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

2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodec-1-yl]oxy]-, (2*R*)-
2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.0^{2,5}]dodec-1-yl]oxy]-, (2*S*)-
2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.0^{2,5}]dodec-8-yl]oxy]-, (2*R*)-
2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.0^{2,5}]dodec-8-yl]oxy]-, (2*S*)-

Assessment statement (CA09757/CA09835/CA09836/CA09837)

13 November 2023

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AICIS assessment statement (CA09757/CA09835/CA09836/CA09837)

Chemicals in this assessment

Name	CAS registry number	Application no.
2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2*R*)-	2411391-25-6	CA09757
2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2*S*)-	2411391-27-8	CA09835
2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-8-yl]oxy]-, (2*R*)-	2952782-14-6	CA09836
2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-8-yl]oxy]-, (2*S*)-	2952782-15-7	CA09837

Reason for the assessment

Applications for assessment certificates under section 31 of the *Industrial Chemicals Act 2019* (the Act).

Certificate Application type

AICIS received assessment certificate applications for four chemicals in a Health Focus type. The chemicals will be imported together as a multi-component introduction and will not be separated during introduction or use.

Defined scope of assessment

The chemicals have been assessed together as a multi-component introduction, manufactured together at the following concentrations and not to be separated during introduction or use:

- 2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2*R*)- at up to 25%
- 2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2*S*)- at up to 25%
- 2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-8-yl]oxy]-, (2*R*)- at up to 15%
- 2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-8-yl]oxy]-, (2*S*)- at up to 15%.

The four components combined together:

- Imported into Australia at up to 1 tonne per year when used as fragrance ingredients.
- Imported in fragrance formulations at up to 10% concentration for local reformulation into cosmetics and household products in:
  - body lotion, face cream and hand cream at up to 0.1% concentration
  - deodorant spray at up to 0.03% concentration
  - fine fragrances at up to 0.11% concentration

    - hairspray at up to 0.44% concentration
    - air fresheners at up to 5% concentration
    - other leave-on and rinse-off cosmetic and household products at up to 0.6% concentration.
- Imported in finished products for sale in:
    - body lotion, face cream and hand cream at up to 0.1% concentration
    - deodorant spray at up to 0.03% concentration
    - fine fragrances at up to 0.11% concentration
    - hairspray at up to 0.44% concentration
    - air fresheners at up to 5% concentration
    - other leave-on and rinse-off cosmetic and household products at up to 0.6% concentration.

Summary of assessment

Summary of introduction, use and end use

The assessed chemicals will not be manufactured in Australia. They will be imported either in fragrance formulations at up to 10% combined concentration for local reformulation into end use cosmetics and household products or in end use cosmetics and household products at various combined concentrations as shown below:

Product type	Proposed combined end use concentration (%)
Body lotion	0.1
Face cream	0.1
Hand cream	0.1
Deodorant spray	0.03
Fine fragrances	0.11
Hairspray	0.44
Air fresheners	5
Other leave-on and rinse-off cosmetic products	0.6
Other household products	0.6

The cosmetics and household products containing the assessed chemicals are proposed to be used by professional workers under industrial or non-industrial settings and by members of the general public.

Human health

Summary of health hazards

The data provided on all components together are:

- likely to be of low acute oral toxicity
- not irritating to the skin and eyes
- not considered to be genotoxic
- not likely to cause systemic toxicity following repeated oral exposure at concentrations introduced (no-observable-adverse-effect-level (NOAEL) = 222 mg/kg bw/day in male rats and 263 mg/kg bw/day in female rats for an analogue chemical)

The data also indicate that the assessed chemicals are skin sensitisers that require classification.

No inhalation toxicity data submitted on the assessed chemicals.

Hazard classifications relevant for worker health and safety

The assessed chemicals satisfy the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety as adopted for industrial chemicals in Australia as follows:

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

Summary of health risk

Public

There will be widespread and repeated exposure of the public to the assessed chemicals at up to 5% combined concentration through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal and inhalation, while incidental oral or ocular exposure is also possible. Inhalation exposure occurs particularly from the use of air care products and other products applied by spray.

