).

Information relating to safe introduction and use

The information in this statement, including recommended hazard classifications, should be used by a person conducting a business or undertaking 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 potential exposure to the assessed chemical during reformulation activities:
    - Use of engineering controls such as
        - Enclosed and automated processes
        - Adequate workplace ventilation to avoid accumulation of vapours, mists, or aerosols
    - Use of safe work practices to
        - Avoid contact with skin and eyes
        - Avoid inhalation of mists, aerosols, or vapours
    - Workers should wear the following personal protective equipment (PPE)

    - Impervious gloves
    - Protective clothing
    - Respiratory protection where general ventilation may be inadequate

- As the assessed chemical is a skin sensitiser, control measures may need to be supplemented with health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

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

Conclusions

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

Considering the 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. 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.
- the means of managing the risks identified during this assessment are implemented.

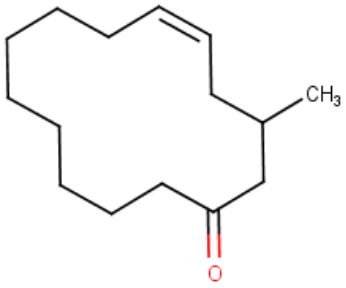
Note: Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	5-Cyclotetradecen-1-one, 3-methyl-
CAS No.	1117765-92-0
Synonyms	3-Methyl-5-cyclotetradecen-1-one
Molecular formula	$C_{15}H_{26}O$
Molecular weight (g/mol)	222.37
SMILES (canonical)	O=C1CCCCCCCCC=CCC(C)C1

Representative structure



Chemical description

The assessed chemical contains two geometric isomers with combined degree of purity of greater than or equal to 81 and less than or equal to 100% where each geometric isomer is racemic.

The typical concentrations of the racemic geometric isomers in the assessed chemical are:

Isomer chemical name	CAS No.	Range conc. % (w/w)
5-Cyclotetradecen-1-one, 3-methyl-, (5*E*)-	259854-70-1	≥ 60 – ≤ 70
5-Cyclotetradecen-1-one, 3-methyl-, (5*Z*)-	259854-71-2	≥ 20 – ≤ 30

Relevant physical and chemical properties

Physical form	Liquid
Melting point	< -50 °C
Boiling point	258 °C at 101.3 kPa (extrapolated via dynamic method, decomposition at 191.5 °C at 15.95 kPa)

Density	932 kg/m^3 at 20 °C
Vapour pressure	0.9 x10^{-3} kPa at 20 °C
Surface tension	61.4 mN/m at 20 °C
Water solubility	4.6 mg/L at 20 °C
Flash point	134 °C at 101.3 kPa
Autoignition Temperature	246 °C
Explosive Properties	Not expected to have explosive properties
Oxidising Properties	Not expected to have oxidising properties
Ionisable in the environment?	No
log K_{ow}	5.6
log K_{oc}	3.8

Human exposure

Workers

Reformulation

Typically, reformulation processes may incorporate blending operations that are manual or automated and may occur in a fully enclosed/contained environment, followed by manual or automated filling using sealed delivery systems into containers of various sizes. Dermal, ocular and inhalation exposure (if aerosols or mists are formed) of workers to the assessed chemical in its neat form is possible during weighing and transfer stages, blending, quality control analysis and cleaning, and during maintenance of equipment. However, the exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of PPE such as protective clothing, eye protection, impervious gloves, and appropriate respiratory protection where general ventilation is insufficient.

Professional end use

Exposure to the assessed chemical in end-use products at less than 1% concentration may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g., hairdressers and workers in beauty salons). These products, depending on their nature, could be applied in a number of ways, such as by hand, using an applicator or sprayed. The principal routes of exposure will be dermal and inhalation (for air care products and spray products), while ocular exposure is also possible. Professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the end-use products containing less than 1% of the assessed chemical.

The assessed chemical is also indicated for use in the professional end uses of washing and cleaning products, and polishes and wax blends. In this setting, these products are used by workers for public and/or private hygiene. These workers are specialised cleaners that use similar products frequently, by mixing the products in water and applying them in liquid form with rollers, brushes or sprays. In other applications, the workers may treat articles by dipping, pouring or immersion.

