Cyclopropanecarboxylic acid, 2-methyl-2-[[(2*E*)-1,2,4-trimethyl-2-penten-1-yl]oxy]propyl ester

Assessment statement (CA09529)

31 October 2022

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AICIS assessment

Chemical in this assessment

Name	CAS registry number
Cyclopropanecarboxylic acid, 2-methyl-2-[[(2*E*)-1,2,4-trimethyl-2-penten-1-yl]oxy]propyl ester	1835697-72-7

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 focus

Based on the introduction, use and end use information described in the application, the human health and environment exposure bands of the introduction are 4 and 2 respectively [table item 6 Clause 1 and table item 2 Clause 3, Schedule 1 of the Industrial Chemicals (General) Rules 2019 (the Rules)]. The assessed chemical has hazard characteristics in human health hazard band B (table items 12 and 14, clause 2, Schedule 1 of the Rules), and environment hazard band B (table item 8, clause 4, Schedule 1 of the Rules). In accordance with item 5 subsection 28(1) and item 12 subsection 29(1) of the Rules, the indicative human health risk for the proposed introduction is medium to high and the indicative environment risk for the proposed introduction is low.

Defined scope of assessment

The chemical was assessed for use by professionals and consumers as a fragrance ingredient in cosmetic, personal and household products:

- imported into Australia at up to 1 tonne per year
- imported at up to 100% concentration for reformulation of end use products at less than 1% concentrations for consumers and professional use

Summary of assessment

Summary of introduction, use and end use

The chemical will not be manufactured in Australia. It will be imported into Australia at up to 100% concentration for further reformulation to less than 1% concentrations in end use products.

The reformulated end use products containing the assessed chemical at < 1% concentrations will be used in cosmetics, and household products for consumer use at:

- less than 1% in air care products

- up to 0.1% in polishes and wax blends
- up to 0.3% in washing and cleaning products
- less than 1% in perfumes/fragrances, body cream, shower gel, liquid spray and aerosol hair styling products, solid, liquid or spray deodorant, aerosol antiperspirant and liquid antiperspirant.

The assessed chemical at less than 1% concentrations in washing/cleaning products and polishes/wax blends will be available for professionals and industrials use.

Human health

Summary of health hazards

Based on the available data the assessed chemical is likely to be sensitising to skin, and it may cause damage to organs through prolonged or repeated exposure (see supporting information), warranting hazard classification (see below).

The available toxicity data indicate that the assessed chemical:

- is likely to be of low acute oral and dermal toxicity;
- is slightly irritating to the skin and eyes (but is not classified as skin irritant nor eye irritant under GHS regulation); and
- is unlikely to be genotoxic.

No inhalation toxicity data were provided on the assessed chemical.

Health hazard classification

The chemical satisfies the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (United Nations, 2017) for hazard classes relevant for worker health and safety as follows. This does not consider classification of physical and environmental hazards.

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin Sens. 1B	H317: May cause an allergic skin reaction
Specific target organ toxicity – repeated exposure	STOT Rep. Exp. 2	H373: May cause damage to organs through prolonged or repeated exposure

Summary of health risk

Workers

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

Exposure to the assessed chemical in end use products (at < 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) or the use of household products in the cleaning industry.

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

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 customers.

Public

When introduced and used in the proposed manner, there will be widespread and repeated exposure of the public to the assessed chemical at < 1% concentrations through the use of a wide range of cosmetic and household products containing the assessed chemical and 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.

