3-methyl-4-(1-methylethyl) phenol: Human health tier II assessment

25 November 2016

CAS Number: 3228-02-2

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.

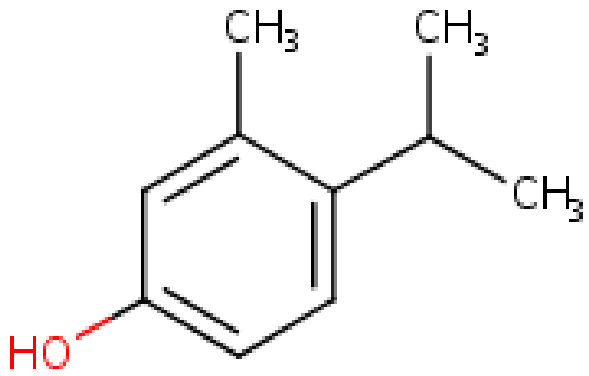
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	o-cymen-5-ol Biosol p-thymol 4-isopropyl-m-cresol 3-methyl-4-isopropylphenol
Structural Formula	
Molecular Formula	C10H14O
Molecular Weight (g/mol)	150.22
Appearance and Odour (where available)	Colourless and odourless crystalline solid
SMILES	c1(C)c(C(C)C)ccc(O)c1

Import, Manufacture and Use

Australian

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

International

The chemical has reported cosmetic use as a preservative. Information collected by the United States Food and Drug Administration (US FDA) from a voluntary cosmetic registration program indicated that the chemical is used as an ingredient in 55 cosmetic formulations at concentrations of ≤0.1 % (Cosmetic Ingredient Review (CIR), 1984).

The chemical is listed in the US Personal Care Products Council International Nomenclature of Cosmetics Ingredients (INCI) Dictionary as an ingredient in cosmetic products such as:

- aftershave lotions;
- bath preparations;
- hand and body cream;
- make up bases;

- mascara;
- cleansing products (cleansing lotions and eye makeup removers); and
- skin care products (moisturisers, night cream, paste masks).

The chemical has reported commercial use in the preparation of other phenolic compounds and in the stabilisation of resin blends (CIR, 1984).

The following non-industrial uses have been identified internationally:

- in oral care products to prevent periodontal diseases;
- as an insect repellent; and

as antimould and antimicrobial agents (CIR, 1984).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- ASEAN Cosmetic Directive Annex VI Part A - List of preservatives allowed for use in cosmetic products at a maximum authorised concentration of 0.1 %.
- European Union (EU) Cosmetic Directive 76/768/EEC Annex VI Part 1 List of preservatives allowed at a maximum authorised concentration of 0.1 %.
- EU Regulation(EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products - Annex V List of preservatives allowed in cosmetic products - Maximum concentration in ready for use preparation of 0.1 %.
- New Zealand Cosmetic Products Group Standard - Schedule 7: Preservatives cosmetic products may contain with restrictions - Table 1: List of preservatives allowed at a maximum authorised concentration of 0.1 %.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (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 has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in mice is >2000 mg/kg bw.

In an acute oral study similar to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 401, Slc:ddy mice (7/sex/dose) were administered a single dose of the chemical via gavage at 10 and 22 mL/kg bw (equivalent to 1000 and 2200 mg/kg bw, respectively). There was no mortality reported. No abnormalities were observed at necropsy. The LD50 was determined as >2200 mg/kg bw (REACH; CIR, 1984).

In another acute oral study similar to OECD TG 401, male mice (strain not specified) were administered a single dose of the chemical by intragastric injection at 2500 and 6280 mg/kg bw. The LD50 was reported as 6280 mg/kg bw. Sublethal effects including decrease in locomotor activity, piloerection, hind limb paralysis and tachypnoea (rapid breathing) were reported (REACH).

Dermal

The chemical has low acute toxicity following dermal exposure. The LD50 in rats is >2000 mg/kg bw. No mortality was observed. No abnormalities were reported at necropsy. Erythema and crust formation were reported at the treatment site.