Public

The assessed chemical is indicated for use as a fragrance ingredient in a range of cosmetic and household products, including washing and cleaning products, polishes and wax blends and air care products. There will be widespread and repeated exposure of the public to the assessed chemical at less than 1% concentration through the use of these products. The principal route of exposure will be dermal, while ocular and/or inhalation exposures are also possible, particularly if the products are applied by spray or when used in air fresheners.

Data on typical use patterns of products (SCCS 2012; Cadby et al. 2002; ACI 2010; Loretz et al. 2006) in which the assessed chemical may be used are shown in the following tables. For the purposes of exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A worst-case dermal absorption (DA) rate of 100% was used along with a lifetime average female body weight (BW) of 70 kg (enHealth 2012) for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Steiling et al. 2014; Rothe et al. 2011; Earnest Jr. 2009). An adult inhalation rate of 20 m^3/day (enHealth 2012) was used assuming the fraction of the assessed chemical inhaled is 50%. Exposure from the use of polishes and wax blends was not considered but is not expected to contribute greatly to the overall systemic exposure at the assessed end use concentrations.

The following tables provide information on exposure estimates obtained using the above parameters.

Cosmetic products (dermal exposure)

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.99	1	1.1060
Face cream	1,540	0.99	1	0.2178
Hand cream	2,160	0.99	1	0.3055
Fine fragrances	750	0.99	1	0.1061
Deodorant (non-spray)	1,500	0.23	1	0.0493
Deodorant (spray)	690	0.23	1	0.0227
Aerosol antiperspirant	1,430	0.23	1	0.0470
Sunscreen	18,000	0.99	1	2.5457
Shower gel	18,670	0.99	0.01	0.0264
Hair styling products	4,000	0.16	0.1	0.0091
Total				**4.4355**

C = maximum intended concentration of assessed chemical; RF = retention factor
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household products (Indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.05	0.95	10	0.0016
Fabric softener	90	0.1	0.95	10	0.0012
Total					**0.0028**

C = maximum intended concentration of assessed chemical
Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact area (cm^2)	Product use C (g/cm^3)	Film thickness (cm)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.05	1,980	0.01	0.01	0.007	< 0.0001
Dishwashing liquid	3	0.05	1,980	0.009	0.01	0.03	0.0001
All-purpose cleaner	1	0.1	1,980	1	0.01	0.007	0.0020
Total							**0.0021**

C = maximum intended concentration of assessed chemical
Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × DA)/BW

Hair spray (inhalation exposure)

Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure duration (Zone 1) (min)	Exposure duration (Zone 2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
9.89	0.16	20	1	20	50	1	10	**0.0047**

C = maximum intended concentration of assessed chemical
Total daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (zone 2) × body weight)]

The worst-case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the assessed chemical at the maximum intended concentrations specified by the applicant in various product types. This would result in a combined internal dose of 4.45 mg/kg bw/day for the assessed chemical. It is acknowledged that inhalation exposure to the assessed chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, the combination of the conservative hair spray inhalation exposure assessment parameters used and the aggregate exposure from use of the dermally applied products (using a conservative dermal absorption rate of 100%), are sufficiently protective to cover additional inhalation exposure to the assessed chemical from the use of other spray cosmetics and household products containing it with low potential exposure (e.g., air fresheners).

Health hazard information

Toxicokinetics

Given the low water solubility (4.6 mg/L at 20 °C) and the partition coefficient (log K_{OW} = 5.6) of the assessed chemical, absorption across biological membranes is expected to be limited.

Acute toxicity

Oral

In an acute oral toxicity study (OECD TG 423), two groups of three fasted female Wistar rats were administered a single dose of 2,000 mg/kg bw of the assessed chemical in vehicle (corn oil) via oral gavage. The animals were observed for 14 days after administration. The body weight of the animals was within the range commonly recorded for this strain and age. All animals survived until the end of the study period. No macroscopic findings were recorded at necropsy. The acute oral LD50 value was determined to be > 2,000 mg/kg bw.

