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

08 March 2019

CAS Number: 15323-35-0

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.

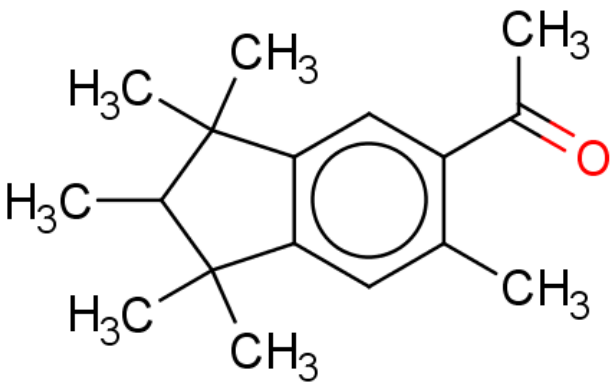
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	5-acetyl-1,1,2,3,3,6-hexamethylindan phantolide acetyl hexamethyl indan
Structural Formula	
Molecular Formula	C17H24O
Molecular Weight (g/mol)	244.38
Appearance and Odour (where available)	off-white crystals or solid with strong sweet fruity musk odour
SMILES	C1(C)(C)c2c(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); the US Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary and Cosmetic Ingredients; Cosmetic Ingredients and Substances (CosIng).

The chemical has reported cosmetic use 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 is also listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011), indicating its use in one cosmetic product.

The chemical has reported domestic uses in:

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

The chemical is used in smaller volumes than some other polycyclic musks, such as galaxolide and tonalide (HERA, 2004; Mogensen et al., 2004). 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

Using the chemical in cosmetics in the European Union is subject to the restrictions described in EU Regulation Annex III. This chemical may be used in cosmetics and personal care products at a maximum concentration of 2 % (CosIng).

Restrictions have been recommended by IFRA on the use of the chemical in finished products at concentrations of maximum 2 % in leave-on products (IFRA, 2015).

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 structure and 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

The chemical is expected to have moderate acute toxicity via the oral route and warrant hazard classification (see ***Recommendation*** section). The reported median lethal doses (LD50) were in the range of 271–797 mg/kg bw in rats.

In an acute toxicity study conducted similarly to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, Wistar rats (5/sex/dose) were orally treated (gavage) with single doses of 700, 840, 1008, 1209 or 1451 mg/kg bw of phantolide in isopropyl myristate (w/v) and observed for 14 days. Mortalities occurred at all doses. Clinical signs of toxicity included sluggishness; piloerection; haematuria; encrustations around eyes and nostrils; and signs of emaciation. The reported LD50 was 797 mg/kg bw (REACH).

In another acute toxicity study conducted similarly to OECD TG 401, 5 female Sprague Dawley (SD) rats received single doses of 100, 215 or 464 mg/kg bw of phantolide and observed for 7 days. The reported LD50 was 271 mg/kg bw (REACH).

An LD50 of 1700 mg/kg bw was reported from a non-guideline study in 10 mice receiving single doses of phantolide up to 5000 mg/kg bw (REACH).

Dermal

Based on the available data the chemical is expected to have low acute toxicity via the dermal route. The reported LD50 value is >10000 mg/kg bw.

In a dermal acute toxicity study conducted similarly to OECD TG 402, female SD rats (5/dose) were treated with a single application of 464, 1000, 2150, 4640 or 10000 mg/kg bw of phantolide and observed for 7 days. The LD50 was >10000 mg/kg bw (REACH).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available animal and human data (see ***Observation in humans*** section) the chemical is unlikely to be a skin irritant. Animal studies indicate that the chemical may be irritating after irradiation with ultraviolet (UV) light; however, these effects have not been reproduced in humans (see ***Observation in humans*** section).

Several in vivo non-guideline photoirritation studies have been conducted with phantolide. In five guinea pig photoirritation studies, dermal reactions were observed at concentrations between 5–50 % of phantolide in ethanol up to 72 h after irradiation. Non-irradiated control sites (chemical only) showed minimal or no erythema. In rabbits, positive photoirritation reactions were reported at concentrations between 1–20 % of phantolide in ethanol. Non-irradiated control sites were negative for skin irritation (IFRA, 2015; REACH).

Eye Irritation

The chemical may be slightly irritating to eyes. The effects are not sufficient to warrant hazard classification.

In an eye irritation study conducted similarly to OECD TG 405, 0.1 g of the chemical was applied to one eye of 3 male New Zealand White (NZW) rabbits while the other eye served as the control. The irritation scores for the individual rabbits at the 3 different time-points (24, 48 and 72 h) were combined and averaged. The average irritation scores were 0 for corneal opacity; 0 for iris irritation; 1 for chemosis and 1 for conjunctival redness. After 7 days, slight conjunctival redness was observed in two rabbits (REACH).

Observation in humans

In a photo irritation study, test patches with 0.2 mL of as solution of phantolide (10 % in 3:1 ethanol and diethyl phthalate) was applied to each forearm of 10 human subjects (2 male and 8 female). After 24 h, the patch was removed followed by ultraviolet A (UVA) irradiation of one of the forearms. Observations were made at 24, 48 and 72 h after patch removal. No reactions were observed on the irradiated or non-irradiated sites. (IFRA, 2015; REACH).