The repeated dose toxicity potential of the assessed chemicals was estimated by calculating the margin of exposure (MoE), with total daily systemic exposure estimated as 0.3150 mg/kg bw/day (see **Supporting information**). Using a NOAEL of 222 mg/kg bw/day derived from a repeated dose oral toxicity study on an analogue chemical in male rats, the MoE was estimated to be 705. A MoE value of greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

The assessed chemicals are moderate skin sensitisers. However, these effects are not expected at the proposed end use concentrations in consumer products.

In the HRIPT, the assessed chemicals at 1% combined concentration were determined as not eliciting a sensitisation response. Consideration of the details of the submitted study allowed the derivation of an Acceptable Exposure Level (AEL) of 4.05 µg/cm^2/day for consumers using an overall safety factor of 100. Based on the QRA calculations, this AEL was considered to be greater than or equal to each of the individual consumer exposure levels (CELs) for various household and cosmetic products with intended maximum combined use concentrations as proposed in the application. Since the AEL is greater than or equal to CEL, induction of skin sensitisation associated with the use of the assessed chemicals in a single consumer product at a low concentration is unlikely to occur. However, it is acknowledged that consumers may

be exposed to multiple products containing the assessed chemicals, and a quantitative assessment based on aggregate exposure has not been conducted.

The EC3 value 4.33% derived from GARD™ skin dose-response (OECD 442E) also indicates similar levels as acceptable concentrations, including 0.09% combined concentration for fine fragrance, when using the QRA methodology (AEL is greater than or equal to CEL).

Overall if the assessed chemicals are 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.

Workers

Reformulation workers may incidentally be exposed to the assessed chemicals at up to 10% combined concentration during reformulation processes mainly via the dermal route, while ocular and inhalation exposures are also possible. To mitigate skin sensitisation and potential repeated exposure risks to reformulation workers, control measures would be required (see **Means for managing risk**) to minimise the exposure. It is anticipated by the applicant that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible. Use of appropriate personal protective equipment (PPE) such as safety glasses, impervious chemical resistant gloves, protective clothing and respiratory protection will reduce worker exposure.

Professional workers in cleaning or cosmetic businesses may experience exposure via dermal, inhalation and accidental ocular exposure to the assessed chemicals during the use of cleaning or cosmetic products containing the assessed chemicals at up to 5% combined concentration. The professional workers may wear some PPE (including gloves, coveralls and safety glasses or face masks). 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 same end use products containing the assessed chemicals, requiring no specific risk management measures for these workers.

Environment

Summary of environmental hazard characteristics

According to domestic environmental hazard thresholds and based on the available data the assessed chemicals are:

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

Environmental hazard classification

The assessed chemicals satisfy the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE, 2017) as Acute Category 1 (H400) and Chronic Category 1 (H410) based on the toxicity data for aquatic organisms. Considerations were also made for the rapid biodegradation and bioaccumulation potential of the assessed chemicals.

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short-term)	Aquatic Acute 1	H400: Very toxic to aquatic life
Hazardous to the aquatic environment (long-term)	Aquatic Chronic 1	H410: Very toxic to aquatic life with long lasting effects

Summary of environmental risk

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

The assessed chemicals are readily biodegradable and are not persistent. The assessed chemicals have a high potential for bioaccumulation and are toxic to aquatic organisms.

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

Means for managing risk

Workers

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.

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 **Hazard classifications relevant for worker health and safety**).

Information relating to safe introduction and use

- The following control measures could be implemented to manage the risk arising from exposure to the assessed chemicals during reformulation activities:
    - Use of engineering controls such as
        - Enclosed and automated systems where possible
        - Adequate workplace ventilation to avoid accumulation of vapours, mists or aerosols
    - Use of safe work practices to
        - Avoid contact with skin
        - Avoid inhalation of vapours, mists or aerosols
    - Use of personal protective equipment (PPE)
        - Impervious gloves

        - Protective clothing
        - Respiratory protection where local ventilation may be inadequate
- These 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 employees.