Given the proposed low use concentrations of the assessed chemical (at < 1% concentration) in cosmetics and household products (including aerosol and spray air fresheners), skin sensitisation and adverse systemic effects from repeated exposure are not expected. The assessed chemical is not persistent in the environment and therefore, not expected to cause inhalation risk when using at <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 use of multiple products simultaneously by an individual. The total daily systemic exposure was estimated as 0.5155 mg/kg bw/day (see Human exposure section under **Supporting information**). Using a No Observed Adverse Effect Level (NOAEL) of 50 mg/kg bw/day for the assessed chemical, MOE of 97 was calculated. MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. The MOE would be 98 (50 mg/kg bw/day ÷ 0.5088 mg/kg bw/day) excluding the laundry products (not applied to the skin deliberately and any accidental spillage is expected to be washed-off immediately). In addition, the MOE of 97 was derived for the worst case systemic exposure scenario considering a dermal absorption rate of 100%. The dermal absorption rate of the assessed chemical is expected to be lower than 100% due to the low water solubility (14 mg/L at 20°C) of the assessed chemical.

Overall if the assessed chemical is introduced and used in accordance with the terms of the assessment certificate, no risks are identified for public health during this assessment that require specific risk management measures.

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)
- Not toxic (not T)

Environmental hazard classification

Although the chemical is classified as not toxic according to domestic criteria for PBT assessment, it is formally classified under the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) (United Nations, 2017) as Acute Category 2 (H401) and Chronic Category 2 (H411) based on the toxicity to fish. Considerations were also made for the bioaccumulation potential of the assessed chemical.

Environmental Hazard	Hazard Category	Hazard Statement
Acute Aquatic	Acute aq. – Cat. 2	H401: Toxic to aquatic life
Chronic Aquatic	Chronic aq. – Cat. 2	H411: 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 degradable and is not persistent. The assessed chemical has potential to bioaccumulate and is not toxic to aquatic organisms.

As the assessed chemical is not a PBT chemical, 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 risks

Workers

Recommendation to Safe Work Australia

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

Information relating to safe introduction and use

- The information in this statement includes recommended hazard classifications and 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 should be implemented to manage the risk arising from 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 or eyes
        - Avoid inhalation of vapours, mists, or aerosols

    - Workers should wear the following personal protective equipment (PPE)
        - Impervious gloves
        - Protective clothing
        - Respiratory protection where local ventilation may be inadequate

- As the assessed chemical is a skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin sensitisation.

- Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

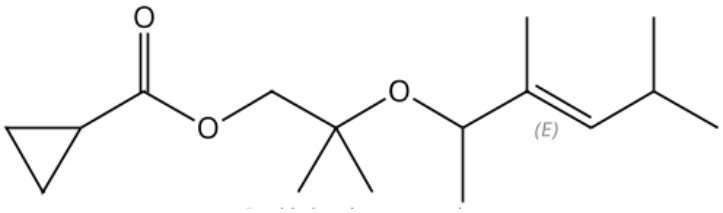
The conclusions of this assessment are based on the information described in this statement.

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 apply.

Supporting information

Chemical identity

Chemical name	Cyclopropanecarboxylic acid, 2-methyl-2-[[(2*E*)-1,2,4-trimethyl-2-penten-1-yl]oxy]propyl ester
CAS No.	1835697-72-7
Synonyms	2-Methyl-2-[[(2*E*)-1,2,4-trimethyl-2-penten-1-yl]oxy]propyl cyclopropanecarboxylate (*E*)-2-(3,5-dimethylhex-3-en-2-yloxy)-2-methylpropyl cyclopropanecarboxylate Sylkolide
Structural formula	
Molecular formula	$C_{16}H_{28}O_3$
Molecular weight (g/mol)	268.39
SMILES	O=C(OCC(OC(C(=CC(C)C)C)C)(C)C)C1CC1

Relevant physical and chemical properties

Physical form	Appearance at 20 ºC and 101.3 kPa: colourless liquid at 97% concentration
Freezing point	< -50 °C
Boiling point	309.9 °C at 101.3 kPa
Density	928 kg/m^3 at 20 °C
Vapour pressure	4.59 × 10^{-4} kPa at 20 °C
Flash point	131 °C at 101.3 kPa
Autoignition Temperature	280 °C
Explosive Properties	Not expected to have explosive properties
Oxidising Properties	Not expected to have oxidising properties
Surface tension	56.1 mN/m at 20°C

Water solubility	14 mg/L at 20°C
Ionisable in the environment?	No
log K_{ow}	4.4
Log K_{oc}	3.7

Human exposure

Workers

Reformulation

Typically, reformulation processes may incorporate blending operations that are automated or manual 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.

