4H-Inden-4-one, 1,2,3,5,6,7-hexahydro-1,1,2,3,3-pentamethyl-: Human health tier II assessment

08 March 2019

CAS Number: 33704-61-9

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.

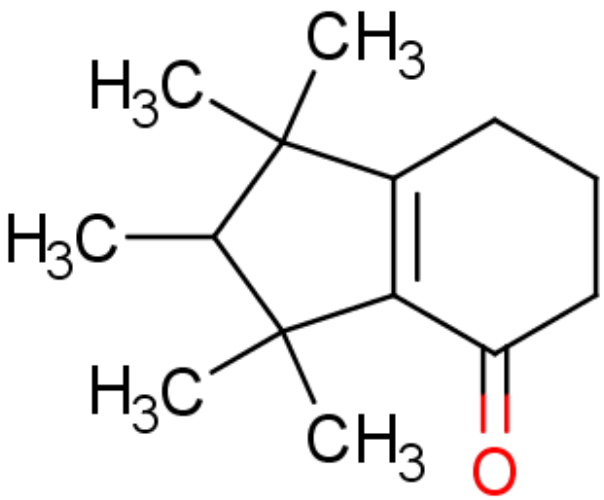
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4(5H)-indanone, 6,7-dihydro-1,1,2,3,3-pentamethyl cashmeran 6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone DPMI musk indanone
Structural Formula	
Molecular Formula	C14H22O
Molecular Weight (g/mol)	206.33
Appearance and Odour (where available)	colorless to pale yellow semi-solid to solid with diffusive, spicy, musk-like odour
SMILES	C1(=O)C2C(C)(C)C(C)C(C)(C)C=2CCC1

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) dossier; Substances and Preparations in the Nordic countries (SPIN) database; United States (US) Department of Health National Toxicology Program (NTP); US Environmental Protection Agency (EPA) Chemical and Product Categories (CPCat); US Household Product database (HPD); and EU Cosmetic Ingredients and Substances (CosIng) database.

The chemical has reported cosmetic uses as a fragrance ingredient in perfumes and personal care products. The chemical (6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone) is listed on the International Fragrance Association (IFRA) transparency list of fragrance materials (IFRA, 2017).

The chemical has reported cosmetic use in deodorants at concentrations between 0.1–1 % (HSDB).

The chemical has reported domestic uses in odour and masking agents including air fresheners at concentrations between 0.1–1 % (HPD).

Restrictions

Australian

No known restrictions have been identified.

International

Restrictions have been recommended by IFRA on the use of the chemical in finished products at concentrations of 0.34–8.7 % depending on the product category (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

Acute Toxicity

Oral

The chemical is expected to have low acute toxicity via the oral route. The reported median lethal dose (LD50) in rats is 2901 mg/kg bw.

In an acute toxicity study similar to the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 401, Sprague Dawley (SD) rats (10/sex/dose) were orally treated (gavage) with a single dose of the chemical at 2000, 3200, 4000 or 5000 mg/kg bw. Mortalities were observed at all doses. Clinical signs of toxicity included decreased activity, diarrhoea, salivation, lacrimation, ptosis, poor grooming, piloerection, changes in muscle tone, abnormal stance and gait, dyspnoea, tremors, convulsions, red discoloration, writhing and prostration. Haemorrhagic lungs, discoloured and fluid-filled intestines, distended stomachs and multiple lesions in the stomachs were observed upon necropsy. The reported LD50 was 2901 mg/kg bw (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the in vitro data, the chemical is considered a skin irritant, warranting hazard classification (see ***Recommendation*** section).

In an in vitro study conducted according to OECD TG439 (in vitro skin irritation: reconstructed human epidermis test method), the chemical was applied to reconstructed human epidermis for 15 min. The mean tissue viability was 10.8 % compared to control. Substances that reduce viability by more than 50 % are considered skin irritants. Therefore, the chemical is considered a skin irritant (REACH).

Eye Irritation

The chemical may be moderately irritating to eyes. The information available is not sufficient for hazard classification.

In an ex vivo study in isolated chicken eyes (ICE) according to OECD TG 438, the chemical (30 µL) 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

caused moderate swelling of the cornea (20%; ICE class III), moderate to severe corneal opacity (2.2; ICE class III) and moderate or moderate to severe fluorescein retention (2.3; ICE class III). These results indicate that the chemical does not cause severe eye damage (REACH). However, the test does not measure the eye irritation potential of a chemical, where it does not reach the threshold for severe eye damage.

Sensitisation

Skin Sensitisation

Based on the weight of evidence from human, animal and in silico 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 25, 50 or 100 % (w/w) of the chemical in acetone/olive oil on three consecutive days. The reported stimulation indices (SI) were 2.69, 3.66 and 3.52 for concentrations 25, 50 and 100 %, respectively. The reported concentration producing a three-fold increase in lymphocyte proliferation (EC3) was 33 %, indicating weak sensitisation potential (REACH).