In another photo irritation study, no dermal reactions were observed in subjects exposed to 10 % of phantolide in 3:1 ethanol diethyl phthalate followed by UVA or ultraviolet B (UVB) irradiation (IFRA, 2015).

Sensitisation

Skin Sensitisation

The chemical was negative in the in vitro assays for the first two key events (KE) in the adverse outcome pathway (AOP) for skin sensitisation. 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, and human studies (see ***Observation in humans*** section) the chemical is unlikely to be a skin sensitiser.

Two 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) and induction of antioxidant genes in keratinocytes (skin cells) (OECD TG 442D).

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 cysteine- and lysine-containing peptides using defined ratios

of peptide to test item (1:10 cysteine peptide, 1:50 lysine peptide). The chemical was reported as negative for peptide depletion, indicating that the chemical is not likely to have protein binding ability (REACH). This finding is consistent with in silico data (see ***In silico data*** section) .

In an in vitro study performed in accordance with OECD TG 442D [in vitro skin sensitisation: antioxidant response element (ARE)-Nrf2 luciferase test method], the activation of the ARE-dependent pathway was assessed by measuring luminescence induction. The activities (Imax) of 1.26 and 1.4 were observed at the estimated concentrations of 1.95 µM and 0.98 µM of the chemical, respectively. The luciferase activity induction (compared to control) was below 1.5 in the two assays (cell viability of >90 %), indicating the test substance as negative for the second KE in the AOP for skin sensitisation (REACH).

In silico data

The (quantitative) structure activity relationship [(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 (skin metabolism and autoxidation).

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 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 25 human volunteers at 4 % phantolide in petrolatum (REACH).

Repeated Dose Toxicity

Oral

Based on the limited available data, the chemical is unlikely to cause serious damage to health from repeated oral exposure due to the low severity of the reported effects.

In an oral study conducted according to OECD TG 407, Wistar rats (5/sex/dose) received daily doses of the chemical in the diet at nominal doses of 0, 5, 15 or 50 mg/kg bw/day for 4 weeks. Clinical signs of toxicity included alopecia (males and females) hunched posture, piloerection and emaciation (females) in the highest dose group. The overt neurotoxicity associated with another polycyclic musk versalide (NICNASc) was not reported for phantolide. Increased salivation was observed in all dose groups in the dose-dependent manner. At the end of the study body weights were reduced in high-dose rats. In females from the 15 mg/kg bw/day group body weights and food consumption were reduced. Relative liver and kidney weights were increased in males and females of the highest dose group. At this dose, slight increases in liver enzymes in females and decreases in protein and calcium levels in males were also noted. The findings were associated with liver discolouration and moderate centrilobular hypertrophy (males and females) as well as increased deposition of iron positive pigment in Kupffer cells and an increase in hepatocyte mitoses in females. Females receiving the high dose had discoloured kidneys. Mild haematological effects were observed in both sexes at the highest dose and in females at 15 mg/kg bw/day. A no observed adverse effect level (NOAEL) of 5 mg/kg bw/day was reported based on reduced body weight, and mild haematological effects in females at 15 mg/kg bw/day and in males and females at 50 mg/kg bw/day (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available in vitro data the chemical is not expected to be mutagenic (REACH).

The chemical was negative in:

- point mutation studies in *Salmonella typhimurium* strains TA97, TA98 TA100, TA1535, 1537 and the *Escherichia coli* WP2 uvrA strain at concentrations up to 5000 µg/plate, with and without metabolic activation;
- a micronucleus tests in human peripheral lymphocytes at concentrations up to 205 µM (lymphocytes) with and without metabolic activation and human hepatoma cells (metabolically competent) at concentrations up to 409 µM for 48 h; and
- in an *E. coli* PQ37 genotoxicity assay (SOS chromotest) at concentrations up to 50 µg/mL with and without metabolic activation.

Equivocal results were obtained in a chromosome aberration assay in Chinese hamster lung (CHL) cells at concentrations up to 42 µg/mL for 24 and 48 h without metabolic activation, and at concentrations up to 33 µg/mL for 3 h with metabolic activation. However, the increase was not dose related and in a second experiment the chemical did not induce chromosome aberrations at any dose.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is acute toxicity from oral exposure.

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 chemical is expected to have lower use than some other polycyclic musks (see ***Use*** section) and concentrations of the chemical in cosmetic and domestic products are expected to be low due to international restrictions (see ***International Restrictions*** section).

Although the public could be exposed to the chemical through potential cosmetic and domestic uses, given the low hazard of the chemical, and expected low concentrations in cosmetic and personal care products the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, oral 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 health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see ***Recommendation*** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

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

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from oral exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- minimising manual processes and work tasks through automating processes;

- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the Managing risks of hazardous chemicals in the workplace—Code of practice available on the Safe Work Australia website.

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.

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 chemicals are 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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