Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Ethanone, 1-[(3*R*,3a*R*,7*R*,8a*S*)-2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1*H*-3a,7-methanoazulen-5-yl]- (acetylcedrene)

Evaluation statement

14 September 2021

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AICIS evaluation statement

Subject of the evaluation

Ethanone, 1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)-, [3R-(3.alpha.,3a.beta.,7.beta.,8a.alpha.)]- (acetylcedrene)

Chemical in this evaluation

Name	CAS registry number
Ethanone, 1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)-, [3R-(3.alpha.,3a.beta.,7.beta.,8a.alpha.)]-	32388-55-9

Reason for the evaluation

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

Parameters of evaluation

A human health risk assessment for all identified uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

There is currently no information about the chemical use and volume of use in Australia.

Based on international use information, the chemical is used in a wide range of industrial applications, including in cosmetic products (as a fragrance ingredient) and in domestic products (washing and cleaning products). The reported concentration of the chemical in personal care products is 0.1–1.5%, and a maximum dermal exposure to 3.9% has been reported following the use of consumer products containing the chemical.

Human health

Summary of health hazards

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

Information on toxicokinetics of the chemical is limited. The available information shows it can be absorbed via oral and dermal routes of exposure.

The chemical has low acute oral toxicity with a median lethal dose (LD50) of 4500 mg/kg bw in rats and low acute dermal toxicity with an LD50 of >2000 mg/kg bw in rabbits.

The chemical is slightly irritating to skin and eyes. Slight to moderate erythema and oedema were observed in a skin irritation studies in rabbits with the undiluted chemical. Slight skin irritation was reported in several guinea pig studies at lower concentrations (20–50%). Two out of five human studies reported slight skin irritation in a small number of study subjects following exposure to 5% and 30% concentration of the chemical, respectively (Scognamiglio et al. 2013). An in vitro study found no signs of skin irritation after exposure of reconstituted human epidermis skin to the undiluted chemical.

In a study similar to OECD TG 405, no eye irritation was observed in rabbits. However, in 5 non-GLP compliant eye irritation studies similar to OECD TG 405, slight to moderate eye irritation was reported in rabbits after treatment with the chemical.

The chemical is a skin sensitiser based on positive results seen in a local lymph node assay (LLNA) and some guinea pig maximisation tests (GPMT). The concentration producing a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 13.9%, indicating that the chemical is weak sensitiser and unlikely to induce sensitisation at low use concentrations. This is supported by observations in humans where limited sensitisation reactions were reported in human patch test studies using 5% solutions of the chemical.

The chemical is not expected to cause serious systemic health effects following repeated oral exposure based on the reversibility and low severity of the observed effects. A no observed adverse effect level (NOAEL) of 80 mg/kg bw/day was established in subchronic oral study in Wistar rats based on effects observed in the liver higher dose levels. Repeated dose dermal studies did not show any adverse effects by this route.

The chemical was negative in two in vitro bacterial reverse mutation assays and in a chromosome aberration assay.

The carcinogenic potential of the chemical has not been investigated in standard studies, but on the basis of the essentially negative findings in the mutagenicity tests, it is not expected to cause cancer by a genotoxic mechanism.

There are no reproductive toxicity data available for the chemical. In a developmental study in which pregnant SD rats were administered the chemical, no gross external, soft tissue or skeletal alterations (malformations or variations) were observed in the foetus.

Health hazard classification

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 sensitisation	Category 1B	H317: May cause allergic skin reaction

Summary of health risk

Public

Based on its international use pattern, the public may be exposed to the chemical:

- by direct skin contact during use of cosmetic products
- by incidental skin and eye contact with the chemical during use of domestic products
- by inhaling aerosols/vapours

Given the concentrations expected to be in use in personal care and domestic products, and toxicology data showing limited sensitisation potential at these concentrations, there are no identified risks to the public that require management.

