Ethanone, 1-[2,3-dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1H-inden-5-yl]-: Human health tier II assessment

08 March 2019

CAS Number: 68140-48-7

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

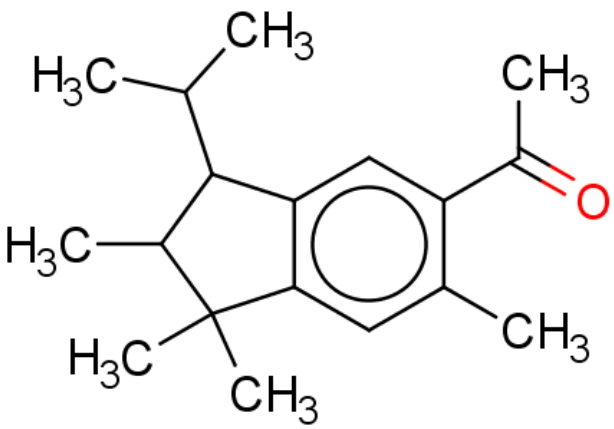
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	ketone, 3-isopropyl-1,1,2,6-tetramethyl-5-indanyl methyl traseolide 5-acetyl-3-isopropyl-1,1,2,6-tetramethylindane
Structural Formula	
Molecular Formula	C18H26O
Molecular Weight (g/mol)	258.40
Appearance and Odour (where available)	Pale yellow clear viscous liquid with dry, sweet, herbal, creamy, odour
SMILES	C1(C)(C)c2c(C(C(C)C)C1C)cc(C(C)=O)c(C)c2

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses were identified through Galleria Chemica; the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Substances and Preparations in the Nordic countries (SPIN) database; the United States (US) Environmental Protection Agency (EPA) Chemical and Product Categories (CPCat); Cosmetic Ingredients and Substances (CosIng)

The chemical has reported cosmetic use as a fragrance ingredient in perfumes and personal care products (CosIng).

The chemical was detected in 7 out of 36 perfumes at a maximum concentration of 0.5 % (Peters, 2005).

The chemical is listed on the IFRA transparency list of fragrance materials (IFRA, 2017).

The chemical is not listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011).

The chemical is not listed in the US Personal Care Product Council database.

The chemical has reported domestic uses in:

- washing and cleaning products;
- air care products;
- polishes and wax blends.

The chemical is not listed in the US household product database.

The registration of the chemical in the lowest tonnage band (0–10) indicates relatively low use of the chemical in the European Union.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

There are no toxicokinetic data available for the chemical; however, based on data from other polycyclic musks with similar physicochemical properties, dermal absorption is expected to be low (NICNASa).

An environmental assessment determined that the chemical is persistent and toxic to the environment; however, it was not considered bioaccumulative (NICNASb).

Acute Toxicity

Oral

Based on the limited available information, the chemical is expected to have low acute toxicity via the oral route. The reported median lethal doses (LD50) were >2000 mg/kg bw in rats.

The acute oral LD50 in rats was reported to be 2.22 mL/kg which corresponds to 2173 mg/kg (95 % CL 1987–2389) based on the reported density of 0.979 g/cm^3 (Opdyke et al., 1983; REACH).

An LD50 of 2199 mg/kg bw for the chemical was reported in the training set data of OASIS TIMES version 2.28.1 (OASIS LMC). The chemical was predicted to act via basic toxicity, which is a non-specific mechanism whereby neutral chemicals accumulate in the cell and disrupt cell physiology.

In the Danish (Quantitative) structure activity relationship [(Q)SAR] database (Technical University of Denmark), the chemical was predicted to have an LD50 of 2600 mg/kg bw in rats using the Advanced Chemistry Development (ACD)labs acute toxicity module, with a reliability index of 0.84.

Dermal

Limited data are available.

An LD50 >1250 mg/kg bw in rabbits has been reported (Opdyke, 1983).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical may be slightly irritating to skin particularly following repeated exposure (see ***Repeated dose toxicity*** section). The effects are not sufficient to warrant hazard classification.

In a skin irritation study in 6 New Zealand White (NZW) rabbits, traseolide was concluded to be a mild irritant. However, the reporting of the scores were not clear enough to support the conclusion (REACH).

Traseolide was slightly irritating to intact or abraded skin of rabbits after occlusive treatment for 24 h (Opdyke et al., 1983).

Eye Irritation

The chemical may be slightly irritating to eyes. The information is not sufficient to warrant hazard classification.

In an eye irritation study conducted similarly to OECD TG 405, 0.1 g of traseolide was applied to one eye of 6 NZW rabbits. Observations were made at 24, 48 and 72 h, and after 7 days. There was no indication of eye irritation in the study (REACH).

In another eye irritation study traseolide produced slight irritation to the conjunctivae of rabbit eyes (Opdyke et al., 1983).

Observation in humans

Traseolide (5 % in petrolatum) produced no irritation in a 48 h closed patch-test in human subjects (number of subjects not reported) (Opdyke et al., 1983).

