Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

3-Cyclohexene-1-methanol, 2,4,6-trimethyl- (isocyclogeraniol)

Evaluation statement

14 January 2022

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AICIS evaluation statement

Subject of the evaluation

3-cyclohexene-1-methanol, 2,4,6-trimethyl- (isocyclogeraniol)

Chemical in this evaluation

Name	CAS number
3-Cyclohexene-1-methanol, 2,4,6-trimethyl-	68527-77-5

Reason for the evaluation

The Evaluation Section Analysis indicated a potential risk to human health.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).This evaluation is a human health risk assessment for all identified uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

There is no specific information about the introduction, use and end use of the chemical in Australia.

The chemical is used as a fragrance ingredient in domestic and cosmetic products. Based on international use information, the chemical is used in finished products including lipstick, body lotion, face moisturisers, fine fragrances, air freshener products (aerosol), polishes and waxes, washing and cleaning products and leave on and rinse off personal care products (Api et al. 2019; NLM; REACH).

In Europe, the use of the chemical in cosmetic products is restricted to a maximum allowable concentration of 0.5% in ready for use preparations (REACH) with concentrations in use of 0.12% (95th percentile) reported.

A global volume of up to 100 t/y (Api et al. 2019) and up to 10 t/y in European Union (REACH) has been reported.

The use of the chemical is expected to be widespread as it is present in various types of domestic products, as well as in cosmetic products.

Human health

Summary of health hazards

The critical health effects for risk characterisation are related to local effects (skin sensitisation, and skin and eye irritation).

The chemical has low acute oral toxicity based on animal data, with a median lethal dose (LD50) of >2000 mg/kg bw in rats. There were no information on acute dermal toxicity and acute inhalation toxicity of the chemical.

The chemical is considered to be a skin and eye irritant. Positive results were reported in an in vitro skin irritation study. While no experimental eye irritation data were available for the chemical, it contains an aliphatic monoalcohol group, which, according to Toxtree (Toxic Hazard Estimation by decision tree approach) show the potential for serious eye irritation (Toxtree). Test results obtained from a read across chemical (2,4-dimethylcyclohex-3-ene-1-methanol (CAS 67634-17-7)) with closely related structure, showed irreversible effects on the eyes of rabbits, supporting the conclusion that the chemical is an eye irritant.

The chemical is a weak skin sensitiser according to the available data. While some studies showed negative results, including a local lymph node assay (LLNA) and in vitro studies, there was a clear evidence of skin sensitisation in a Buelher test and human patch tests. Based on HRIPT (human repeated insult patch test) results, a NESIL (No Expected Sensitization Induction Level) of 3800 µg/cm^2 was established for the chemical (Api et al. 2019).

There were no experimental data available on the repeat dose toxicity, carcinogenicity and reproductive toxicity endpoints for the chemical.

The threshold of toxicological concern (TTC) values for repeat dose, reproductive toxicity and local respiratory effects were derived (0.03 mg/kg/day, 0.03 mg/kg bw/day and 1.4 mg/day, respectively), based on a Cramer classification I for the chemical when used as fragrance ingredient (Kroes et al. 2007; Laufersweiler et al. 2012).

Very limited experimental information were available on genotoxicity. These indicated that the chemical has no genotoxic potential. The chemical was found negative in 2 bacterial reverse mutation assays (OECD TG 471) and in a mammalian cell BluScreen HC™ assay. In addition, in silico methods provided no structural alerts for genotoxicity, carcinogenicity or reproductive toxicity (QSAR Toolbox 4.2).

Health hazard classification

Based on the available data, the 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 work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Skin irritation	Skin irrit. 2	H315: Causes skin irritation.
Eye irritation	Eye irrit. 2	H319: Causes serious eye irritation

Sensitisation	Skin sens. 1B	H317: May cause an allergic skin reaction

Summary of health risk

Public

Based on the international use pattern, which is expected to be relevant to Australia, the public may be exposed to the chemical:

- by direct skin contact during use of cosmetic products (applied to skin, hair and lips)
- by incidental skin and eye contact during use of domestic products
- by inhalation of aerosols/vapours from air freshener products

There is potentially widespread public exposure, as the chemical is present in various types of domestic and cosmetic products.