Workers

During product formulation, dermal and ocular 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 systemic acute and local health effects, the chemical could pose a risk to workers. Control measures to minimise dermal exposure are needed to manage the risk to workers (refer to **Recommendation** section).

Conclusions

The conclusions of this evaluation are based on the information described in the 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 provided 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 below.

Recommendations

Workers

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

Advice to industry

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

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

- 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 the manner in which the chemical is used.

These control measures should 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.

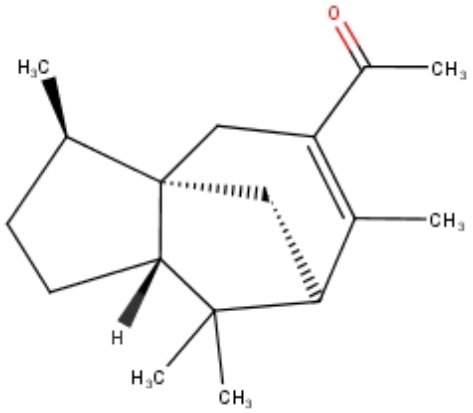
Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New 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 chemicals. 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

Chemical identity

Synonyms	1-[(3*R*,3a*R*,7*R*,8a*S*)-2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1*H*-3a,7-methanoazulen-5-yl]ethanone (ACI) 1*H*-3a,7-Methanoazulene, ethanone deriv. (3R-(3α,3aβ,7β,8aα))-1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)ethan-1-one

	1-((3R,3AR,7R,8aS)-3,6,8,8-tetramethyl-2,3,4,7,8,8a-hexahydro-1*H*-3a,7-methanoazulen-5-yl)ethan-1-one methyl cedryl ketone acetylcedrene
Structural formula	
Molecular formula	C17H26O
Molecular weight (g/mol)	246.39
SMILES	O=C(C1=C(C)C2CC3(C1)C(C)CCC3C2(C)C)C
Chemical description	-

Relevant physical and chemical properties

Physical form	Liquid
Boiling point	320.9°C at 101.8 kPa
Vapour pressure	0.25 x 10^{-3} Pa at 25°C
Water solubility	6 mg/L at 23°C
log K_{ow}	5.9

Introduction and use

Australia

No information is available on the use of this chemical in Australia.

International

The following international uses have been identified through Galleria Chemica; the United States Environmental Protection Agency (US EPA) Chemical Data Reporting 2016; the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; International Fragrance Association (IFRA) Transparency List; the Substances and Preparations in Nordic countries (SPIN) database; the European Cosmetic Ingredient Database (CosIng); the US EPA Chemical and Product Categories database.

The chemical has reported cosmetic use as a fragrance ingredient.

The Consumer Product Information Database (CPID) reports concentrations of the chemical in personal care products of 0.1–1.5%. The maximum dermal exposure following the chemical's use in consumer products is reported to be 3.9% (Belsito et al. 2013).

The chemical has reported domestic use, including in:

- polishes/wax blends
- washing/cleaning products
- air freshener products.

The chemical has reported commercial uses, including in polishes and wax blends.

The chemical has reported non-industrial uses, including in biocidal products (e.g. disinfectants, pest control).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

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

International regulatory status

Exposure standards

No specific controls are currently available for the chemical.

Health hazard information

Toxicokinetics

A full absorption, distribution, metabolism, and excretion (ADME) toxicokinetic study is not available.

In an in vitro skin penetration study conducted according to Food and Drug Administration (FDA) guidelines, 1% of the radiolabelled chemical in ethanol (w/v) was applied to human epidermal membranes from breast or abdominal skin (comprising both the stratum corneum and the epidermis). After 48 hours, 11.3% of the applied dose had permeated the membranes. Overall, recovery was 68.1% of the applied dose (Scognamiglio et al. 2013).

In an oral absorption study, acetylcedrene administered orally (by gavage) to pre-mated Sprague Dawley (SD) rats (18/dose) at 2 and 20 mg/kg bw during and after pregnancy, was detected in breast milk (Scognamiglio et al. 2013).