In an acute dermal toxicity study compliant with Good Laboratory Practice (GLP) and conducted according to the OECD TG 402, the chemical (2000 mg/kg bw) was applied to the intact skin of Wistar rats (5/sex) and covered with a semi-occlusive patch for 24 hours, with observations up to 14 days. No mortality or systemic effects were reported. The LD50 was determined as > 2000 mg/kg bw (REACH).

Inhalation

The chemical has low acute toxicity in animals based on results from animal tests following inhalation exposure. The median lethal concentration (LC50) in rats is >1.41 mg/L (mean maximum attainable atmospheric concentration).

In an acute inhalation study compliant with GLP and conducted according to the OECD TG 403, Sprague Dawley (SD) rats (5/sex) were exposed by nose only inhalation to the chemical (as dust) at a concentration of 1.41 mg/L (nominal concentration of 77 mg/L) for 4 hours. No mortality was observed. No macroscopic abnormalities were reported at necropsy. Observed sub-lethal effects included increased respiratory rate, hunched posture, piloerection, and isolated cases of red/brown staining to the eyes and/or snout (REACH).

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate skin in animal studies. The effects were not sufficient to warrant hazard classification.

In a dermal irritation study compliant with GLP and conducted according to the OECD TG 404, the chemical (neat moistened with distilled water) was applied on the clipped skin of New Zealand White (NZW) rabbits (3 males) and covered in semi-occlusive patches for up to 4 hours, with observation periods of 1, 24, 48 and 72 hours after removal of patches. There was no evidence of skin irritation during the study (REACH).

In another study, 0.1 % and 1 % of the chemical in petrolatum was applied to the clipped skin of albino rabbits for 24 hours under a patch. The test sites were either abraded (4 animals) or intact (4 animals). No irritation was observed at either concentration at either intact or abraded skin (CIR, 1984).

Skin irritation was also studied in albino rabbits (8 animals) following exposure to 5 % of the chemical in polyethylene glycol (PEG) 400. The chemical was applied to either clipped intact (4 animals) or abraded skin (4 animals) on the back of each animal. The patches were removed after 24 hours. A "very low" degree of primary skin irritation was reported (CIR, 1984).

In three male albino guinea pigs, 10 % of the chemical in ethanol was applied on the clipped flank of each animal daily for three days. A "very low" degree of primary skin irritation was reported (CIR, 1984).

In an in vitro skin corrosion study compliant with GLP and conducted according to the OECD TG 439, EPISKIN from reconstructed human epidermis was treated with the chemical (moistened with 0.9 % w/v sodium chloride solution) in duplicate for 3, 60 and 340 minutes. The relative mean viabilities of the treated tissues were 119.2 %, 116.9 % and 183.7 % at 240, 60 and 3 minutes exposure, respectively. The chemical was not considered corrosive under these test conditions (REACH).

Eye Irritation

The chemical was reported to cause "serious eye damage" when tested according to the OECD TG 437. The reported findings on the in vitro eye irritation study were sufficient to warrant a hazard classification for the chemical as an eye irritant.

In an in vitro eye irritation study (bovine corneal opacity and permeability test method for identifying ocular corrosives and severe irritants) compliant to GLP and conducted in accordance with the OECD TG 437, the chemical was applied to the cornea at a concentration of 20% w/v in sodium chloride solution for 240 minutes. Negative and positive controls were tested concurrently. The opacity (measured as decreased light transmission through the cornea) and permeability (increased passage of sodium fluorescein dye through the cornea) were combined to give an in vitro irritancy score (IVIS). The IVIS for the chemical, negative controls and positive controls were 46.9, 2.3 and 95.3, respectively. The IVIS score for the cornea treated with the chemical was below the cut-off for classification of serious eye damage at > 55. However, in two of the three treated corneas sloughing was observed and considered severe resulting in lower opacity values (upper cloudy layers of the cornea have sloughed away revealing clearer layers underneath). It was reported that if the sloughing was not so severe in the two corneas, the overall IVIS would be predicted to be higher. In addition, all three treated corneas induced fluorescein permeability values greater than in positive control group. The chemical was determined to cause "serious eye damage" under these test conditions (REACH).