(Q)SAR predictions

The (Q)SAR modelling for skin sensitisation using the OECD QSAR Toolbox (version 4.2) indicated alerts for skin sensitisation for the chemical and one of its metabolites (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 a non-sensitiser.

Chemtunes (version 1.2) predicted the chemical to be a weak skin sensitiser. The prediction was within the applicability domain of the model.

Observation in humans

In a human repeated insult patch test (HRIPT) 53 volunteers were treated with the chemical at 4 % in Alcohol SD 39C on the upper back under occlusion. The treatment was repeated 9 times during the induction period. After 10–21 days, challenge patches were applied on untreated test sites and scored after 24 and 48 h. No skin reactions were observed in any of the volunteers (REACH).

In an HRIPT conducted according to a modified Shelanski-Shelanski procedure human patch test method, 120 human volunteers were treated with the chemical at 10 % (w/w) in ethanol:diethylphtalate) (EtOH:DEP) (1:3) on the upper back under occlusion for 24 h. The treatment was repeated 9 times during the induction period. After 2 weeks, challenge patches were applied on untreated test sites for 24 h. No skin reactions were observed in any of the volunteers (REACH).

Repeated 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, SD rats (10/sex/dose) were administered the chemical (gavage) at 10, 50, 125 or 250 mg/kg bw/day for 90 days. After the treatment period, 5 females and 5 males from the control and high dose groups were maintained without treatment for 4 weeks (recovery group). No treatment-related mortality occurred during the study. Clinical signs included: increased salivation; ungroomed coat; urine stained fur; respiratory crackles; and pigmented

secretion from the nose. All effects were reversible in the high-dose recovery group after cessation of dosing. Absolute body weights were reduced from day 28 in males receiving 125 and 250 mg/kg bw/day. The reduced body weight was not completely reversible during the treatment free period in recovery group males. Food intake was not affected by the chemical (US EPA, 2009; REACH).

Increased kidney weights and changes in urinalysis parameters including decreases in urine pH, and increased urinary ketones, were observed in almost all dose groups except at 10 mg/kg bw/day. High-dose males had increases in urinary nitrates and orange coloured urine. Treatment-related mild to moderate changes in kidney histopathology consistent with chronic progressive nephropathy (CPN) were reported in both sexes of the 50, 125 and 250 mg/kg bw/day dose groups. CPN is a common renal disorder in rats but does not occur in humans (Hard et al., 2012) and the effects were reversible during the treatment free period in the recovery group (US EPA, 2009; REACH).

Relative and absolute (females only) liver weights were increased at the three highest doses. Reversible increases in bilirubin and cholesterol were observed in both sexes in the highest dose groups. Haematology parameters were not affected by the treatment. A no-observed-adverse-effect-level (NOAEL) of 10 mg/kg bw/day was reported based on kidney effects and liver weight changes at 50 mg/kg bw/day (US EPA, 2009; REACH).

In a reproduction/developmental toxicity screening test (see ***Reproductive and Devlopmental*** toxicity section), dose-related increases in liver and kidney weights were observed in males at doses of 40 and 125 mg/kg bw/day. Neither effect was accompanied by any significant macroscopic or microscopic changes (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.

The chemical was negative in the following studies (REACH):

- gene mutation assays in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 uvr A at concentrations up to 78.1 µg/plate without metabolic activation and 313 µg/plate with metabolic activation;
- a chromosome aberration assay in human peripheral lymphocytes at concentrations up to 242.5 µM for 72 h with and without metabolic activation;
- a chromosome aberration assay in the metabolically competent human hepatoma cell line Hep G2 at concentrations up to 485 µM for 2 h; and
- gene mutation study of the thymidine kinase (tk) locus in L5178Y mouse lymphoma cells treated with the chemical up to 100 µg/mL without metabolic activation and up to 155 µg/mL with metabolic activation for 4 h.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to show specific reproductive or developmental toxicity.

In a reproduction/developmental toxicity screening test (OECD TG 421), Wistar rats (12/sex/dose) received the chemical via the diet at nominal doses of 10, 40 or 125 mg/kg bw/day for 30 (males) or up to 42 (females) days. Treatment continued from two weeks pre-mating up to four days of mating, 21–22 days of gestation and four days of lactation.

No statistically significant treatment-related effects were observed on any reproductive indices, except for an increase in pre-implantation loss and reduction in pups/litter in the highest dose group. However, the values for control and low dose groups were below the historical control range for post-implantation loss and above the historical control range for pups/litter. Therefore, the effects seen were not likely to be treatment related. Parental effects were only observed in males (see ***Repeated dose toxicity: Oral*** section).