A total systemic exposure of 0.0029 mg/kg/day was calculated, assuming 100% oral and dermal absorptions of the chemical when used as a fragrance ingredient in cosmetic products (Api et al., 2019). This total systemic exposure is below the TTC for repeat dose and reproductive toxicity (0.03 mg/kg/day). The inhalation exposure was calculated to be 0.074 mg/day, assuming 100% absorption via inhalation, much lower than the TTC value for inhalation of 1.4 mg/day.

Based on the NESIL of 3800 µg/cm^2 and the calculated low total systemic exposure, the maximum acceptable concentrations in finished products were estimated to range between 0.086–3.3% in cosmetic products and up to 11% in domestic products with intended skin contact (Api et al. 2019).

Based on international data the chemical is used at concentrations below 0.5%.

There are currently no restrictions on domestic and cosmetic uses of the chemical in Australia. While exposure from consumer products is widespread and skin sensitisation is of concern, the quantitative assessment suggests that the chemical is not expected to pose a risk to the public. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical local health effects, the chemical could pose a risk to workers.

Control measures to minimise dermal and ocular exposure are needed to manage the risk to workers (refer to **Recommendations** section).

Conclusions

The conclusions of this evaluation are based on the information described in this statement. Obligations to report additional information about hazards under section 100 of the Industrial Chemicals Act 2019 apply.

The Executive Director is satisfied that the identified human health 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. The proposed means of managing the risks identified during this evaluation are set out in the Recommendations section.

Recommendations

Workers

Recommendation to Safe Work Australia

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

Information on managing identified risks

The information in this report, including hazard classifications, should be used by persons conducting a business or undertaking (PCBU) at the workplace (such as an employer) to determine the appropriate controls under the Model Work Health and Safety Regulations.

Control measures that could be implemented to manage the risk arising from occupational exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate, or manage risks arising from storing, handling and using a hazardous chemical depend on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting 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.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or

sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

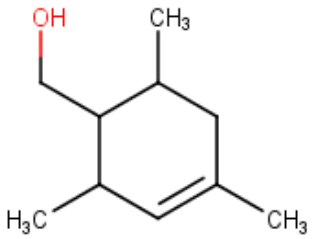
Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemical. Your Work Health and Safety regulator should be contacted for information on Work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

Supporting information

Rationale

Where data are not available for the chemical, read across information from structurally related chemicals 3-cyclohexene-1-methanol, 2,4-dimethyl- (CAS 67634-17-7) and 3-cyclohexene-1-methanol, 3,5-dimethyl- (CAS No 67634-16-6) are used, for eye irritation and genotoxicity, respectively.

Chemical identity

Chemical name	3-Cyclohexene-1-methanol, 2,4,6-trimethyl-
CAS No.	68527-77-5
Synonyms	isocyclogeraniol 2,4,6-trimethylcyclohex-3-ene-1-methanol
Structural formula	
Molecular formula	C10H18O
Molecular weight (g/mol)	154.25
SMILES	CC1CC(=CC(C)C1CO)C
Chemical description	-

Relevant physical and chemical properties

Physical form	Pale to colourless clear liquid with a spicy, floral odour (Api et al., 2019)
Melting point	-20°C (experimental; ECHA) 13.51°C (calculated; Api et al., 2019)
Boiling point	224.9°C (experimental; ECHA) 237°C (calculated; Api et al., 2019)

Flash point	94°C (experimental; ECHA)
Vapour pressure	2.4 Pa at 24°C (experimental; ECHA) 0.00439 mm Hg (0.5 Pa) at 20°C (calculated; Api et al., 2019) 0.00747 mm Hg (0.9 pa) at 25°C
Water solubility	656 mg/L (experimental; ECHA) 360 mg/L (calculated; Api et al., 2019)
Partition coefficient (log K_{ow})	3.6 (experimental; ECHA) 3.3 (calculated; Api et al., 2019)

Introduction and use

Australia

No specific information is available on the introduction and use of the chemical in Australia.

International

The chemical has reported cosmetic use as fragrance ingredient.

The chemical has reported domestic uses in:

- Air fresheners
- Cleaning and washing products
- Polishes and waxes

In general, the chemical has been reported to be used in various types of products, ranging from cosmetic and personal care products to non-industrial products such as biocidal products (disinfectant) and pest control products. The 95th percentile concentration in hydroalcoholics is 0.12% (Api et al. 2019)

Existing Australian regulatory controls

AICIS

There are currently no restrictions on the use of this chemical in Australia.