Observation in humans

In a human repeat insult patch test (HPIRT), patch tests containing petrolatum, 0.1 % chemical in petrolatum and 1 % chemical in petrolatum were applied to the forearm of 53 female volunteers. The patches were left for 24 hours and skin reactions were evaluated within 3 hours following removal of the patches. There was no skin irritation observed (CIR, 1984).

Sensitisation

Skin Sensitisation

The chemical was not found to induce dermal sensitisation when tested according to the OECD TG 429.

In a local lymph node assay (LLNA) compliant with GLP and conducted according to the OECD TG 429, the chemical was topically applied to CBA/Ca female mice (5 animals/dose) at concentrations of 10, 25 and 50 % w/w in dimethylformamide. The stimulation index (SI) values were reported to be 1.54, 0.87 and 2.64, respectively. An EC3 value (concentration of the chemical necessary to produce a threefold increase lymph node cell proliferation) could not be determined. The chemical was not classified as a skin sensitiser according to the conditions of the study (REACH).

Observation in humans

A maximisation test was conducted on 27 male volunteers. Prior to induction exposure, 5 % aqueous sodium lauryl sulfate (SLS) was applied to the forearm under occlusive patch for 24 hours. Following pre-treatment, induction patches containing Vaseline (vehicle control) , 1 % chemical in Vaseline, in a cream base (vehicle control), 1 % chemical in cream base, and petrolatum (negative control) were applied to each subject for 48 hours. After 10 to 14 days, occlusive application of 5 % aqueous SLS for 30 minutes was followed by challenge patches containing 0.1 % chemical applied to previously untreated sites for 48 hours. Challenge patches were also applied without SLS pre-treatment. On the SLS treated sites, several low grade irritation reactions were reported at 48 and 72 hours observations. No reactions were reported on treated sites without SLS treatment (CIR, 1984).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is expected to have low toxicity following repeated oral exposure.

In a combined oral repeated dose and reproductive toxicity study compliant with GLP and conducted according to the OECD TG 442, the chemical at doses of 1400, 4500 or 15000 ppm was administered in the diet to Crl:CD(SD) rats (10/sex/dose). Males were treated daily for two weeks prior to pairing and up to necropsy (minimum of five consecutive weeks). Females were treated daily for two weeks prior to pairing, throughout pairing, during gestation and until day 6 of lactation. The offspring (F1 generation) were sacrificed on day 7 of lactation. The achieved dose levels for males were 98, 289 and 1038 mg/kg bw/day prior to pairing. The achieved dose levels for females were 110, 320 and 1010 mg/kg bw/day prior to pairing; 104, 323 and 1048 mg/kg bw/day during gestation; and 206, 608 and 1888 mg/kg bw/day during lactation. At the highest dose, transient effects on body weight and food consumption attributed to the palatability of the feed were observed. Minor changes in haematological parameters were reported. Increased kidney and liver weights without histopathological changes were also reported. Increased incidence and severity of thymic involution (shrinking) were seen in all high dose females, which were indicative of a stress response secondary to reduced food intake. A no observed adverse effect level (NOAEL) of 15000 ppm (approximatley 1000 mg/kg bw/day) was determined (REACH).

In a non-guideline repeated dose toxicity study, the chemical at doses of 10, 100, 1000 and 2000 mg/kg bw/day was administered to rats (4-5 animals/dose; strain not specified) in the diet for 90 days. No mortality was reported. No gross and histopathological changes were observed. Body weights were decreased in a dose dependent manner during the first 30 days of feeding but recovered except for the highest dose group. At the highest dose, motor activity was decreased and drowsiness was observed during the first 15 days of feeding. The NOAEL was 1000 mg/kg bw/day (REACH).

In another non-guideline repeated dose toxicity study, mice (2/dose at 0, 10, 30 and 50 mg/kg bw/day and 3 animals at 80 mg/kg bw/day; sex and strain not specified) were fed diets containing the chemical for 30 days. There were no mortalities reported at doses 10 and 30 mg/kg bw/day. Decreases in body weight and mortalities were reported at 50 mg/kg bw/day. At the highest dose (80 mg/kg bw/day), all animals died. The NOAEL was 10 mg/kg bw/day (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available well-conducted in vitro genotoxicity studies, the chemical is not considered to be genotoxic. There are no available in vivo studies on the chemical.