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 chemicals are introduced and used in accordance with the terms of the assessment certificates 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 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.

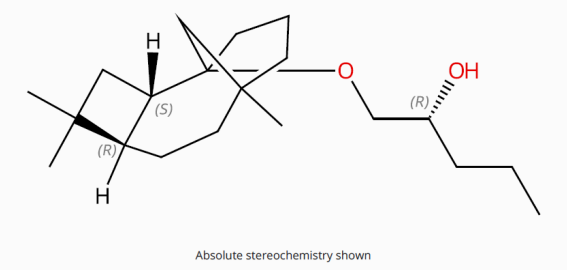
Supporting information

Chemical identity

Chemical identity of CA09757

Chemical name	2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2*R*)-
CAS No.	2411391-25-6
Molecular formula	$C_{20}H_{36}O_2$
Molecular weight (g/mol)	308.5
SMILES (isomeric)	O(C[C@@H](CCC)O)C12[C@@]3([C@](C(C)(C)C3)(CCC(C)(C1)CCC2)[H])[H]

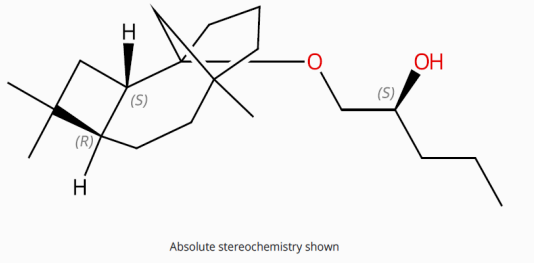
Structural formula



Chemical identity of CA09835

Chemical name	2-Pentanol, 1-[[(2*S*,5*R*)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2*S*)-
CAS No.	2411391-27-8
Molecular formula	$C_{20}H_{36}O_2$
Molecular weight (g/mol)	308.5
SMILES (isomeric)	O(C[C@H](CCC)O)C12[C@@]3([C@](C(C)(C)C3)(CCC(C)(C1)CCC2)[H])[H]

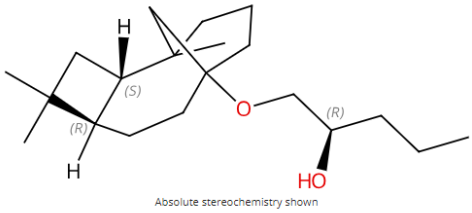
Structural formula



Chemical identity of CA09836

Chemical name	2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.0^{2,5}]dodec-8-yl]oxy]-, (2*R*)-
CAS No.	2952782-14-6
Molecular formula	$C_{20}H_{36}O_2$
Molecular weight (g/mol)	308.5
SMILES (isomeric)	CC12[C@@]3([C@](C(C)(C)C3)(CCC(OC[C@@H](CCC)O)(C1)CCC2)[H])[H]

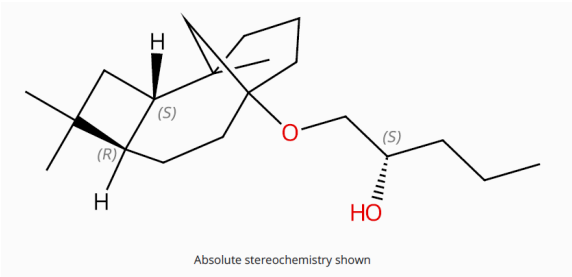
Structural formula



Chemical identity of CA09837

Chemical name	2-Pentanol, 1-[[(2*S*,5*R*)-1,4,4-trimethyltricyclo[6.3.1.0^{2,5}]dodec-8-yl]oxy]-, (2*S*)-
CAS No.	2952782-15-7
Molecular formula	$C_{20}H_{36}O_2$
Molecular weight (g/mol)	308.5
SMILES (isomeric)	CC12[C@@]3([C@](C(C)(C)C3)(CCC(OC[C@H](CCC)O)(C1)CCC2)[H])[H]

Structural formula



Chemical description

The four chemicals in this assessment have been manufactured together and have been assessed as a multi-component introduction with a combined purity around 70%.