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) or the use of household products in the cleaning industry. 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 route 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.

Public

There will be widespread and repeated exposure of the public to the chemical at less than 1% concentration through the use of a range of cosmetic and household 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. Given the low molecular weight (268.39 g/mol) of the assessed chemical, there is potential for it to cross biological membranes, including the skin. However, the partition coefficient (log P_{ow} = 4.4) implies low water solubility of the chemical to absorb through biological membranes. 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 and it was conservatively assumed that the fraction of the assessed chemical inhaled is 50%.

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	7820	0.33	1	0.3687
Deodorant	1500	0.07	1	0.0150
Shower gel	18670	0.99	0.01	0.0264
Hair styling products	4000	0.99	0.1	0.0566
Total				**0.4667**

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	0.3	0.95	10	0.0094
Fabric softener	90	0.3	0.95	10	0.0037
Total					**0.0130**

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	0.3	1980	0.01	0.01	0.007	0.0001
Dishwashing liquid	3	0.3	1980	0.009	0.01	0.03	0.0007
All-purpose cleaner	1	0.3	1980	1	0.01	0.007	0.0059
Total							**0.0067**

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)

Product type	**Amount** (g/day)	**C** (%)	**Inhalation Rate** (m^3/day)	**Exposure duration (Zone 1)** (min)	**Exposure duration (Zone 1)** (min)	**Fraction Inhaled** (%)	**Volume (Zone 1)** (m^3)	**Volume (Zone 2)** (m^3)	**Daily systemic exposure** (mg/kg bw/day)
Hairspray	9.89	0.99	20	1	20	50	1	10	**0.0291**

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 0.5155 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 100% dermal absorption rate), are sufficiently protective to cover additional inhalation exposure to the assessed chemical from the use of other spray cosmetic and household products containing it with low exposure (e.g., air fresheners).

Health hazard information

Toxicokinetics

Given the relatively low molecular weight (268.39 g/mol), low water solubility (14 mg/L at 20°C) and the partition coefficient (log K_{ow} = 4.4) of the assessed chemical, absorption across biological membranes is limited.

Acute toxicity

Oral

Based on acute oral and dermal toxicity studies (conducted according to OECD TG 423 and 402, respectively), the assessed chemical is likely to be of low acute toxicity to rats via the oral and dermal routes (LD50 > 2000 mg/kg bw).

No acute inhalation toxicity data are available for the assessed chemical.

Corrosion/Irritation

Skin irritation

The assessed chemical was slightly irritating to the skin in an *in vivo* study conducted in New Zealand rabbits according to OECD TG 404. Based on the mean tissue viability of > 50%, the assessed chemical is not classified as a skin irritant according to the GHS criteria in a study conducted using a protocol similar to the OECD TG 439.

Eye irritation

The assessed chemical was slightly irritating to the eye in an *in vivo* study conducted in New Zealand rabbits according to OECD TG 405. In an *in vitro* Eye Irritation test (Human Cornea Model Test - in house method), the assessed chemical was considered not irritating to the eyes.

Sensitisation

Skin sensitisation

The skin sensitisation potential of the assessed chemical was assessed using a local lymph node assay (LLNA) in mice (OECD TG 429). The assessed chemical was topically administered to the ears of mice.

There were no deaths or symptoms of local toxicity at the ears of the animals or signs of systemic toxicity, and body weights were within the range for animals of this strain and age. However, there was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the assessed chemical. The Stimulation Indices (SI) were 1.39, 2.63 and 5.96 with the test substance at concentrations of 5%, 10% and 25%. An EC3 value of 11.7% was calculated. Based on the GHS criteria for classification, the assessed chemical is determined to be a Category 1B skin sensitiser.