Public

There are currently no restrictions on the use of this chemical in Australia.

Workers

The chemical is not listed on the Hazardous Chemical Information System (HCIS) and no exposure standards are available in Australia (Safe Work Australia).

International regulatory status

Exposure standards

No exposure standards are available for the chemical (NLM).

European Union

The chemical is listed in Annex III of the EU Cosmetic Regulation (EC) No. 1223/2009, restricting its use in cosmetic products at a maximum concentration of 0.5% in ready for use preparations (CosIng).

New Zealand

The chemical is listed in the New Zealand Cosmetic Products Group Standard — Schedule 5 Components Cosmetic Products Must Not Contain Except Subject to the Restrictions and Conditions Laid Down: the maximum authorised concentration in the finished cosmetic product is 0.5% (NLM).

Health hazard information

Toxicokinetics

No data are available on toxicokinetics.

Acute toxicity

The chemical has low acute oral toxicity based on animal data.

In an acute oral toxicity study following OECD TG 423, the median lethal dose (LD50) was found to be >2000 mg/kg bw in rats (n = 3/sex/group). No mortality was reported at up to 2000 mg/kg bw. Clinical signs of toxicity included lethargy, flat posture, hunched posture and/or uncoordinated movements (REACH).

No data are available for other routes of exposure.

Corrosion/Irritation

Skin irritation

The chemical is considered a skin irritant.

In an in vitro reconstructed human epidermis (RHE) skin irritation study conducted in accordance with OECD TG 439, the chemical was determined to be irritating to the skin. Skin tissue was exposed to 25 µL of undiluted chemical for 15 minutes, then incubated for an observation period of 42 hours. A mean tissue viability value of 12% was reported when compared with negative controls, indicating positive result for skin irritation (REACH).

The interpretation of results obtained from a single OECD TG 439 study does not allow for distinction between irritation and corrosion. However, based on the absence of clear

corrosive effects in skin sensitisation studies (see **Skin sensitisation** section) and the positive result obtained in the above in vitro study, the chemical is considered a skin irritant.

Eye irritation

No data are available for the chemical. Read-across information from structurally similar chemical, 3-cyclohexene-1-methanol, 2,4-dimethyl- (CAS No. 67634-17-7) suggests that the chemical is a serious eye irritant.

In an eye irritation study conducted in accordance with OECD TG 405, the undiluted analogue was instilled into one eye for each of the 3 white rabbits. The eyes were observed at 1, 24, 48, 72 hours, then 7 and 14 days post-exposure. The following mean scores were reported:

- for animal 1: corneal opacity 2/4, iritis 0/2, conjunctival redness 2.33/3 and chemosis 2/4
- for animal 2: corneal opacity 2.33/4, iritis 1/2, conjunctival redness 2.66/3 and chemosis 2.33/4
- for animal 3: corneal opacity 2/4, iritis 1/2, conjunctival redness 2.33/3 and chemosis 1.66/4

Most of the observed effects were reversible in all animals within 7 to 14 days. One animal had higher score for corneal opacity (2.33/4) associated with non-fully reversible circumcorneal vascularisation. The analogue chemical was considered to cause irreversible effects on the eye (REACH).

Skin sensitisation

Based on the weight of evidence, the chemical is considered to cause skin sensitisation. There is sufficient evidence to warrant hazard classification of the chemical.

In a skin sensitisation study similar to OECD TG 406 (Buehler test), 10 female Hartley guinea pigs were treated with the chemical at 60% in ethanol, under occlusion for 6 hours, 3 times a week for a total of 9 exposures. The concentration of 60% was determined as the highest non-irritating concentration following a preliminary range-finding study conducted in 4 animals treated with 20%, 40%, 60% or 100% chemical. A control group of 5 guinea pigs was treated with ethanol only. All treated animals were then challenged with the chemical at 60% in ethanol, 17 days after induction. After 24 h, 8/10 of challenged animals had a positive response to the chemical (slight to moderate erythema) at both induction and naive sites, compared to none in the control group. After 48 h, 10/10 and 7/10 of challenged animals had a positive response (slight to moderate erythema) at induction and naïve sites, respectively, compared to none in the control group. The chemical was reported to be sensitising in this study (REACH).