The typical concentrations of each of the assessed chemicals are:

Isomer chemical name	CAS No.	Typical conc. %(w/w)	Range conc. %(w/w)
2-Pentanol, 1-[[(2S,5R)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2R)-	2411391-25-6	23.5	≥ 20 - ≤ 25
2-Pentanol, 1-[[(2S,5R)-4,4,8-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-1-yl]oxy]-, (2S)-	2411391-27-8	23.5	≥ 20 - ≤ 25
2-Pentanol, 1-[[(2S,5R)-1,4,4-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-8-yl]oxy]-, (2R)-	2952782-14-6	11.4	≥ 10 - ≤ 15
2-Pentanol, 1-[[(2S,5R)-1,4,4-trimethyltricyclo[6.3.1.$0^{2,5}$]dodec-8-yl]oxy]-, (2S)-	2952782-15-7	11.4	≥ 10 - ≤ 15

Relevant physical and chemical properties of the chemicals

Physical form	Yellow viscous liquid
Melting point	-9 °C
Boiling point	317 °C at 101 kPa
Density	974 kg/m^3 at 20 °C
Vapour pressure	1.41 × 10^{-5} kPa at 25 °C
Water solubility	1.28 mg/L at 20°C
Ionisable in the environment?	No
log K_{ow}	> 6.5
log K_{oc}	5.04 to > 5.63
Flash point	168 °C
Autoignition Temperature	256 °C at 100 to 101 kPa

Human exposure

Workers

As indicated by the applicant, reformulation and packaging processes at the facilities may incorporate blending operations that are highly automated. Dermal, ocular and maybe inhalation exposure (if aerosols or mists are formed) of workers to the assessed chemicals at

up to 10% combined concentration is possible during weighing, transferring, blending, quality control, packaging, cleaning and maintenance of equipment.

According to the applicant, the exposure is expected to be minimised through the use of PPE such as protective clothing, chemical resistant gloves, and appropriate respiratory protection. In addition, the facilities are expected to provide adequate local ventilation if required. The production processes are expected to be in compliance with the Good Manufacturing Practices.

Public

There will be widespread and repeated exposure of the public to the assessed chemicals at up to 5% combined concentration through the use of a wide range of cosmetic and household products including air fresheners. The main routes of exposure will be dermal and inhalation, while incidental oral or ocular exposures are also possible.

Dermal exposure

Data on typical use patterns of cosmetic products (SCCS 2012; Cadby et al. 2002; ACI 2010; Loretz et al. 2006) in which the assessed chemicals may be used are shown in the following table. A dermal absorption (DA) rate of 100% was used as a worst-case scenario along with a combined average body weight (BW) for males and females of 70 kg (enHealth 2012) for calculation purposes.

Cosmetic products (dermal exposure from using cosmetic products)

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.100	1.000	0.1117
Face cream	1,540	0.100	1.000	0.0220
Hand cream	2,160	0.100	1.000	0.0309
Fine fragrances	750	0.110	1.000	0.0118
Deodorant (non-spray)	1,500	0.030	1.000	0.0064
Shampoo	10,460	0.600	0.010	0.0090
Conditioner	3,920	0.600	0.010	0.0034
Shower gel	18,670	0.600	0.010	0.0160
Hand wash soap	20,000	0.600	0.010	0.0171
Hair styling products	4,000	0.600	0.100	0.0343
Total				**0.2668**

Daily systemic exposure = (Amount × Combined Chemical concentration (C) × RF × DA absorption)/BW (RF = retention factor; DA = dermal absorption; BW = body weight)

Household products (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	0.6	0.95	10	0.0187
Fabric softener	90	0.6	0.95	10	0.0073
Total					**0.0261**

Daily systemic exposure = (Amount × C × PR × PT × DA)/BW
(C = combined chemical concentration; PR = product retained; PT = product transferred; DA = dermal absorption; BW = body weight)

Household products (dermal exposure from using products):

Product type	Frequency (use/day)	C (%)	Contact area (cm^2)	Product usage (g/cm^3)	Film thickness (cm)	Time scale factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.6	1,980	0.01	0.01	0.007	0.0002
Dishwashing liquid	3	0.6	1,980	0.009	0.01	0.03	0.0014
All-purpose cleaner	1	0.6	1,980	1	0.01	0.007	0.0119
Total							**0.0134**

Daily systemic exposure = (Frequency × C × Contact area × Product Usage × Film Thickness × Time Scale Factor × DA)/BW
(C = combined chemical concentration; DA = dermal absorption; BW = body weight)

Inhalation exposure

Hairspray was taken as a worst-case scenario example 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 chemicals inhaled is 50%.

