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

2*H*-Pyran-4-ol, 2-(1-ethylpropyl)tetrahydro-4-methyl-

Assessment statement (CA09685)

6 October 2023

Final

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AICIS assessment statement (CA09685)

Chemical in this assessment

Name	CAS registry number
2*H*-Pyran-4-ol, 2-(1-ethylpropyl)tetrahydro-4-methyl-	1099648-69-7

Reason for the assessment

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

Certificate Application type

AICIS received the application in a Very Low to Low Risk type.

Defined scope of assessment

The chemical has been assessed:

- as a fragrance component imported into Australia at up to 1 tonne/year
- as imported in fragrance formulations at up to 2% concentration for reformulation of end use cosmetic and household products
- as imported or reformulated in continuous action air fresheners at up to 2% concentration, in fine fragrances at up to 0.5% concentration, in instant action air fresheners at up to 0.2% concentration, in other cosmetic products at up to 0.05% concentration and in other household products at up to 0.02% concentration

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will not be manufactured in Australia. It will be imported either in fragrance formulations at up to 2% concentration or in end use cosmetic and household products at various concentrations as shown below:

Product type	Proposed end use concentration (%)
Continuous action air fresheners	2.0
Fine fragrances	0.5
Instant action air fresheners	0.2
Other leave-on and rinse-off cosmetic products	0.05

Product type	Proposed end use concentration (%)
Other household products	0.02

The cosmetic and household end use products containing the assessed chemical 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 submitted toxicological data on the assessed chemical (see **Supporting Information** section) indicate that the assessed chemical is:

- of low acute oral toxicity
- not irritating to skin
- not a skin sensitiser
- not expected to be genotoxic

The submitted data warrant hazard classification of eye irritation Cat. 2A for the assessed chemical (see section below).

No inhalation or repeated dose toxicity data were submitted on the assessed chemical.

Hazard classifications relevant for worker health and safety

The assessed chemical satisfies 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
Serious eye damage/eye irritation	Category 2A	H319: Causes serious eye irritation

Summary of health risk

Public

There will be widespread and repeated exposure of the public to the assessed chemical at up to 2% 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 assessed chemical in neat form is irritating to eyes. However, eye irritation effects are not expected to occur from use of the assessed chemical at the proposed low end use concentrations of up to 2% in cosmetic and household products.

No inhalation toxicity data were provided for the assessed chemical. Due to low concentrations of the assessed chemical in the end use products, it is not expected to pose health risk through inhalation when the chemical is used according to the assessed use scenarios.

No repeated dose toxicity data were provided on the assessed chemical. Based on the quantitative risk assessment (QRA) for the worst case exposure scenario, consumers simultaneously using multiple cosmetic and household products may be systemically exposed to the assessed chemical at approximately 156 µg/kg bw/day through repeated or prolonged exposure (see **Supporting information** section). Considering the low systemic exposure level to the assessed chemical for the worst case exposure scenario (less than 1 mg/kg bw/day), health risks from repeated exposure to the public are not expected.

Overall, this assessment does not identify any risks to public health that would require specific risk management measures if the assessed chemical is introduced and used in accordance with the terms of the assessment certificate.

Workers

Reformulation workers may incidentally be exposed to the assessed chemical at up to 2% concentration during reformulation processes mainly via the dermal route, while ocular and inhalation exposures are also possible. To mitigate 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 chemical during the use of cleaning or cosmetic products containing the assessed chemical at up to 0.5% concentration. The professional workers may wear some PPE (including gloves, safety glasses, coveralls and 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 chemical, 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 chemical is:

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

Environmental hazard classification

Based on the ecotoxicological information available for the assessed chemical, it is not expected to be harmful to aquatic life. Therefore, the assessed chemical is not formally classified under the GHS (UNECE, 2017) for acute and chronic aquatic toxicities.

Summary of environmental risk

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

The assessed chemical is not readily biodegradable and is persistent in water. The assessed chemical is predicted to degrade in the air compartment. The assessed chemical has a low potential for bioaccumulation and is not expected to cause toxic effects in aquatic organisms.

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 the expected 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

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 classifications 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 should be implemented to manage the risk arising from exposure to the assessed chemical during reformulation:
    - Use of engineering controls such as
        - automated and enclosed systems where possible
        - adequate workplace ventilation to avoid accumulation of vapours, mists, or aerosols
    - Use of safe work practices to
        - avoid contact with eyes
        - avoid inhalation of vapours, mists or aerosols
    - Use of personal protective equipment (PPE)
        - overalls
        - gloves
        - respiratory protection if required
- 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 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.