The reported NOAEL for reproductive and developmental toxicity was 125 mg/kg bw/day (nominal dose) which corresponds to an actual dose of 115 mg/kg bw/day for males and 122 mg/kg bw/day for females (US EPA, 2009; REACH).

Other Health Effects

Neurotoxicity

In a repeated dose toxicity study in rats (see ***Repeated dose toxicity: Oral*** section), movement was increased in males and females at the highest dose (250 mg/kg bw/day) during week 11 of the study. No other treatment-related differences were observed in any of the functional observational battery (FOB) parameters during week 11. During week 17 of the study (recovery period), the movement was still increased in females of the highest dose group, while males were not affected. No other treatment-related differences were observed in the FOB parameters (REACH).

Endocrine Disruption

An in vitro study suggests that the chemical has weak endocrine activity by binding to the oestrogen receptor (ER), although at much lower potency than endogenously produced oestrogens. At this stage there is no evidence of the weak oestrogenic activity causing adverse effects in animals or humans.

The chemical demonstrated evidence of weak agonism towards the ER-alpha, in an in vitro assay using Chinese hamster ovary (CHO) cells stably transfected with the receptor. The chemical was at least 10 000 times less potent than the positive control (endogenous ligand 17beta-estradiol). The chemical did not modify activity of the human androgen or thyroid hormone receptors (Mori et al., 2007).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are local effects including skin irritation and skin sensitisation.

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 distribution of the chemical for fragrance purposes is expected to be controlled by members of IFRA. The restriction of the chemical under the IFRA Standard (see ***Restrictions*** section) is expected to sufficiently address the public risks associated with chemical exposure through the uses as fragrance (e.g. concentration limit in finished products between 0.34–8.7 %) (IFRA).

Occupational Risk Characterisation

During product formulation, dermal exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may 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 an unreasonable risk to workers unless adequate control measures to minimise dermal exposure are implemented. 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 HCIS (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.

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 about the chemical and determine if further assessment may be required.

Regulatory Control

Public Health

Provided the chemical is used as recommended no further controls are needed.

Matters to be taken into consideration include skin sensitisation effects of the chemical and the maximum concentrations recommended by IFRA (see ***Restrictions*** section).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonised 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]
Irritation / Corrosivity	Not Applicable	Causes skin irritation - Cat. 2 (H315)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (H317)

[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 consumers

Products containing the chemicals should be used according to label instructions.

Advice for industry

Control measures to minimise the risk from exposure to the chemical through dermal route 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 chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- 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 chemicals.

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 these chemicals has not been undertaken as part of this assessment.

References

Chemtunes, Molecular Networks GmbH, Nuremberg, Germany Accessed November 2018 at www.mn-am.com

CosIng. Cosmetic Ingredients and Substances. Accessed October 2018 at http://ec.europa.eu/growth/tools-databases/cosing/

DEREK Nexus:6.0 Lhasa Limited (2018) . Accessed November 2018 at https://www.lhasalimited.org/

Globally Harmonized System of Classification and Labelling of Chemicals (GHS) 2009. United Nations. 3rd edition. Accessed October 2018 at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Hard GC, Banton MI, Bretzlaff RS, Dekant W, Fowles JR, Mallett AK, McGregor DB, Roberts KM, Sielken Jr RL, Valdez-Flores C. and Cohen SM 2012. Consideration of rat chronic progressive nephropathy in regulatory evaluations for carcinogenicity. toxicological sciences, 132(2) pp.268-275.

International Fragrance Association (IFRA) 2015. The 48rd Ammendment of the IFRA Standard – 6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone (DPMI) Accessed November 2018 at http://www.ifraorg.org/en-us/standards

International Fragrance Association (IFRA) 2017 Transparency List. Accessed November 2018 at http://www.ifraorg.org/en/ingredients

Mori T, Iida M, Ishibash H, Kohra S, Takao Y, Takemasa T and Arizono K, 2007. Hormonal activity of polycyclic musks evaluated by reporter gene assay. Environmental sciences: an international journal of environmental physiology and toxicology, 14(4), pp.195-202.

Organization for Economic Cooperation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox Version 4.2

Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed November 2018 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). (CAS 33704-61-9). Accessed November 2018 at https://echa.europa.eu/search-for-chemicals

Safe Work Australia (SWA). Hazardous Chemicals Information System (HCIS). Accessed November 2018 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

Substances in Preparations in Nordic countries (SPIN) database. Accessed November 2018 at http://www.spin2000.net/spinmyphp/

The Poisons Standard October 2018. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 22. Accessed November 2018 at https://www.tga.gov.au/publication/poisons-standard-susmp

United States Environmental Protection Agency (US EPA) Chemical and Product Categories database (CPCat). Accessed November 2018 at https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

United States Environmental Protection Agency (US EPA) ChemView 2009. Accessed November 2018 at https://chemview.epa.gov/chemview

Last update 08 March 2019

Share this page