Alicyclic ketones such as acetylcedrene are typically reduced to the corresponding secondary alcohol and excreted primarily as glucuronic acid conjugates in the urine (REACH).

Acute toxicity

Oral

Based on the available data, the chemical has low acute oral toxicity.

In an acute toxicity study similar to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, SD rats (8/sex/dose) were administered (gavage) a single dose of 2000, 3000, 4000, 5000, 7980 or 12650 mg/kg bw of the chemical. The majority of rats survived at doses below 4000 mg/kg bw. Reported sublethal signs of toxicity included irritability and passivity soon after dosing; and animals remained subdued up to 48 hours. The reported LD50 was 4500 mg/kg bw (REACH).

Similar findings were reported in a non-guideline study in male albino Wistar rats (10/dose) treated with single doses of 4000, 5000, 6250 and 7800 mg/kg bw of the chemical. Animals were observed for 14 days. The reported LD50 value was 5200 mg/kg bw (Scognamiglio et al. 2013).

Dermal

Based on the available data, the chemical has low acute dermal toxicity.

In a non-guideline study in New Zealand White (NZW) rabbits (10/dose) the chemical was applied to the skin of the animals at a dose of 2000 mg/kg bw for a 24 hour period. Animals were observed for 7 days following treatment. No clinical signs were observed during the study. The reported LD50 value was >2000 mg/kg bw (Scognamiglio et al. 2013).

Inhalation

No data are available.

Observation in humans

No data are available.

Corrosion/Irritation

Skin irritation

The chemical is slightly irritating to the skin. Repeated (see Repeat dose toxicity – Dermal) or prolonged exposure to low concentrations of the chemical also resulted in slight irritant effects. The effects are not significantly severe to warrant hazard classification.

In an in vitro skin irritation study conducted according to the OECD TG 439, reconstituted human epidermis skin cultured in vitro was exposed to 10 µL of undiluted chemical for 15 minutes. The percentage mean viability of the chemical was 76.2 ± 4.6% of the negative control. As the mean tissue viability is greater than 50%, the chemical is not considered to be a skin irritant (REACH).

In a skin irritation study similar to OECD TG 404, NZW rabbits (n=8) displayed slight to moderate erythema and oedema after treatment with the undiluted chemical (no scores reported) (Scognamiglio et al. 2013).

Several non-guideline guinea pig studies with limited reported information available demonstrated that prolonged exposure to the chemical at concentrations between 5–20% induced slight irritation (Scognamiglio et al. 2013).

Eye irritation

In an eye irritation study similar to OECD TG 405, 0.1 mL of the chemical (neat) was instilled into one eye each of 6 female NZW rabbits for 24 hours and the animals were monitored for 7 days. No eye irritation was observed (REACH).

In 5 non-GLP compliant eye irritation studies similar OECD TG 405, 0.1 mL of the chemical (neat) was instilled into one eye of 3 rabbits for 24 hours. Slight, but reversible eye irritation was reported in the majority of the rabbits (no scores reported) (Scognamiglio et al. 2013).

Several non-guideline studies in rabbits with limited data reported slight to moderate eye irritation at concentrations between 2.5–50% of the chemical (Scognamiglio et al. 2013).

The effects were not significantly severe to warrant hazard classification.

Observation in humans

Two out of 5 human studies reported slight skin irritation in a small number of study subjects after exposure to 5% and 30% concentration of the chemical, respectively (Scognamiglio et al. 2013).

Sensitisation

Skin sensitisation

Based on the weight of evidence from human and animal studies the chemical is a weak skin sensitiser, warranting hazard classification (see **Recommendation** section).