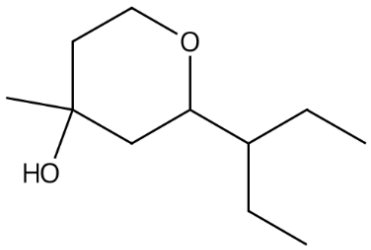
Note: Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

Supporting information

Chemical identity

Chemical name	2*H*-Pyran-4-ol, 2-(1-ethylpropyl)tetrahydro-4-methyl-
CAS No.	1099648-69-7
Synonyms	2-(1-Ethylpropyl)tetrahydro-4-methyl-2*H*-pyran-4-ol
Molecular formula	$C_{11}H_{22}O_2$
Molecular weight (g/mol)	186.29
SMILES (Canonical)	OC1(C)CCOC(C1)C(CC)CC
Purity	> 96 - < 100% (w/w)

Representative Structure



Chemical description

The assessed chemical is a mixture of 4 stereoisomers: the *cis*- isomers, (2S, 4R) and (2R, 4S) and the *trans*- isomers, (2S, 4S) and (2R, 4R).

Relevant physical and chemical properties

Physical form	colourless liquid
Melting point	-62.1 ± 0.2 °C
Boiling point	244.2 ± 0.7 °C
Relative Density	0.9628 ± 0.0001 at 20 °C
Vapour pressure	0.00227 kPa at 25 °C
Water solubility	7020 mg/L at 20°C, pH 7
log K_{ow}	2.2 at 20°C, pH 5.7-9.4

log K_{oc}	1.58 - 1.63 (calculated)
Flash point	118.8 ± 0.4 °C
Auto-ignition temperature	279 ± 3 °C

Human exposure

Public

There will be widespread and repeated exposure of the public to the assessed chemical at up to 0.5% concentration through the use of cosmetic and household products and up to 2% concentration when using continuous action 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 chemical 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.

Product type	Amount (mg/day)	C (%)	RF	Daily systemic exposure (µg/kg bw/day)
Body lotion	7,820	0.05	1	56
Face cream	1,540	0.05	1	11
Hand cream	2,160	0.05	1	15
Fine fragrances	750	0.5	1	54
Deodorant (non-spray)	1,500	0.05	1	11
Shampoo	10,460	0.05	0.01	1
Conditioner	3,920	0.05	0.01	0
Shower gel	18,670	0.05	0.01	1
Hand wash soap	20,000	0.05	0.01	1
Hair styling products	4,000	0.05	0.1	3
Total				**153**

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

Dermal exposure from using household cleaning products and wearing clothes will result in approximately additional 1 µg/kg bw/day systemic exposure, considering low concentrations and retention factors for these products.

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 chemical inhaled is 50%.

Amount of hairspray applied	9.89	g/day
Maximum intended concentration of the chemical	0.05	%
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	**2**	**µg/kg bw/day**

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)]

It is acknowledged that inhalation exposure to the assessed chemical 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 chemical at the maximum intended concentrations specified in various product types. This would result in a combined internal dose of 156 µg/kg bw/day (= 0.156 mg/kg bw/day) for the assessed chemical. This low level of worst-case systemic exposure is unlikely to pose health risk to the public with repeated use of products containing the assessed chemical.

Health hazard information

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

Endpoint	Test guideline	Results and Conclusion
Rat, acute oral toxicity	OECD TG 423	LD50 > 2,000 mg/kg bw; low acute oral toxicity
Rabbit, skin irritation	OECD TG 404	Non irritating
Rabbit, eye irritation	OECD TG 405	Irritating
Skin sensitisation – Local Lymph Node Assay (LLNA)	OECD TG 429	Non sensitising
Mutagenicity – bacterial reverse mutation	OECD TG 471	Non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	OECD TG 473	Non clastogenic

Acute toxicity

Oral

The acute oral toxicity potential of the assessed chemical was tested following the OECD TG 423. The assessed chemical was administered by oral gavage to six female Sprague Dawley rats at a single dose of 2,000 mg/kg bw. One test animal was found dead at the 24-hour observation. Macroscopic examination of the animal revealed the presence of red foci on the corpus and the lungs and a thinning of the forestomach. A decrease in spontaneous activity was noted in all test animals. This was associated with bradypnea (3/6 animals), absence of Preyer's reflex (2/6 animals) and complete or partial closure of the eyes (2/6 animals), and an absence or a decrease of righting reflex (4/6 animals) during the 1st day of the test. The animals recovered on the 2nd day of the test. The body weight gain remained in the normal range in all test animals. The macroscopical examination of the surviving test animals at the end of the study did not reveal treatment-related changes. Based on the results of this study, the assessed chemical is of low acute oral toxicity (LD50 > 2,000 mg/kg bw).

Corrosion/Irritation

Skin irritation

The skin irritation potential of the assessed chemical was tested in rabbits following the OECD TG 404. Skin of 3 New Zealand White male rabbits were exposed to the undiluted assessed chemical at a dose of 0.5 mL for 4 hours under semi-occlusive conditions. No erythema or oedema was noted in any of the test animals at the 24 h reading and the subsequent readings after that. Based on the results, the assessed chemical is considered as non irritating to the skin.

