Ethanone, 1-[6-(1,1-dimethylethyl)-2,3-dihydro-1,1-dimethyl-1H-inden-4-yl]-: Human health tier II assessment

26 October 2018

CAS Number: 13171-00-1

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.

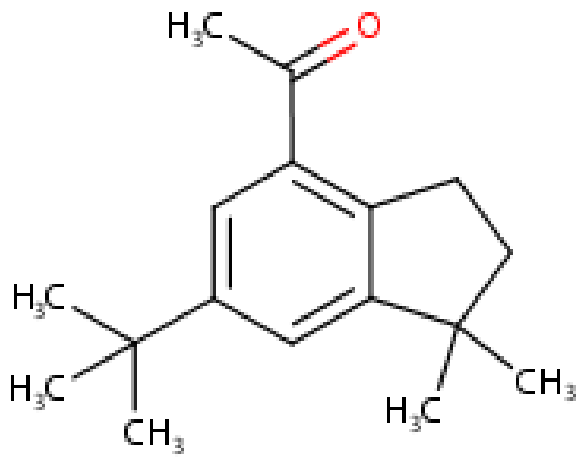
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	ketone, 6-tert-butyl-1,1-dimethyl-4-indanyl methyl acetyl tert-butyl dimethylindan celestolide 6-tert-butyl-1,1-dimethylindan-4-yl methyl ketone
Structural Formula	
Molecular Formula	C17H24O
Molecular Weight (g/mol)	244.38
Appearance and Odour (where available)	white solid with musk odour
SMILES	C(C)(=O)c1c2c(C(C)(C)CC2)cc(C(C)(C)C)c1

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; US Environmental Protection Agency (EPA) Chemical and Product Categories (CPCat); the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary and Cosmetic Ingredients; Government of Canada; and Cosmetic Ingredients and Substances (CosIng) database.

The chemical has reported cosmetic uses as a fragrance ingredient in perfumes and personal care products. The chemical is listed on the IFRA transparency list of fragrance materials (IFRA, 2017).

The chemical has reported domestic uses in:

- washing and cleaning products;
- polishes and waxes; and
- air care products.

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

No toxicokinetic data are available for the chemical. In general, aromatic ketones are converted to their corresponding alcohols in vivo. The more polar alcohol is then excreted in the urine as glucuronic acid conjugates (Adams et al., 2007).

Acute Toxicity

Oral

The chemical is expected to have low acute toxicity via the oral route. The reported median lethal doses (LD50) are >2000 mg/kg bw.

In an acute toxicity study similar to the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 401, rats (10/sex/dose) were orally treated (gavage) with a single dose of 5000 mg/kg bw of the chemical. Four mortalities were observed during the first seven days of observation. Clinical signs of toxicity included enteritis and pneumonia (REACH).

An LD50 in rat of 3690 mg/kg bw was reported, but no study details are available (Adams et al., 2007).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is not considered a skin irritant based on in vitro, in vivo and human studies (see ***Observation in humans***).

In the in vitro study conducted according to OECD TG439 (in vitro skin irritation: reconstructed human epidermis test method), the chemical was applied on reconstructed human epidermis for 15 min. There was no reduction in tissue viability. Therefore, the chemical is not considered a skin irritant (REACH).

The chemical did not cause irritation when applied at full strength to intact or abraded rabbit skin for 24 hr under occlusion (RIFM, 1976). No further details are available.

Eye Irritation

The chemical is not irritating to eyes according to an OECD TG 438 study.

In an ex vivo study in isolated chicken eyes according to OECD TG 438, the chemical (30 mg) was applied to 3 eyes for 10 seconds. The positive (30 µL sodium hydroxide) and negative control (30 µL saline) were applied the same way. The chemical and the negative control did not cause any corneal effects at examination 0, 30, 75, 120, 180, and 240 minutes after treatment. The positive control caused severe corneal effects (REACH).

Observation in humans

The chemical was not irritating to skin when tested at 4 % in petrolatum in a 48-hr closed-patch test on human subjects (RIFM, 1976). No further study details are available.

Sensitisation

Skin Sensitisation

The chemical was negative for skin sensitisation in a local lymph node assay (LLNA) and in human volunteers. It did not display any structural alerts for skin sensitisation using two in silico tools (see ***(Q)SAR predictions***). In the in vitro adverse-outcome pathway (AOP) for skin sensitisation the chemical was negative for 2 out of 3 events. Importantly, the chemical was negative for the key initiating event 1 (protein binding). This was supported by the in silico data. Therefore, based on the weight of evidence from in silico, in vitro, in vivo and human studies (see ***Observation in humans***) the chemical is not considered to be a skin sensitiser.

In an LLNA performed in accordance with OECD TG 429 female CBA/J mice (5/dose) received topical applications of 5.0, 10 and 25 % (w/w) of the chemical in acetone/olive oil on three consecutive days. The highest test concentration of 25 % was the maximum attainable concentration in acetone/olive oil. The reported stimulation indices (SI) were 1.65, 1.55 and 2.37 for concentrations 5.0, 10 and 25 %, respectively. Because all SI values were below 3 the chemical was considered a non-sensitiser (REACH).

Three in vitro studies were undertaken. Each of these guideline studies represents a key event of the AOP for skin sensitisation including: protein binding to form a hapten (OECD TG 442C); induction of antioxidant genes in keratinocytes (skin cells) (OECD TG 442D); and activation of a monocytes (immune cells) (OECD TG 442E).