Sensitisation

Skin Sensitisation

Based on the weight of evidence of the available data from animal, human (see ***Observation in humans*** section) and in silico studies, and data for structurally related polycyclic musks, which contain all the structural features of traseolide (NICNASa; NICNASc; NICNASd), it is not expected to be a skin sensitiser.

In an intradermal guinea pig test with limited information available, male guinea pigs (3–6; strain not specified) were administered a 5 % solution of the of the chemical in water intradermally for 7 days. This was followed by a challenge with 2.5 % of the chemical in vaseline. No indications of skin sensitisation were reported (REACH).

The chemical was reported to be negative for skin sensitisation in several guinea pig tests (Api et al., 2017). No further details are available.

No reactions were observed in a guinea pig patch test conducted according to the Landsteiner/Draize method with a 0.25 % suspension of the traseolide in 0.85 % saline (Opdyke, 1983).

The (Q)SAR modelling for skin sensitisation using the OECD QSAR Toolbox version 4.2 indicated that there were no alerts for skin sensitisation for either the chemical or its metabolites (by skin metabolism and autoxidation).

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.0 (Lhasa Limited) was utilised to estimate the skin sensitisation potential of the chemical . The chemical did not match any structural alerts or examples for skin sensitisation or contain any unclassified or misclassified features. Therefore, the chemical was predicted to be a non-sensitiser.

Observation in humans

The chemical produced no reactions in maximisation tests in 28 human volunteers using 5 % of traseolide in petrolatum (Opdyke, 1983).

In a human maximisation study traseolide showed no sensitisation reactions at 3450 µg/cm^2 (Api et al., 2017).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

Based on the limited information available traseolide is unlikely to cause serious damage to human health from repeated dermal exposure. The effects observed were of low severity or reversible. Skin irritation from repeated dermal applications is likely to limit the exposure to high dermal doses of the chemical.

In a 14-week dermal toxicity study, female albino rats (15/dose) received topical applications of traseolide at 0, 1, 10 or 100 mg/kg bw/day. An additional group of 5 rats were maintained treatment free for a period of 6 weeks from the control and high dose treatment groups. After 8 days of treatment, the dose was reduced from 100 mg/kg bw/day to 10 mg/kg bw/day due severe erythema and inflammation at the application site. A no observed adverse effect level (NOAEL) of 1 mg/kg bw/day was reported based on inflamed skin, decreased body weight and food intake, alterations in haematology, urinalysis and clinical chemistry parameters. Alterations in liver histopathology were observed in high dose rats; however, those were not observed in the recovery group (Api et al., 2017). The overt neurotoxicity associated with another polycyclic musk, versalide (NICNASe), was not reported for traseolide. No further details are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence of the available data from vitro and in silico studies, and data for structurally related polycyclic musks, which contain all the structural features of traseolide (NICNASa; NICNASc; NICNASd), it is not expected to be mutagenic (REACH).

In vitro

Traseolide was negative in point mutation studies in *S. typhimurium* strains TA97, TA98 TA100, TA1535, 1537 and the *E. coli* WP2 uvrA strain at concentrations up to 5000 µg/plate, with and without metabolic activation.

In silico

The (Q)SAR modelling for genotoxicity using the OECD QSAR Toolbox version 4.2 indicated that there were no alerts for genotoxicity for either the chemical or its metabolites (by skin metabolism and autoxidation).

The knowledge based expert system DEREK Nexus version 6.0.0 (Lhasa Limited) was utilised to estimate the mutagenic potential of the chemical. The chemical did not match any structural alerts or examples for bacterial in vitro mutagenicity or

contain any unclassified or misclassified features. Therefore, the chemical was predicted to be inactive in the bacterial in vitro (Ames) mutagenicity test.

In the Danish (Q)SAR database (Technical University of Denmark), the chemical was predicted to be negative for Chromosome Aberrations in Chinese hamster lung (CHL) cells, mutations in HGPRT locus in Chinese hamster ovary (CHO) cells and sex-linked recessive lethal (SLRL) test in *Drosophila melongaster* using a battery approach combining results from CASE Ultra, Leadscope and SciQSAR. The applicability domain of the model was satisfied, indicating that the performance statistics of the data in the model were applicable to the chemical.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

No critical health effects associated with the chemical have been established.

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that could contain the chemical, the main route of public exposure is expected to be through the skin, inhaled from products applied as aerosols, and potential oral exposure from lip and oral hygiene products.

The available data do not indicate any hazards associated with exposure to the chemical. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, dermal, oral 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 available data for the critical health effects, the risk to workers from this chemical is not considered to be unreasonable. Information in this report can be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls. The chemical currently has no hazard classification for worker health and safety, which is considered appropriate based on the available data.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

No specific controls are required.

Work Health and Safety

The chemical is not recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). This does not consider classification of physical hazards and environmental hazards.

Advice for industry

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical is prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the Preparation of safety data sheets for hazardous chemicals—Code of practice and Labelling of workplace hazardous chemicals—Code of practice, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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