A Repeated Insult Patch (HRIPT) test with challenge, was performed in 105 subjects (86 F, 19 M; age ranged from 18 to 70 years). While 101/105 subjects completed the test procedure, 4/105 subjects discontinued for personal reasons unrelated to the conduct of the study. The assessed chemical at 2.5% concentration in ethanol/diethyl phthalate (EtOH/DEP) (1:3) did not induce skin irritation nor showed any evidence of induced allergic contact dermatitis during the study. Therefore, the assessed chemical at 2.5% concentration was non-irritating or non-sensitising under the conditions of the test.

Repeat dose toxicity

Oral

Repeated dose Study 1

A 28-day repeated dose oral (gavage) toxicity study in rats (OECD TG 407) was conducted, in which the assessed chemical was administered at 0, 100, 300 and 1000 mg/kg bw/day for 28 consecutive days. As the animals treated with 1000 mg/kg bw/day developed severe symptoms the highest dose group was changed to 600 mg/kg bw/day. A recovery group at high dose (600 mg/kg bw/day) was also added.

At 100 and 300 mg/kg bw/day, mean daily food consumption and body weight gain were not affected in males or females.

There were statistically significant increases of blood urea levels in females at 100 and 300 mg/kg bw/day and in males at 300 mg/kg bw/day (not statistically significant).

Increased levels of ketones were detected in the urine of males at 100 and 300 mg/kg bw/day, showing statistical significance at 300 mg/kg bw/day. These differences exceeded the historical control ranges.

Minimal to moderate myocardial necrosis impacted four of five males at 300 mg/kg bw/day.

Males at 300 mg/kg bw/day had significantly increased mean red blood cell count, compared with the control group.

In females treated at 300 mg/kg bw/day, the mean absolute liver weight was statistically significantly increased (+18.6%) when compared with the control mean. In four of five females at 100 mg/kg bw/day and all females at 300 mg/kg bw/day, the liver was clay-coloured, being associated with increased periportal hepatocellular vacuolation. Minimal to moderate periportal hepatocellular vacuolation was observed in females at 100 and 300 mg/kg bw/day and in males at 300 mg/kg bw/day.

At 600 mg/kg bw/day, two treated females died, and three more females were removed during the treatment for ethical reasons. Clinical observations such as ataxia, slight sedation,

salivation, dyspnea, transiently decreased activity, hunched posture, ruffled fur, bilateral ptosis and visible weight loss were observed in several animals at this dose level.

At 600 mg/kg bw/day, the mean cholesterol level in males was statistically significantly lower compared with the control group (-18.3%). This parameter was mildly reduced in females without statistical significance. Triglycerides were significantly higher in males (+53.1%), but not in females.

Increased urine output in both sexes at 600 mg/kg bw/day after 4 weeks was reported to be related to the impaired ability of the kidney to concentrate urine. A dose-dependent increase in ketone concentration was observed in males (+1133%) (with statistical significance at 600 mg/kg bw/day).

Minimal to moderate myocardial necrosis impacted two of five males at 600 mg/kg bw/day.

Females died prematurely (2/5 at 600 mg/kg bw/day) had marked to severe atrophy of the thymus.

Recovery group at 600 mg/kg bw/day:

There was no surviving treated females. Following the recovery period, three of five males had minimal to marked ventricular dilation and one male had moderate epicarditis and myocardial necrosis. The mean absolute and relative heart weights were significantly higher in males and correlated with minimal to marked ventricular dilation.

There were several statistically significant differences in blood parameters of recovery males including reduced mean corpuscular haemoglobin level.

Following the recovery period, minimal to moderate cellular debris was found in the epididymides of three of five males. Two of these animals had minimal to moderate tubular atrophy of the testes.

One recovery male had minimal haemorrhagic necrosis and slight periportal fibrosis in the lungs. This animal also had increased alveolar histiocytosis in the lung and necrosis and epicarditis in the heart.