In a local lymph node assay (LLNA) performed in accordance with OECD TG 429, female CBA mice (n = 4/group) received topical applications of 1, 2.5, 5, 10 or 25% of the chemical in ethanol:diethyl phthalate (EtOH:DEP), 1:3 (w/v) for 3 days. The reported stimulation indices (SI) were 1.0, 1.5, 2.0, 1.5 and 2.3, respectively. The estimated concentration producing a 3 fold increase in lymphocyte proliferation (EC3) was therefore >25%, indicating absence of or only weak sensitisation potential. No further details were provided on skin reactions or clinical signs of toxicity (REACH).

Unpublished data were briefly reported as follows (Api et al. 2019):

- The chemical was negative in an *in vitro* direct peptide reactivity assay (DPRA), KeratinoSens, and U937-CD86 test
- The chemical was positive in a human cell line activation test (h-CLAT)
- In human repeated insult patch tests (HRIPTs), each with less than 100 subjects, the chemical induced sensitization reactions at 10% (5000 µg/cm^2) or 5% (2500 µg/cm^2)
- In a confirmatory human repeated insult patch test (HRIPT) with a dose of 3897 µg/cm^2 of the chemical in 1:3 (EtOH:DEP), no sensitisation reactions were observed in any of the 103 volunteers

Repeat dose toxicity

No data are available. The chemical is classified as Cramer Class I substance by Toxtree (Kroes et al., 2007; Laufersweiler et al., 2012). The calculated total systemic exposure of 0.0029 mg/kg/day for the chemical (Api et al., 2019; QSAR Toolbox 4.2) is lower than the TTC value (0.03 mg/kg/day) for the repeat dose toxicity endpoint of a Cramer Class I substance when used as a fragrance ingredient. This indicates that the chemical is unlikely to cause serious systemic toxicity effects following repeated exposure. The exposure calculations for the main routes of exposure (dermal and inhalation) also indicate that systemic effects are not expected when used as fragrance ingredients in various finished products.

Genotoxicity

Only limited experimental information is available on the chemical. Overall, the chemical has no genotoxic potential.

The chemical was found negative in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 and *Escherichia coli* WP2 uvrA, with and without metabolic activation, at concentrations up to 1250 µg/plate in DMSO (REACH).

The chemical was found negative in another bacterial reverse mutation assay (OECD TG 471) using *S. typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvrA, with and without metabolic activation, at concentrations up to 5000 µg/plate in DMSO (Api et al., 2019).

The chemical was found negative with and without metabolic activation in a non-guideline mammalian cell assay BlueScreen HC™ (Api et al., 2019). No details are available on the study, but the BlueScreen HC™ is a mammalian cell-based assay a genetically modified strain of cultured human lymphoblastoid TK6 cells (GLuc-T01). This test is a screening tool used ‘as supporting evidence when using a read-across approach, and to adjust the threshold of toxicological concern (TTC)’ (RIFM 2021).

In addition, in silico methods indicated no structural alerts of genotoxicity for the chemical (Danish EPA 2021; QSAR Toolbox v4.2 2021)

Read-across on the genotoxic profile of a structurally similar chemical was discussed in the RIFM safety assessment report (Api et al. 2019). In an *in vitro* micronucleus test conducted in accordance with OECD TG 487, human peripheral blood lymphocytes were treated with 3-cyclohexene-1-methanol, 3,5-dimethyl- (CAS No. 67634-16-6) in DMSO at concentrations up to 1400 µg/mL, with and without metabolic activation for 4 and 24 h. The analogue gave negative results with and without metabolic activation.

Reproductive and development toxicity

No data are available. The chemical is classified as Cramer Class I substance by Toxtree (Kroes et al. 2007; Laufersweiler et al. 2012). The calculated total systemic exposure of 0.0029 mg/kg/day for the chemical (Api et al. 2019; QSAR Toolbox 4.2) is lower than the TTC value (0.03 mg/kg bw/day) for the reproductive toxicity endpoint of a Cramer Class I substance when used as a fragrance ingredient. This indicates that the chemical is unlikely to cause serious reproductive toxicity effects. The exposure calculations for the main routes of exposure (dermal and inhalation) also indicate that reproductive effects are not expected when used as fragrance ingredients in various finished products.

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