Eye irritation

The eye irritation potential of the assessed chemical was tested in rabbits following the OECD TG 405. Eyes of 3 New Zealand White female rabbits were exposed to the undiluted assessed chemical at a dose of 0.1 mL. All three test animals exhibited moderate ocular reactions, including conjunctive chemosis (24, 48 and 72 hours mean scores were 0.7, 1.3 and 1.3, respectively) and redness (24, 48 and 72 hours mean scores were 1.3, 1.3 and 1.3

respectively), iris lesions (24, 48 and 72 hours mean scores were 0.3, 0.0 and 0.0 respectively) and corneal opacity (24, 48 and 72 hours mean scores were 2.0, 2.0 and 1.7 respectively), which were totally reversible between Day 7 and Day 11. Based on the results, the assessed chemical meets the GHS criteria for classification as irritating to eyes (Cat 2A: H319: Causes serious eye irritation).

Sensitisation

Skin sensitisation

The skin sensitisation potential of the assessed chemical was tested using a local lymph node assay (LLNA) in mice (OECD TG 429). The mice were treated by daily application of 25 µL of the chemical at concentrations of 25%, 50% or 100% (acetone/olive oil 4:1 as vehicle) to the dorsal surface of each ear for 3 consecutive days. There were no mortalities or signs of systemic toxicity and no cutaneous reactions were observed. The stimulation index (SI) at the 25%, 50% and 100% concentrations were 0.94, 1.19 and 1.03, respectively. Based on the results of this study, the assessed chemical is not considered sensitising to the skin.

Genotoxicity

The mutagenic potential of the assessed chemical was tested in a bacterial reverse mutation assay following the OECD TG 471 using the plate incorporation and pre-incubation methods. *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 and *Escherichia coli* strain WP2(pKM101) were used for the test. The chemical was tested at up to 5 µL/plate in the absence or presence of metabolic activation. No test substance mediated increase in the number of revertant colonies were observed under the test conditions and the chemical was not considered as mutagenic.

An in vitro chromosome aberration test following the OECD TG 473 was conducted to assess clastogenic potential of the assessed chemical using cultured human lymphocytes. When tested at up to precipitation and / or cytotoxic concentrations, the assessed chemical did not induce any statistically significant increase in the frequency of cells with chromosome aberrations under the test conditions. The chemical was not considered as clastogenic to human lymphocytes in vitro.

Environmental exposure

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

The assessed chemical will be included in a wide range of products, resulting in a variety of potential exposure scenarios.

Consumer and professional end use of the assessed chemical in cosmetic and household 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 partitioning of the assessed chemical was not determined. The chemical is treated as if it is mobile in the environment as a worst-case scenario.

Degradation

Based on its measured degradation in water, the assessed chemical is categorised as persistent.

The result of a supplied biodegradation study conducted using the OECD TG 301F test guideline demonstrated 7% degradation of the assessed chemical in 28 days. The study was prolonged to 60 days to assess any further degradation, however, the assessed chemical showed only 20% degradation in 60 days. Therefore, the assessed chemical is not readily biodegradable in water.

Another supplied study conducted according to OECD TG 310 showed 8.5% degradation in 28 days, indicating the assessed chemical is not readily biodegradable.

The half-life of the assessed chemical in air is calculated to be 2.61 hours, based on reactions with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). When the assessed chemical partitions to or is directly released to air, it is expected to degrade. As the half-life in air is below the domestic threshold value of 2 days, the assessed chemical is not expected to persist in air compartment.

Bioaccumulation

No bioaccumulation information was provided for the assessed chemical. The experimental partition coefficient of the assessed chemical (log K_{OW} = 2.2) is below the domestic bioaccumulation threshold of log K_{OW} = 4.2 (EPHC, 2009). Therefore, bioaccumulation of the assessed chemical is not expected.

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 chemical is 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 chemical 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 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	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

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

Taxon	Endpoint	Method
Fish	96 h LC50 > 115 mg/L	*Gobjocypris rarus* (Rare minnow) Mortality OECD TG 203 Semi-static Measured concentration
Invertebrate	48 h ErC50 = 136 mg/L	*Daphnia magna* (water flea) Growth rate iSafeRat HA-QSAR v1.8 Ecotox module Calculated concentration
Algae	72 hr ErC50 > 100 mg/L	*Desmodesmus subspicatus* (green algae) Growth rate OECD TG 201 Static 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 this chemical are greater than 0.54 mg/L. With a conservative assessment factor of 1,000, the lowest calculable PNEC is > 0.54 µg/L.

Categorisation of environmental hazard

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

Persistence

Persistent (P). Based on measured degradation studies, the assessed chemical is categorised as Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on a measured log K_{OW} value < 4.2, the assessed chemical is categorised as Not Bioaccumulative.

Toxicity

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

Environmental risk characterisation

Although the assessed chemical is persistent in water, 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.

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 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 chemical that each exceed 0.54 mg/L.

Therefore, based on the expected RQ < 1 the assessed chemical is not expected to pose a significant risk to the environment. As such, the environmental risks associated with the assessed chemical can be managed.

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