Dermal

In an acute dermal toxicity study (OECD TG 402), the assessed chemical was applied at a single dose of 2,000 mg/kg bw evenly on the intact skin of 10 Wistar rats (n = 5/sex) and covered with a semi-occlusive dressing for 24 hours. No deaths or signs of systemic toxicity were observed. Slight general erythema was noted in all animals on test day 2 and persisted in six of these animals up to test day 7. Slight scaling was observed in one male and three females from test day 4 to test day 10, indicating irritation effects to the assessed chemical. The LD50 was determined to be greater than 2,000 mg/kg bw. Based on the results of this study, the assessed chemical is likely to be of low acute dermal toxicity.

Inhalation

In an acute inhalation toxicity study (OECD TG 403), the assessed chemical was administered by nose-only inhalation to one group of five male and five female Wistar rats as an aerosol for 4 hours. The animals were observed for 14 days following inhalation exposure. The time-weighted mean actual concentration was 5.1 ± 0.1 mg/L. No mortality occurred.

During exposure, slow breathing was seen for the animals. After exposure, lethargy, hunched or flat posture, tremors, chromodacryorrhoea (secretion of red pigmented tears), laboured respiration and piloerection were seen for the animals up to Day 4. Rales was seen for one male on Day 7, hypersensitivity to touch was noted for one female on Days 7, 8 and 9. Overall, mean body weight gain in males and females was within the range expected for rats of this strain and age used in this type of study. No abnormalities were found at macroscopic post-mortem examination of the animals. The inhalation LC50 in Wistar rats was established to exceed 5 mg/L, indicating low acute inhalation toxicity.

Corrosion/Irritation

Skin irritation

The assessed chemical was investigated for skin irritating potential in rabbits (OECD TG 404). In this study, a single 4-hour topical semi-occlusive application of the assessed chemical to the intact skin of three young adult New Zealand White rabbits resulted in slight, early-onset

and transient signs of irritation such as erythema, oedema and scaling. These effects were reversible and were no longer evident at the end of the observation period for all animals (Day 10); no other skin reactions or clinical signs were noted in any animal. The mean erythema/eschar score of the three animals was 0.67, 0.67 and 1.33, respectively, and the mean oedema score was 0.33 for all three animals. Therefore, under the conditions of this study, the assessed chemical is considered to be slightly irritating to the skin. Due to the reversibility of the effects, the assessed chemical does not satisfy the criteria for classification as a skin irritant under the GHS (UNECE 2017).

Eye irritation

The eye irritation potential of the assessed chemical was investigated in rabbits (OECD TG 405). A volume of 0.1 mL of the assessed chemical was placed into the conjunctival sac of one eye of each of three young adult New Zealand White rabbits. The other eye remained untreated and was used for control purposes. Assessment of ocular damage/irritation was made at approximately 1, 24, 48, and 72 hours following treatment. A single application of the assessed chemical produced no corneal or iridial effects at any time point. Slight to moderate early-onset and transient ocular changes, such as reddening of the conjunctivae and sclerae, discharge and chemosis were noted at 1 hour after treatment. These effects were reversible and no longer evident at 48 hours after treatment. No staining of the treated eyes and no other clinical signs were observed. The assessed chemical is considered to be slightly irritating to the eye. Due to the reversibility of the effects, the assessed chemical does not satisfy the criteria for classification as an eye irritant under the GHS (UNECE 2017).

Sensitisation

Skin sensitisation

Based on the submitted information, the assessed chemical is considered to be a skin sensitiser (Category 1B).

In a local lymph node assay (LLNA) (OECD TG 429), three groups of four female mice (CBA/CaOlaHsd) received topical applications at 1%, 10% and 25 % (w/v) concentrations of the assessed chemical in acetone:olive oil 4:1 (v/v) to the dorsum of each ear lobe (left and right) for 3 consecutive days. The maximum concentration of 25% (w/v) was chosen to avoid systemic toxicity and local irritant effects. A control group of four mice was treated with the vehicle (acetone:olive oil, 4:1(v/v)) only. The reported stimulation indices (SI) were 1.4, 1.8 and 4.6 for assessed chemical concentrations of 1%, 10% and 25%, respectively. The reported concentration of assessed chemical producing a three-fold increase in lymphocyte proliferation (EC3) was 16.4%, indicating moderate skin sensitisation potential to the assessed chemical.