In a reverse gene mutation assay conducted similar to OECD TG 471, *Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537, TA1538) and *Escherichia coli* strain (WP2*uvr*A) were exposed to the chemical at concentrations up to 800 µg/plate with and without S9. No significant increases in revertant colonies were reported for any of the bacterial strains at any dose level with or without S9 (REACH).

In an in vitro mammalian cell gene mutation assay compliant with GLP and conducted in accordance to OECD TG 476, mouse lymphoma L5178Y cells were exposed to the chemical at concentrations up to 1500 µg/mL for 3 hours without metabolic activation (S9) and up to 150 µg/mL for 24 hours (continuous exposure) without S9. Negative results were obtained with and without S9.

In an in vitro chromosome aberration assay compliant with GLP and conducted in accordance to OECD TG 473, cultured human lymphocytes were exposed to the chemical at concentrations up to 1502.2 µg/mL for 3 hours with and without S9, and 21-hour continuous treatment in the absence of S9. For a 3-hour treatment, the chemical did not cause a statistically significant increase in the number of chromosomal aberrations at any concentration in the presence and absence of S9. For a 21-hour continuous treatment, the chemical caused statistically significant increase in the number of chromosomal aberrations in the absence (50, 80 and 90 µg/mL) of S9. No statistically significant increases in polyploidy were observed. The toxicological significance of the observed increased in the choromosomal aberration without S9 was not clear (REACH).

No structural alert was identified for mutagenicity of the chemical in Derek software (Derek Nexus:4.1.0, Nexus 2.0.0). The chemical was predicted as "not mutagenic to bacteria in vitro" (REACH).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a repeated dose oral toxicity study compliant with GLP and conducted according to the OECD TG 442 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test), the chemical at concentrations of 1400, 4500 or 15000 ppm was administered in the diet to Crl:CD(SD) rats (10/sex/dose) (Refer to **Repeat Dose Toxicity** section). Males were treated daily for two weeks prior to pairing and up to necropsy (minimum of five consecutive weeks). Females were treated daily for two weeks prior to pairing, thoughout pairing, during gestation and until day 6 of lactation. The offspring (F1 generation) were not treated and euthanised on day 7 of lactation. For parental animals, statistically significant decreases in heart and ovary weights for females were reported at the highest dose. Decreased in thymus weight was also reported at 4500 ppm and above. The chemical did not affect the pre-coital interval, fertility, gestation length and gestation index. The number of implantations and mean litter size were lower at the highest dose group females compared with controls, but there was no subsequent effect on offspring survival. The parental NOAEL was determined as 15000 ppm (approximately 1000 mg/kg bw/day). The body weight gain was lower in offspring of parental animals dosed at 15000 ppm compared with control group. The low body weight gain of the offspring was attributed to low maternal body weight and food consumption, and maternal stress. The no observed effect level (NOEL) for the offspring (F1 generation) was determined as 15000 ppm (approximately 1000 mg/kg bw/day) (REACH).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is eye irritation.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used as a preservative in cosmetic products overseas, (CIR, 1984). The general public could be exposed through the skin or eye when using cosmetic products containing the chemical. The chemical is reported to be used overseas in cosmetic products at a maximum concentration of 0.1% (CIR, 1984). At this concentration, the chemical is not considered to be sufficiently high to cause corrosive or irritant effects. 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 ocular exposure may 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 local health effect, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise ocular 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 the Hazardous Substances Information System (HSIS) (Safe Work Australia) (refer to **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

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36)	Causes serious eye irritation - Cat. 2A (H319)

[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 chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from ocular 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:

- using closed systems or isolating operations;
- 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 chemical 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.

References

Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

Cosmetic Ingredient Review (CIR) 1984. Final report on the safety assessment of o-Cymen-5-ol. Journal of the American College of Toxicology, Volume 3, Number 3, 131-138.

Galleria Chemica. Accessed November 2016 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHd) Dossier. 3228-02-2. Accessed November 2016 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia. Hazardous Substances Information System (HSIS). Accessed November 2016 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2016. Accessed November 2016 at https://www.legislation.gov.au/Details/F2016L01638

United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed November 2016 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

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