Amount of hairspray applied	9.89	g/day
Maximum intended combined concentration of the chemicals	0.44	%
Inhalation rate of the user	20	m^3/day
Exposure duration in zone 1	1	minutes
Exposure duration in zone 2	20	minutes
Fraction inhaled by the user	50	%

Volume of zone 1	1	m^3
Volume of zone 2	10	m^3
Daily systemic exposure	**0.0130**	**mg/kg bw/day**

C = maximum intended combined concentration of assessed chemicals
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)]

It is acknowledged that inhalation exposure to the assessed chemicals from use of other cosmetic and household products may also occur.

Overall, the worst-case scenario estimation is for a person who is a simultaneous user of all products listed in the above tables that contain the assessed chemicals. This would result in a combined internal dose of 0.3150 mg/kg bw/day for these assessed chemicals. It is acknowledged that inhalation exposure to the assessed chemicals from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative (screening level) hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of all dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the assessed chemicals from use of other spray cosmetic and household products with lower exposure factors (e.g., air fresheners).

Health hazard information

The results from toxicological investigations conducted on the assessed chemicals provided by the applicant are summarised in the following table.

Endpoint	Test guideline	Results and Conclusion
Rat, acute oral toxicity	OECD TG 420	LD50 > 2,000 mg/kg bw; low acute oral toxicity
Skin irritation - *in vitro* Reconstructed Human EpiDermis (RHE) test	OECD TG 439	Non irritating
Skin irritation - *in vitro* EPIDERM™ Skin Corrosion test	OECD TG 431	Non corrosive
Eye irritation – *in vitro* Bovine Corneal Opacity and Permeability (BCOP) test	OECD TG 437	Non irritating
Skin sensitisation – *in chemico DPRA test*	OECD TG 442C	Negative
Skin sensitisation – *in vitro* ARE-Nrf2 luciferase test	OECD TG 442D	Positive
Skin sensitisation – *in vitro* Human Cell Line Activation test	OECD TG 442E	Positive

Endpoint	Test guideline	Results and Conclusion
Skin sensitisation – *in vitro* Genomic Allergen Rapid Detection (GARD™) for assessment of skin sensitisers (GARD™skin)	OECD TG 442E	Positive
Skin sensitisation – HRIPT (1%)	-	No evidence of sensitisation
Repeat dose oral toxicity – rat, 90 days (analogue)	OECD TG 408	NOAELs of 222 mg/kg bw/day in males and 263 mg/kg bw/day in females
Mutagenicity – bacterial reverse mutation	OECD TG 471	Non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	OECD TG 473	Non clastogenic

Acute toxicity

Oral

In an acute oral toxicity study (OECD TG 420), the assessed chemicals were administered by oral gavage to Wistar rats initially with 1 female each dosed at 300 and 2,000 mg/kg bw, followed by 4 females dosed at 2,000 mg/kg bw. All animals survived until the end of the 14-day study period. No clinical signs of reaction to treatment were noted throughout the study. The mean body weight gain of the test animals over the study period was considered to be normal. No macroscopic findings were recorded at necropsy. The oral median lethal dose (LD50) of the assessed chemicals was determined to be higher than 2,000 mg/kg bw. Under the conditions of the study and according to the test guideline, the assessed chemicals were of low acute oral toxicity.

No acute dermal or inhalation toxicity data were submitted for the assessed chemicals.