In a local lymph node assay (LLNA) performed in accordance with OECD TG 429, female CBA/J mice (5/dose) received topical applications of 2.5, 5, 10, 25 and 50% (w/v) of the chemical in 3:1 diethyl phthalate/ethanol on three consecutive days. The reported stimulation indices (SI) were 1.67, 1.69, 2.39, 4.72 and 25.09 respectively. The reported concentration producing a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 13.9%; hence, the chemical is considered to be a potential skin sensitiser (REACH).
Four guinea pig maximisation tests (GPMT) similar to OECD TG 406 reported no reaction at intradermal induction concentrations between 0.25% and 0.4%, topical induction concentrations between 10% and 40% and challenge concentrations between 1% and 10% of the chemical (Scognamiglio et al. 2013).

Extreme sensitisation effects were observed in a GPMT using 10% of the chemical for both induction and challenge concentrations (no further details reported) (Scognamiglio et al. 2013).

An open epicutaneous test was conducted on groups of 6–8 male and female guinea pigs. Daily applications were made for 3 weeks to a clipped 8 cm^2 area on the flank of each guinea pig. The test sites were not covered and the reactions were read 24 h after each application. A total of 21 applications of 0.1 mL test material in an unspecified vehicle were made for 21 days. No sensitisation was observed at a concentration of 30% of the chemical. It was not specified if the concentration reported in the results (30%) was the minimal irritating concentration or a lower primary non-irritating concentration (Scognamiglio et al. 2013).

Observation in humans

No sensitisation reactions were seen in a human repeated insult patch test (HRIPT) study at concentrations between 5% and 30% in a total of 137 human subjects, or in a human maximisation test study, using a 30% solution of the chemical in 25 healthy male subjects (Scognamiglio et al. 2013).

In a multi-centre study, using diagnostic patch tests, one out of 100 patients reported sensitisation reactions at 1% concentration of the chemical but no sensitisation was reported at 5% concentration (Scognamiglio et al. 2013).

A multi-centre study using diagnostic patch tests on 1855 male and female patients, who were classified based on a history of adverse reactions to fragrances (certain, probable, questionable, or none), observed three sensitisation reactions at 5% concentration of the chemical (Scognamiglio et al. 2013).

No sensitisation reactions were seen in several separate human patch test studies using 5% solutions of the chemical in a total of 164 patients with either cosmetic dermatitis, non-cosmetic dermatitis or eczema (Scognamiglio et al. 2013).

A case report of a 28 year old male patient with contact dermatitis reported a sensitisation response to 10.8% of the chemical in dipropylene glycol. No reactions were observed when this patient was also tested with dilutions of the chemical, 0.108%, 0.54% and 1.08% in dipropylene glycol (Scognamiglio et al. 2013).

Repeat dose toxicity

Oral

The chemical is not expected to cause serious damage to health from repeated oral exposure, based on the reversibility and low severity of the reported effects.

In an oral study conducted according to OECD TG 408, Wistar rats (10/sex/dose) were administered the chemical (gavage) at 25, 80 or 250 mg/kg bw/day for 90 days. No treatment related mortalities occurred during the study. Slight to severe salivation was reported in both males and females at 250 mg/kg bw/day and in one male and two females at 80 mg/kg bw/day. While there were some effects on bodyweight reported, the mean bodyweights of male and female animals receiving 250 mg/kg bw/day were within the range of the historical control data. (REACH).

In the liver, fatty change associated with single cell death was observed in some males and one female receiving 250 mg/kg bw/day. In the lower dose groups (25 and 80 mg/kg bw), there were subtle increases in fatty changes compared to the control group. In the absence of other degenerative changes, this was considered an adaptive finding. Statistically significant decreases in the thyroid hormones, T3 ($p < 0.01$) and T4 ($p < 0.001$), in male animals treated with 250 mg/kg bw/day were within the range of the historical control data. There were no statistically significant changes in the level of TSH in male or females at any dose and no statistically significant changes in (para)thyroid weight in males or females at any dose group. Proteinaceous deposits were observed in the kidney of male animals only, and they were associated with an increase in alpha 2u-globulin. This effect is specific to male rats and is; therefore, not relevant for the human health risk assessment. A no observed adverse effect level (NOAEL) of 80 mg/kg bw/day was established based on the liver effects at 250 mg/kg bw/day (REACH).