In a non-guideline open epicutaneous test, conducted as per CTFA Safety Testing Guidelines (1991) and under GLP conditions, the assessed chemical was applied epicutaneously to areas of the clipped flank skin during the induction and challenge phase. Six Dunkin-Hartley male albino guinea pigs were used for each test concentration and vehicle group (corn oil) and were treated with 10%, 20%, 40% and 100% concentration of the assessed chemical, 5 times per week for a total of 20 exposures. The animals were challenged with 1%, 3%, 5% and 10% concentration of the assessed chemical at day 29, followed by a rechallenge with 0.1%, 0.25%, 0.5% and 0.75% concentrations at day 51. The reactions were recorded 24 hours after each induction application and 24, 48 and 72 hours after challenging. The fading of observed reactions after the 24-hour reading and the absence of a dose-response relationship led to the conclusion that the reactions in the test animals were not of an allergic nature. Therefore, the assessed chemical is not considered to possess skin sensitisation potential in albino guinea pigs in this non-guideline study.

The skin sensitisation potential of the assessed chemical was further tested in a human repeat insult patch test (HRIPT) study, where human subjects were treated occlusively with the assessed chemical at 20% concentration. This study was conducted with the intent and purpose of Good Clinical Practice regulations described in Title 21 of the U.S. Code of Federal Regulations (CFR), the Declaration of Helsinki and/or Essex Testing Clinic Standard Operating Procedure. Ninety-seven human subjects (female and/or male, 18–74 years old), out of 110 enrolled, satisfactorily completed the test procedure. Thirteen (13/110) subjects discontinued for personal reasons unrelated to the conduct of the study. The proportion of volunteers that presented an allergic reaction was 0%. Therefore, under the conditions of the repeated insult (occlusive) patch test, the assessed chemical at 20% concentration did not induce any evidence of allergic contact dermatitis in 97 human subjects.

In another HRIPT study, human subjects were treated occlusively with the assessed chemical at 10% concentration. Similar to the above study, this study was conducted under Good Clinical Practice regulations described in Title 21 of the U.S. CFR, the Declaration of Helsinki and/or Essex testing Clinic Standard Operating Procedure. One hundred and three human subjects (males/females,19–69 years old), out of 110 enrolled, satisfactorily completed the test procedure. The proportion of volunteers that presented an allergic reaction was 0%. Therefore, under the conditions of the repeated insult (occlusive) patch test, the assessed chemical at 10% concentration did not induce any evidence of allergic contact dermatitis in 103 human subjects.

In a third HRIPT study conducted similarly to the above studies, human subjects were treated occlusively with the assessed chemical at 6% concentration. Fifty-four human subjects (males/females, 20–69 years old), out of fifty-five enrolled, satisfactorily completed the test procedure. A barely perceptible (+) patch test response was observed in one human subject (1/54) during the Induction phase of the study. This response was judged to be non-specific in nature and is not indicative of clinically significant irritation. There were no dermal responses on any subject during the Challenge phase. Therefore, under the conditions of the repeated insult (occlusive) patch test, the assessed chemical at 6% concentration did not induce any evidence of allergic contact dermatitis in 54 human subjects.

Repeat dose toxicity

Oral

In a repeated dose toxicity study (OECD TG 407), the assessed chemical was administered by dietary administration to Wistar rats (n = 5/sex/group) for 28 days. The dose levels for the study were selected to be 0, 1,000, 3,000 and 10,000 ppm, equivalent to doses of 0 (control), 89, 263 and 923 mg/kg bw/day in male rats and 0 (control), 86, 268 and 864 mg/kg bw/day in female rats, respectively.

No clinical signs were noted during the observation period. There were no deaths during the course of this study, and there were also no treatment-related changes in behavioural parameters, functional performance tests, sensory reactivity assessment, food consumption, body weight, body weight gain, and food intake levels. Necropsy did not reveal any treatment-related abnormalities.

Histopathology showed a non-adverse increase in incidence and severity of hyaline droplet accumulation in the kidneys of males at all doses, which partially recovered after a treatment-free period of 14 days. This finding is known to represent alpha2u-globulin, a male rat-specific protein not present in humans, which undergoes re-absorption in the proximal cortical tubules. Therefore, this effect is not relevant for humans.