Corrosion/Irritation

Skin irritation

The assessed chemicals were determined not to be irritating to skin in an *in vitro* Reconstructed Human EpiDermis (RHE) Test (OECD TG 439). After the 15-minute treatment (followed by a 42-hour post-exposure incubation period), the relative mean viability of the treated tissues was 130.1% as compared to the negative control, above the threshold of less than or equal to 50%.

The assessed chemicals were determined not to be corrosive to skin in an *in vitro* EPIDERM™ Skin Corrosion Test (OECD TG 431). The relative mean viability of the treated tissues, as compared to the negative control, was greater than or equal to 50% after 3 min exposure (102.6%) and greater than or equal to 15% after 60 min exposure (108.1%).

Eye irritation

The eye irritation potential of the assessed chemicals was tested in a Bovine Corneal Opacity and Permeability (BCOP) test by application of 750 µL undiluted test substance onto the epithelial surface of isolated bovine cornea for 10 minutes (OECD TG 437). The *in vitro* irritancy score (IVIS) of the test substance was determined to be 0.6 after the treatment. Based on the results and as per the test guideline, the assessed chemicals did not require classification for eye irritation as the IVIS was less than 3.

Sensitisation

Skin sensitisation

One *in chemico* and two *in vitro* cell based assays were conducted to evaluate the skin sensitisation potential of the assessed chemicals. These tests are part of Integrated Approach to Testing and Assessment (IATA) which address specific key events of the Adverse Outcome Pathway (AOP) leading to development of skin sensitisation (OECD TG 497).

The direct peptide reactivity assay (DPRA) is an *in chemico* method and aims to address the first key event (KE) (molecular initiation) of the AOP by measuring the interaction of the assessed chemicals with cysteine and lysine, small synthetic peptides representing the nucleophilic centres in skin proteins (OECD TG 442C). The ARE-Nrf2 luciferase assay aims to address the second key event (keratinocyte activation) of the AOP by measuring the expression of a reporter luciferase gene under the control of a promoter from the antioxidant response element (ARE), a responding gene known to be upregulated by contact sensitisers (OECD TG442D). In the third key event assay, the Human Cell Line Activation test (h-CLAT) assay, the skin sensitisation potential of the test substance is evaluated by measuring the changes in the expression of cell surface markers (CD54 and CD86) associated with the process of dendritic cell activation in the human leukemia cell line (THP-1) following exposure to test substance (OECD TG 442E). The assessed chemicals were negative in the DPRA assay and positive in both the ARE-Nrf2 luciferase KeratinoSens™ and h-CLAT assays. The results of these assays were considered using the applicable defined approaches (DAs) in the OECD Guideline 497. Based on the results of the AOP assays and using the '2 out of 3' DA, the assessed chemicals are skin sensitisers.

An additional *in vitro* skin sensitisation testing using GARD™ for assessment of skin sensitisers was conducted (OECD TG 442E). The assessed chemicals were classified as a sensitiser and the corresponding LLNA EC3 value of 4.33% was predicted using GARD™ skin dose-response (Gradin et al., 2021 and Johansson et at., 2021). There is no OECD TG for the EC3 calculation using GARD™ skin dose-response.

The skin sensitising potential of the assessed chemicals was further evaluated in a human repeat insult patch test (HRIPT) in 111 subjects. The assessed chemicals at 1% combined concentration in a vehicle of ethanol and diethyl phthalate (ethanol: diethyl phthalate 1:3) were applied using occlusive patch to the upper back of each subject and were allowed to remain in direct skin contact for a period of 24 hours. Patches were applied to the same site for three alternative days for a total of 9 applications during the induction period. After a 2-week rest period, the subjects were challenged at a virgin site for 24 hours and the skin reactions were scored over a period of 3 days. No skin reactions were observed during the induction or challenge stage on any subjects. The study authors concluded that the assessed chemicals at up to 1% combined concentration did not demonstrate a potential for eliciting skin irritation or sensitisation under the test conditions.

Repeat dose toxicity

Oral

In a repeated dose oral toxicity study (OECD TG 408), an analogue chemical, bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-, (1*R*,4*E*,9*S*)- (CAS No. 87-44-5), was administered to Sprague-Dawley rats (n=10/sex/dose) by diet for 90 days at 0, 3,500, 7,000 and 21,000 ppm for males and at 0, 3,500, 14,000 and 56,000 ppm for females (Bastaki M, et al., 2020).