Dermal

Based on the information available the chemical is unlikely to cause severe health effects following repeated dermal exposure.

In a sub-chronic dermal toxicity study similar to OECD TG 411, the chemical was applied daily to shaved skin of SD rats (15/sex/dose) at a dose of 50, 150 or 300 mg/kg bw/day over a period of 13 weeks. There were no treatment related adverse effects observed during the study. During treatment and recovery phase, slight dermal irritation was observed. Decreases in mean body weights and food consumption were noted in treated males. Mild chronic inflammation and acanthosis/hyperkeratosis in all dose groups and increased kidney-to-body weight percentages in males at 150 or 300 mg/kg bw were observed. Hyaline droplet formation was noted in the tubular epithelium in males at 300 mg/kg bw/day. All changes had

completely resolved during recovery period (duration not mentioned). The reported NOAEL for dermal toxicity was <50 mg/kg bw based on mild chronic inflammation and acanthosis/hyperkeratosis in all dose groups (Scognamiglio et al. 2013).

In another sub-chronic dermal toxicity study similar to OECD TG 411, the chemical was applied daily to shaved skin of SD rats (15/sex/dose) at a dose of 50, 150 or 300 mg/kg bw/day over a period of 13 weeks. There were no mortalities and no chemical-related effects on body weight, food consumption, haematology, clinical chemistry, organ weights, or gross and histologic pathology. The reported NOAEL was 300 mg/kg bw/day (REACH).

In a 17-day non-GLP study, the chemical was applied daily to the shaved skin of SD rats (5/sex/dose) at a dose of 300, 600 or 1000 mg/kg bw/day. No treatment related effects on body weight, food consumption, or clinical pathology were observed. Treatment related light to moderate erythema, slight to severe oedema, atonia, desquamation, epidermal thickening with abnormal cornification and fissuring (for males) were observed. An increased incidence and severity of hyaline droplet formation in the renal tubular epithelial cells was seen in males in all dose groups. No other systemic effects were reported. The NOAEL for dermal toxicity was <300 mg/kg bw/d (Scognamiglio et al. 2013).

Inhalation

No data are available.

Genotoxicity

In vitro

Based on the available in vitro data, the chemical is not expected to be mutagenic.

Negative results were reported for Acetylcedrene in a:

- bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and the *Escherichia coli* WP2 uvr A pKM 101 strain with and without metabolic activation at concentrations up to 5000 µg/plate (REACH)
- bacterial reverse mutation assay similar to OECD TG 471 in *Salmonella typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 with and without metabolic activation at concentrations up to 5000 µg/plate (Scognamiglio et al. 2013)
- chromosome aberration assay (similar to OECD TG 473) in Chinese hamster ovary (CHO) cells at concentrations up to 50 µg/mL for 4 h (with and without metabolic activation) and 20 h (without metabolic activation) (Scognamiglio et al. 2013).

In vivo

No data are available.

Reproductive and development toxicity

Acetylcedrene does not cause developmental toxicity.

In a developmental toxicity study conducted similarly to OECD TG 414, pregnant SD rats (21-25/dose) were orally administered acetylcedrene by gavage at 0, 25, 50 or 100 mg/kg bw/day in corn oil on days 7–17 of pregnancy. Excessive salivation was observed in animals treated with 50 and 100 mg/kg bw/day of the chemical. Significant reductions in absolute and relative feed consumption and body weight gains in animals treated at 100 mg/kg bw/day were recorded. The NOAEL for maternal toxicity was 50 mg/kg bw/day. No gross external, soft tissue or skeletal foetal alterations (malformations or variations) were attributed to any dose of the chemical. The NOAEL for developmental toxicity was 100 mg/kg bw/day (REACH).

No studies on reproductive toxicity were available.

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