Higher liver weights and hepatocellular hypertrophy were noted in males treated with the assessed chemical at 263 and 923 mg/kg bw/day. Higher liver weights were noted in females treated with the assessed chemical at 86, 268 and 864 mg/kg bw/day at the end of the treatment period. Hepatocellular hypertrophy was observed in females treated with the assessed chemical at 86, 268 and 864 mg/kg bw/day. Thus, higher liver weights in both males and females correlated with hepatocellular hypertrophy at these doses. However, as no morphological evidence of liver damage was noted, the magnitude of liver weight increase was considered to be an adaptive (non-adverse) response by the study author.

Based on the above findings, the NOAEL was established to be 10,000 ppm (corresponding to 923 and 864 mg/kg bw/day for males and females, respectively in this study).

Genotoxicity

A study was performed to evaluate the potential of the assessed chemical to cause point mutations in a bacterial reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 in both the presence and absence of S9-mix (OECD TG 471). No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any concentration of the assessed chemical, either with or without metabolic activation (S9-mix). Under the conditions of this study, the assessed chemical was not considered to be mutagenic in the presence or absence of metabolic activation.

Another study was performed to assess the potential of the assessed chemical to induce structural chromosomal aberrations in V79 cells of Chinese hamster lung cells, with or without the S9-mix (OECD TG 473). Two independent experiments were performed. In both experiments, no biologically relevant increase in the rate of polyploid metaphases (1.1–2.3%) was found after treatment with the test item as compared to the rates of the solvent controls (0.9–2.1%). Under the experimental conditions reported in this study, the assessed chemical was determined to be non-clastogenic.

Environmental exposure

The assessed chemical will be imported into Australia either in end-use products, or in neat form or as a component of fragrance formulations for reformulation into end-use products. Reformulation and repackaging will occur in closed processes. Significant releases of the assessed chemical to the environment are not expected during reformulation, transport or storage.

The assessed chemical is a fragrance ingredient to be included in a range of products, resulting in a variety of potential exposure scenarios.

Industrial end-uses of the assessed chemical in metal surface treatment, washing, cleaning and disinfection products are not expected to result in significant releases of the assessed chemical to the environment as the wastewater containing the assessed chemical is expected to be collected and treated as industrial wastewater.

Consumer and professional end-use of the assessed chemical in polish and wax blends, cosmetic products, washing, cleaning and disinfection products is expected to result in the release of the assessed chemical “down the drain” and into the sewers. Consequently, the assessed chemical will be treated at sewage treatment plants (STPs) before release to surface waters.

Use of the assessed chemical in air-care products will result in direct release of the assessed chemical into the air compartment.

Environmental fate

Partitioning

The assessed chemical has a high log K_{OC} value (log K_{OC} = 3.8). Therefore, the chemical is expected to partition to soils and sediments where it will be immobile.

The assessed chemical is slightly water soluble (water solubility = 4.6 mg/L at 20 °C). If the assessed chemical is released to surface water, a proportion of the assessed chemical is expected to remain in water compartment and a proportion of the chemical is expected to partition to sediments based on its slight water solubility and high log K_{OC} value.

The assessed chemical is moderately volatile (vapour pressure = 0.9 Pa at 20 °C). A small proportion of the assessed chemical is expected to partition to air during STP treatment based on SimpleTreat 3.0 model outputs (Struijs, 1996). Additionally, when the assessed chemical is directly released to air it is not expected to partition to other compartments.

Degradation

Based on its measured degradation in water and predicted degradation in air, the assessed chemical is not persistent.

The half-life of the assessed chemical in air is calculated to be 1.6 hours (US EPA, 2012; calculated using AOPWIN v1.92). As its calculated half-life in air is below the domestic threshold value of 2 days, the assessed chemical is not expected to persist in the air compartment.

Degradation studies conducted in water for the assessed chemical indicate it is inherently and readily biodegradable. The result of an inherent biodegradation study in water for the assessed chemical was 75% degradation (OECD 302C) over 28 days. The result of a ready biodegradation study in water for the assessed chemical was 70% degradation (OECD 301F) over 28 days. While the 10-day window was not satisfied, the substance is a mixture of stereoisomers and sequential degradation may have been occurring. Therefore, the substance is considered readily biodegradable in line with the OECD guidance (OECD, 2006).

Bioaccumulation

The assessed chemical is potentially bioaccumulative based on its log K_{OW} value.