There were no deaths during the study. Clinical observations (including red/black ocular discharge, red nasal discharge, alopecia, hair loss, no resistance during handling, lacrimation, and visible swelling of the right inguinal area corresponding to subcutaneous masses) were considered normal by the study author.

The statistically significant changes observed in haematological, clinical chemistry and urinalysis parameters were not dose dependent, small in magnitude and within the range of historical control values, and/or had no correlating histopathology observations, however, some of these changes may be related to treatment. Observations at the high dose were associated with reduced food consumption because of poor palatability of the test substance. The pattern of histopathological findings in the kidney and liver at mid/high doses was reported to be consistent with commonly reported rodent pathologies in male rats. Unlike the male rats, the increases in kidney weight relative to body weight (but not the absolute weight) in females were associated with small re ductions in body weights (non-statistically significant) and were considered by the study authors to be non-adverse with no direct relationship to the test substance, as supported by the absence of clinical or histopathology observations.

The renal findings were consistent with accumulation of α2μ-globulin and related nephropathy, which is limited to male rats.

Evidence of hepatocellular hypertrophy and increased absolute and relative liver weights were observed in both male and female rats. However, in the absence of degenerative histopathological abnormalities, the hepatic changes were indicative of adaptive responses to the increased metabolic load in the middle and high doses.

The administration of the analogue did not influence oestrous cycle pattern in females, based on mean oestrous cycle length and the number of cycles assessed in two intervals during the study (weeks 6-7 or 12-13). No effects on male reproductive parameters were observed based on sperm morphology, epididymal sperm count, homogenisation-resistant spermatid count and motility measurements.

Erythrocyte infiltration into the sinusoids of the mesenteric lymph nodes was also seen at the middle and high doses, although the adversity of this finding was unclear in the absence of evidence of haemorrhage in the gastrointestinal tract.

A NOAEL of 3500 ppm (equivalent to 222 mg/kg bw/day in males and 263 mg/kg bw/day in females) was established based on histopathological evidence of hepatocyte hypertrophy, increased liver weights, changes in haematological parameters and lymphoid system histopathological findings at the middle and high dietary doses.

Genotoxicity

The assessed chemicals were not mutagenic in the bacterial reverse mutation assay (Ames Test) when tested in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2uvrA, with or without metabolic activation (OECD TG 471). No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains at any tested dose (0, 1.5, 5, 15, 50, 150, 500, 1,500 and 5,000 µg/plate), with or without metabolic activation (S9-mix).

The assessed chemicals were further tested for their clastogenic potential in an *in vitro* mammalian chromosome aberration test using human lymphocytes (OECD TG 473). Three experiments were conducted, 4-hour exposure without S9-mix at 0 to 32 µg/mL, 4-hour exposure with S9-mix at 0 to 64 µg/mL, and 24-hour continuous exposure without S9-mix at 0 to 32 µg/mL. The test substance did not induce any statistically significant increases in the frequency of cells with chromosome aberrations either in the absence or presence of metabolic activation. The test substance did not induce a statistically significant increase in the numbers of polyploid cells at any concentration. Under the conditions of this study, the assessed chemicals were not clastogenic.

Overall, the assessed chemicals are not considered to be genotoxic.

Environmental exposure

The assessed chemicals will be imported into Australia for use as fragrance ingredients in either in end use cosmetics and household products, or as components of fragrance formulations for reformulation into end use cosmetics and household products. Reformulation and repackaging will occur in both closed and open processes. Significant releases of the assessed chemicals to the environment are not expected during reformulation, transport or storage.

The assessed chemicals will be included in a wide range of cosmetic and household products, resulting in a variety of potential exposure scenarios.

Consumer and professional end use of the assessed chemicals in cosmetic and household products is expected to result in the release of the assessed chemicals “down the drain” and into the sewers. Consequently, the assessed chemicals will be treated at sewage treatment plants (STPs) before release to surface waters.