In an in vitro study performed in accordance with OECD TG 442C (in chemico skin sensitisation: direct peptide reactivity assay (DPRA)), the chemical was dissolved in acetonitrile and mixed with 0.5 mM cysteine- and lysine-containing peptides. The final concentration of the chemical was 5 mM and 25 mM for cysteine and lysine, respectively. After 24 h there was no change in peptide depletion, indicating that the chemical is not likely to form allergy-inducing haptens by binding to cysteine or lysine residues in proteins. Therefore, the chemical was considered negative in the assay (REACH). This finding is consistent with the in silico data.

In an in vitro study performed in accordance with OECD TG 442D (in vitro skin sensitisation: ARE-Nrf2 luciferase test method), the activation of the antioxidant response element (ARE)-dependent pathway was assessed by measuring luminescence induction. A >1.5-fold induction (compared to control) of luciferase activity was detected in 2 out of 3 assays (cell viability of >70 %). The induction was dose-dependent with activities (I_{max}) of 1.70 and 1.52 at the estimated concentrations of 23 µM and 40.1, respectively. Test substances that induce a > 1.5-fold response at concentrations <1000 µM without inducing cytotoxicity are predicted to have sensitisation potential. Therefore, the chemical was considered positive in the assay (REACH).

In an in vitro study performed in accordance with OECD TG 442E (human cell line activation test (h-CLAT)), the activation of the monocytic cell line (THP-1) was quantified by measuring increased expression of the cell surface markers CD86 and CD54 using fluorescent antibodies. The cells were treated with 21.8, 26.2, 31.4, 37.7, 45.2, 54.2, 65.1 and 78.1 µg/mL of the chemical in cell culture media for 24 h. The relative induction of fluorescence intensity (RFI) (corresponding to CD86 and CD54 expression) was less than 150 % and 200 %, respectively. Only chemicals that induce an RFI signal of 150 % or greater of CD86 or 200 % or greater of CD54 are considered positive for skin sensitisation. Based on these results the chemical is

considered negative. However, these negative results should be interpreted with caution since chemicals with a log Kow greater than 3.5, such as celestolide (log Kow 5.7) may produce false negative results (REACH).

These three in vitro assays each represent a step in the AOP for skin sensitisation beginning with the molecular initiating event (MIE) of protein binding. As both the in chemico assay and in silico predictions indicate no protein binding potential for the chemical, it is considered that these tests do not indicate sensitising potential.

(Q)SAR predictions

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.0 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 contained any unclassified or misclassified features. Therefore, the chemical was predicted to be a non-sensitiser.

The chemical did not generate any structural alerts for skin sensitisation for the parent chemical or metabolites of the chemical (OECD Toolbox).

Observation in humans

In a maximisation test in 25 volunteers, 4 % of the chemical in petrolatum produced no sensitisation reactions (RIFM, 1976). No further information is available.

Repeated Dose Toxicity

Oral

No data are available.

Dermal

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

In a non-guideline 26-week dermal toxicity study in rats, no treatment related changes were reported at doses of 50, 100 and 200 mg/kg bw/day of the chemical. The no observed adverse effect level (NOAEL) was considered to be equal to or greater than 200 mg/kg bw/day (REACH). No further information is available.

In a sub-chronic (13 weeks) dermal toxicity study (similar to OECD TG 411), female albino rats were treated with the chemical at 1, 10 and 100 mg/kg bw/day. The reported NOAEL was 100 mg/kg bw/day (REACH). No further information is available.

Inhalation

No data are available.

Genotoxicity

In vitro

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

The chemical was negative in point mutation studies (REACH):

- in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 at concentrations up to 5000 µg/plate, with and without metabolic activation; and
- in *Escherichia coli* WP2 uvr A at concentrations up to 5000 µg/plate, with and without metabolic activation.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

No data are available.

Other Health Effects

Endocrine Disruption

In vitro studies suggest that the chemical has weak endocrine activity by binding to steroid hormone receptors. These activities indicate possible mechanisms for causation of endocrine related adverse effects. At this stage there is no evidence of these weak endocrine activities causing adverse effects in animals or humans.

The chemical demonstrated evidence of weak agonism towards the oestrogen receptor (ER)-alpha, in an in vitro assay using Chinese hamster ovary (CHO) cells stably transfected with the ER-alpha. The chemical was at least 10 000 times less potent than the positive control (endogenous ligand 17beta-estradiol). No agonistic effects were observed on the androgen receptor (AR) or the thyroid receptor (TR). The chemical demonstrated weak antagonism towards the androgen receptor with a concentration that inhibits 50 % of the activity (IC50) of 9.8 µM in the AR-EcoScreen in CHO cells. No antagonistic effects were observed for ER or TR (Mori et al., 2007).

In another study the chemical demonstrated very weak antagonism towards the progesterone receptor (PR) using human osteosarcoma (U2-OS) cells stably transfected with PR (IC50, 4.7 µM) and the AR (IC50, 11 µM). The chemical did not display any activity related to the ER-alpha or ER-beta in human embryonic kidney (HEK-293) cells stably expressing the ER-alpha or ER-beta (Schreurs et al., 2004).

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 chemicals, 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. The chemical has been shown to have weak endocrine activity. There is no available evidence that these weak endocrine effects could lead to adverse effects downstream. However, the reproductive toxicity of the chemical in animals systems has not been characterised. Further information is required to evaluate the hazard potential and risk to human health.

Should additional information associated with this weak endocrine activity become available, further assessment of the chemical may be required.

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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the lack 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; this 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.

The chemical has been shown to have weak endocrine activity. However, the available data do not demonstrate the potential of the chemical to cause adverse effects via this endocrine activity. NICNAS will continue to monitor the availability of high quality data emerging on the chemical and determine if further assessment may be required.

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

Obligations under workplace health and safety legislation

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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