A no observed adverse effect level (NOAEL) could not be determined in this study as there were treatment related effects in rats at all dose levels from 100 mg/kg bw/day (blood and urine parameters - blood urea and ketone levels increase including organ weight changes). Myocardial necrosis was observed in 4/5 males at 300 mg/kg bw/day.

Repeated dose Study 2

A 28-day repeated dose oral (gavage) toxicity study in rats (OECD TG 407) was conducted using the assessed chemical at 0, 5, 25, and 50 mg/kg bw/day. No test substance-related toxicity, mean body weights effects, or changes in functional observational battery such as grip strength effects and changes in locomotor activity, were observed during the study period at all dose levels. There were no test substance-related differences in urinalysis parameters, or changes in organ weights, mean clinical biochemistry parameters, and macroscopical or microscopical changes at all dose levels.

The NOAEL was established as 50 mg/kg bw/day as there was no adversity in animals at this dose level, although some blood parameters were affected at 50 mg/kg bw/day, such as

differences in the reticulocyte maturity indices when compared with the controls, the significantly reduced low-fluorescence reticulocytes (-9.5%) in 4/10 males and the elevated high-fluorescence reticulocytes (+49.3%) in 8/10 males.

Considering the two 28-day studies in rats, with adverse effects observed at 300 mg/kg bw/day and above, and based on the GHS criteria for Specific Target Organ Toxicity (STOT) repeated exposure, the assessed chemical is classified as hazardous for STOT (Category 2).

Genotoxicity

The assessed chemical was not mutagenic in the Bacterial Reverse Mutation Assay (Ames Test) when tested in *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, TA102, and *Escherichia coli* WP2 uvrA with or without metabolic activation (OECD TG 471).

The assessed chemical was tested for its potential to induce structural chromosome aberrations in V79 cells of the Chinese hamster in vitro (OECD TG 473). Under the experimental conditions, the test item induced structural chromosome aberrations in V79 cells in the presence of metabolic activation at the top dose alone (2770 µg/mL). No effects were seen at the mid (173.1 µg/mL) or low doses (10.8 µg/mL) in the presence of S9-mix or at any dose in the absence of S9-mix.

The assessed chemical did not induce micronuclei in an in vivo study in mice (OECD TG 474). The highest tolerated dose determined in a preliminary test (750 mg/kg bw) was used in the main test. Clinical signs indicated systemic exposure but there was no cytotoxicity to the bone marrow as measured by the PCE/NPCE ratio. Serum analysis did not detect the assessed chemical. However, this was considered by the study authors to be due to hydrolysis of the ester linkage and formation of metabolites. The assessed chemical is considered to be non-mutagenic in this in vivo micronucleus assay.

Overall, the assessed chemical is not considered to be genotoxic.

Reproductive and development toxicity

In a Reproduction/Developmental Toxicity Screening Test (OECD TG 421), female and male rats (Crl:WI(Han)) (n = 10 per sex per group) were orally administered the assessed chemical at 0, 25, 50 and 75 mg/kg bw/day (once daily for 14 days prior to mating for males and continuing through one day prior to euthanasia (study 0-27 days) and females were dosed for 14 days prior to mating and continuing through lactation day 12. No test substance-related effects were observed at any dose level for F0 males and females. No test substance-related effects were observed at any dose level for mean body weights, body weight gains, and food consumption throughout the treatment in both males and females, including gestation and lactation for females, reproductive performance such as mating, fertility and pregnancy indices, number of oestrous cycles, oestrous cycle length (days) and pre-coital interval (days) or natural delivery observations including mean gestation lengths, gestation index, the mean post-implantation loss (unaccounted-for sites) and implantation sites, thyroid hormone levels in the F0 males and organ weights, gross necropsy and histopathology.