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

Environmental fate

Partitioning

The partitioning of the assessed chemicals was not determined. The chemicals are treated as if it is mobile in the environment as a worst-case scenario.

Degradation

Degradation studies in water indicate that the assessed chemicals are readily biodegradable and not persistent. A supplied OECD 301F biodegradation study for the assessed chemicals

demonstrated 95% degradation of the assessed chemicals over 28 days (according to oxygen demand). The assessed chemicals satisfied the 10-day-window criterion.

Bioaccumulation

Based on its log K_{OW} value, the assessed chemicals have the potential to bioaccumulate.

No bioaccumulation information was provided for the assessed chemicals. The experimental partition coefficient of the assessed chemicals (log K_{OW} higher than 6.5) is above the domestic bioaccumulation threshold of log K_{OW} = 4.2 (EPHC, 2009). This determination is considered to be conservative as the assessed chemicals are not considered to be persistent.

Predicted environmental concentration (PEC)

A predicted environmental concentration (PEC) for Australian waters was calculated assuming the maximum allowable introduction volume for environmental exposure band 2 (1,000 kg/annum) with a release reduction factor of 1 for down-the-drain style end use scenarios. Correspondingly, 100% of the introduction volume is released into sewage treatment plants (STP) over 365 days per annum. The extent to which the assessed chemicals are removed from the effluent in STP processes was not calculated as a worst-case scenario.

This calculated value is conservative as not all uses of the assessed chemicals are expected to result in release to STP.

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 chemicals 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	0%	Mitigation
Daily effluent production	5,085	ML/day
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River	0.54	µg/L
PEC - Ocean	0.05	µg/L

Environmental effects

Effects on aquatic Life

Acute toxicity

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

Taxon	Endpoint	Method
Invertebrate	48 h EC50 = 0.87 mg/L	*Daphnia magna* (Water flea) Immobility/other effect OECD TG 202 Semi-static conditions Geometric mean measured concentration
Algae	72 h E_rC50 > 0.85 mg/L	*Raphidocelis subcapitata* (Green algae) Growth rate OECD TG 201 Static conditions Geometric mean measured concentration

Chronic toxicity

The following measured 10th percentile effective concentration (EC10) value for model organisms were supplied for suitable analogues of the assessed chemicals:

Taxon	Endpoint	Method
Algae	ErC10 = 0.22 mg/L	*Raphidocelis subcapitata* (Green algae) Growth rate OECD TG 201 Static conditions Geometric mean measured concentration

Predicted no-effect concentration (PNEC)

The predicted no-effect concentration is expected to be greater than 0.54 µg/L.

The available standard acute ecotoxicity endpoints for the chemicals are greater than 0.54 mg/L. With a conservative assessment factor of 1,000, the lowest calculable PNEC is greater than 0.54 µg/L.

Categorisation of environmental hazard

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

Persistence

Not Persistent (Not P). Based on a measured degradation study, the assessed chemicals are categorised as Not Persistent.

Bioaccumulation

Bioaccumulative (B). Based on a high measured log kow value greater than 4.2, the assessed chemicals are categorised as Bioaccumulative.

Toxicity

Toxic (T). Based on available ecotoxicity values below 1 mg/L for daphnia and algae, the assessed chemicals are categorised as Toxic.

Environmental risk characterisation

Although the assessed chemicals are bioaccumulative and toxic, they do 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.

Compartment	PEC	PNEC	RQ
River	< 0.54 µg/L	> 0.54 µg/L	< 1
Ocean	< 0.05 µg/L	> 0.54 µg/L	< 0.1

The risk quotient for the aquatic compartment is expected to be less than 1. This is based on a conservative PEC, assuming 100% release of 1 tonne/annum to STPs and no removal from the aqueous stream during STP processes, and a conservative PNEC based on an assessment factor of 1,000 and acute aquatic toxicity endpoints for the chemicals that each exceed 0.54 mg/L.

Therefore, based on the expected RQ of less than 1 the assessed chemicals are not expected to pose a significant risk to the environment. As such, the environmental risks associated with the assessed chemicals can be managed.

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