No bioaccumulation information was provided for the assessed chemical. The experimental partition coefficient of the assessed chemical is log K_{OW} = 5.6, exceeding the domestic bioaccumulation threshold of log K_{OW} = 4.2 (EPHC, 2009). This determination is considered to be conservative, as the assessed chemical it not considered to be persistent.

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming 100% of the introduction volume is released into sewage treatment plants (STPs) over 365 days per annum. This calculated value is conservative as not all uses of the assessed chemical are expected to result in 100% release to STPs. Based on its slight water solubility (4.6 mg/L)

and high log K_{OW} of 5.6, a large proportion of the assessed chemical is expected to adsorb to biosolids and be removed during STP treatment. The chemical is readily biodegradable. Correspondingly, a significant proportion of the assessed chemical is also expected to biodegrade during STP treatment. As a result, only a small proportion of the assessed chemical is expected to be present in STP effluent. The extent to which the assessed substance is removed from the effluent in STP processes is based on its physicochemical properties, modelled by SimpleTreat 3.0 (Struijs, 1996), and is estimated to be 91%. Therefore 9% of the total introduction volume is estimated to be released to the aquatic environment. The calculation of the PEC is detailed in the table below:

Total Annual Import Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	2.74	kg/day
Water use	200	L/person/day
Population of Australia	25.423	Million
Removal within STP	91%	Mitigation
Daily effluent production	5,085	ML/day
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	0.04	µg/L
PEC - Ocean	0.004	µg/L

These PEC values are further considered to be conservative as a portion of the calculated assessed chemical in the STP effluent will partition to sediments, based on the log K_{OC} value of the assessed chemical.

Environmental effects

Effects on Aquatic Life

Acute toxicity

The following measured median effective concentration (EC50) values for model organisms were supplied for the assessed chemical:

Taxon	Endpoint	Method
Invertebrate	48 h EC50 = 0.58 mg/L	*Daphnia magna* (water flea) Immobility OECD TG 202 Static Nominal concentration
Algae	72 h EC50 = 2.6 mg/L	*Pseudokirchneriella subcapitata* (green algae) growth rate OECD TG 201 Static Measured concentration

Chronic toxicity

The following measured 10th-percentile effective concentration (EC10) value for model organisms was supplied for the assessed chemical:

Taxon	Endpoint	Method
Algae	72 h EC10 = 0.88 mg/L	*Pseudokirchneriella subcapitata* (green algae) growth rate OECD TG 201 Static Measured concentration

Predicted no-effect concentration (PNEC)

A predicted no-effect concentration (PNEC) of 0.58 µg/L was calculated for the assessed chemical in the aquatic environment. This value was derived using the most sensitive acute endpoint value, which is for aquatic invertebrates (0.58 mg/L). An assessment factor of 1,000 was applied to this endpoint as acute toxicity data are available for two tropic levels and chronic toxicity data are available for one trophic level (EPHC, 2009). The acute endpoint was selected, over the algal chronic endpoint, in the absence of additional chronic endpoints to support the algal growth rate EC10 (ECHA 2008).

Categorisation of environmental hazard

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

Persistence

Not Persistent (Not P). Based on measured degradation, the assessed chemical is categorised as Not Persistent.

Bioaccumulation

Bioaccumulative (B). Based on a high measured log K_{OW} value, and no evidence of biotransformation, the assessed chemical is categorised as Bioaccumulative.

Toxicity

Toxic (T). Based on available ecotoxicity values below 1 mg/L, the assessed chemical is categorised as Toxic.

Environmental risk characterisation

Although the assessed chemical is toxic and bioaccumulative, it does not meet all three PBT criteria. It is hence unlikely to have unpredictable long-term effects (EPHC 2009). An estimate of risk may therefore be determined using the risk quotient method.

Based on the PEC and PNEC values determined above, Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of the assessed chemical to water:

Compartment	PEC	PNEC	RQ
River	0.04 µg/L	0.58 µg/L	0.07
Ocean	0.004 µg/L	0.58 µg/L	< 0.01

For the river and ocean compartments, an RQ less than 1 indicates that introduction of the assessed chemical, in line with the terms outlined in this assessment certificate, is not expected to pose a significant risk to the environment. As such, the risk from the assessed chemical can be managed, based on consideration of the environmental hazard characteristics and estimated releases.

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