No test substance-related effects were observed at any dose level in the total number of newborn pups, number of live newborn pups, the percentage of males at birth, postnatal survival including live birth, viability, and survival indices, clinical condition of the pups, anogenital distance, and areola/nipple anlagen retention (in males). There were no retained nipples in any group. Slightly lower mean pup body weight gains were observed during postnatal day 1-13 in the 75 mg/kg bw/day group F1 males and females, resulting in lower

mean pup body weights from postnatal day 4 to 13. Due to the lower mean body weight gains, mean absolute body weights at termination (postnatal day 13) were 6.30% and 7.07% lower than controls for males and females, respectively. These changes were considered test substance-related but non adverse, due to the low magnitude of change from the control group. No test substance-related effects were observed on mean pup body weights and body weight gains at 25 and 50 mg/kg bw/day. No test substance-related macroscopic findings were observed in F1 pups at the scheduled necropsy on postnatal day 13, and no test substance-related effects were found in serum T4 levels or mean thyroid/parathyroid weights in the F1 male pups at any dose level on postnatal day 13. Lower mean thyroid/parathyroid weights were observed for female pups in the 75 mg/kg bw/day group, however, similar effects were not observed in male pups on postnatal day 13 and there were no correlating effects on thyroid hormone levels.

The NOAEL for F0 reproductive toxicity and F0 systemic toxicity was established as 75 mg/kg bw/day in this study, based on the absence of any effect on reproductive parameters or any evidence of adverse toxicity for F0 rats. The NOAEL for F1 neonatal toxicity was established by the study authors as 75 mg/kg bw/day, based on the absence of any adverse effects on any F1 rats for the parameters investigated.

Environmental exposure

The assessed chemical will be imported into Australia either in neat form or as a component of liquid fragrance formulations for reformulation into end-use products. Reformulation and repackaging will occur through 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 washing and cleaning 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.

Professional and consumer end-uses of the assessed chemical in polishes and wax blends is not expected to result in significant releases of the assessed chemical to the environment.

Consumer and professional end-uses of the assessed chemical in 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.

Consumer end-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} = 3.7). Therefore, the chemical is expected to partition to and become immobile in soils and sediments.

The assessed chemical is moderately water soluble (water solubility = 14 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 moderate water solubility and high log Koc value.

The assessed chemical is moderately volatile (vapour pressure = 4.59×10^{-4} kPa at 20 °C). A small fraction of the assessed chemical is expected to partition to air during STP treatment based on Simple Treat 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.

Biodegradation of the assessed chemical in water likely occurs through the cleaving of the ether and ester groups within the chemical, producing degradants containing tertiary and/or quaternary carbons that may be resistant to further degradation. However, as two of the ready biodegradation screening tests demonstrated at least 50% mineralisation with 28 days based on oxygen consumption, the chemical is not considered to be persistent (EPHC, 2009).

A supplied OECD TG 301D ready biodegradation screening test showed 67.3% degradation (oxygen consumption) after 28 days. However, the chemical did not meet the 10-day or 14-day window for ready biodegradability.

An OECD TG 301F screening test, run with a lower test concentration than prescribed in the guideline, showed only 14% degradation based on oxygen consumption. However, the test substance concentration was measured throughout the experiment, and was shown to have decreased by 90% after 24 hours. The concentration of the primary degradant was also measured. Both the test substance and the primary degradant were undetected by 28 days. This is supported by a previous extended study conducted according to OECD TG 301F which showed 50% degradation (BOD) at day 28 and 72% degradation (BOD) at day 62, indicating that the assessed chemical is inherently biodegradable.

The assessed chemical slowly hydrolyses under OECD TG 111 test conditions, with hydrolysis half-lives of 39 hours, 107 days, and 49 days at pH 4, pH 7, and pH 9 respectively.

The half-life of the assessed chemical in air is calculated to be 1.2 hours, based on reactions with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). As its 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.

Bioaccumulation

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

No reliable bioaccumulation information was provided for the assessed chemical. The measured partition coefficient of the assessed chemical is log K_{OW} = 4.4, which exceeds 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 moderate water solubility, high log Kow and biodegradability, a large proportion of the assessed chemical is expected to be removed by biodegradation and adsorption to biosolids during STP treatment. The extent to which the assessed chemical is removed from the effluent in STP processes is based on its physicochemical properties, modelled by Simple Treat 3.0 (Struijs, 1996), and is estimated to be 75%. Therefore 25% 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	200.0	L/person/day
Population of Australia	24.386	Million
Removal within STP	75%	Mitigation
Daily effluent production	4 877	ML/day
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River	0.14	µg/L
PEC - Ocean	0.01	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 assessed chemicals log Koc value.

Environmental effects

Effects on Aquatic Life

Acute toxicity

The following measured median lethal concentration (LC50), median effective concentration (EC50) and inhibition concentration (IC50) values for model organisms were supplied for the assessed chemical:

Taxon	Endpoint	Method
Fish	96 h LC50 = 2.9 mg/L	*Cyprinus carpio* (common carp) Mortality OECD TG 203 Semi-static conditions Measured concentration
Invertebrate	Study 1: 48 h EC50 > 2 mg/L[1]	*Daphnia magna* (water flea) Immobility OECD TG 202 Static conditions Measured concentration
	Study 2: 48 h EC50 > 6.04 mg/L[1]	*Daphnia magna* (water flea) Immobility OECD TG 202 Static conditions Measured concentration
Algae	Study 1: 48 h EC50 > 5.7 mg/L[1]	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Measured concentration
	Study 2: 72 h EC50 > 4.97 mg/L[1]	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Measured concentration
Microorganisms	3 h IC50 > 100 mg/L[1]	Activated sludge from a STP Respiration inhibition OECD TG 209 Static Nominal concentration

[1]EC50 or IC50 is beyond the test concentrations.

Chronic toxicity

The following measured no-observed-effect concentration (NOEC) value for a model organism was supplied for the assessed chemical:

Taxon	Endpoint	Method
Algae	72 h NOEC = 0.964 mg/L	*Pseudokirchneriella subcapitata* (green algae) Growth rate OECD TG 201 Static conditions Measured concentration

Effects on terrestrial Life

Acute toxicity

The following measured median lethal concentration (LC50) values for model organisms were supplied for the assessed chemical:

Taxon	Endpoint	Method
Earthworm	14d LC50 = 291 mg/kg soil dw	*Eisenia fetida* (earthworm) Mortality OECD TG 207 Laboratory/artificial soil conditions Nominal concentration

Predicted no-effect concentration (PNEC)

A predicted no-effect concentration (PNEC) of 29 µg/L was calculated for the assessed chemical in the aquatic environment. This value was derived using the most conservative endpoint value for fish (2.9 mg/L). An assessment factor of 100 was applied to this endpoint as acute toxicity data was available for three trophic levels and chronic toxicity data was incomplete (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 NOEC (ECHA 2008).

The assessed chemical is classified as slightly toxic to earthworms based on the provided terrestrial ecotoxicity information (Mensink et al., 1995). However, the assessed chemical is not expected to reach ecotoxicologically relevant concentration in the soil compartment based on the proposed uses and exposure.

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 under screening test conditions, the assessed chemical is categorised as Not Persistent.

Bioaccumulation

Bioaccumulative (B). Based on a measured log k_{OW} value indicating a potential to bioaccumulate, the assessed chemical is categorised as Bioaccumulative.

Toxicity

Not Toxic (Not T). Based on available acute ecotoxicity values above 1 mg/L, the assessed chemical is categorised as Not Toxic.

Environmental risk characterisation

The assessed chemical is not a PBT chemical and is hence unlikely to have unpredictable long-term environmental 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	0.14 µg/L	29 µg/L	< 0.01
Ocean	0.01 µg/L	29 µg/L	< 0.01

For the river and ocean compartments, an RQ less than 1 indicates that the environmental risk from the assessed chemical can likely be managed based on estimated releases, as environmental concentrations are below the levels that are likely to cause harmful effects.

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