Phenol, 2-methoxy-4-(2-propenyl)-: Human health tier II assessment

30 June 2020

CAS Number: 97-53-0

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.

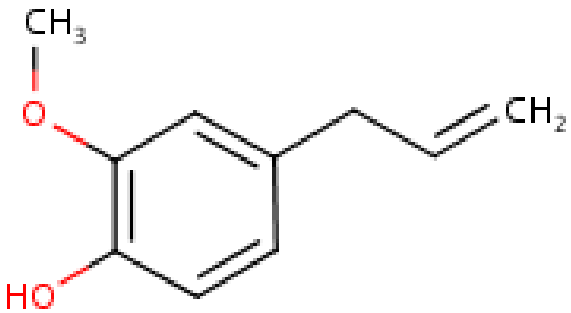
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	eugenol phenol, 4-allyl-2-methoxy 4-allylcatechol-2-methyl ether
Structural Formula	
Molecular Formula	C10H12O2
Molecular Weight (g/mol)	164.2028
Appearance and Odour (where available)	Colourless or pale yellow liquid with a warm-spicy odour
SMILES	c1(O)c(OC)cc(CC=C)cc1

Import, Manufacture and Use

Australian

The chemical has reported cosmetic uses including:

- in moisturisers; and
- in hand and body wash products.

The chemical has reported domestic use as a component of cleaning and polishing products. The chemical also has uses in rubbing compounds for marine applications.

The chemical has reported non-industrial uses including as:

- an active constituent in agricultural chemical products as approved by the Australian Pesticides and Veterinary Medicines Authority (APVMA) (Galleria); and
- a substance that may be used in listed medicines as approved by the Therapeutic Goods Administration (TGA) (Galleria).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier, Galleria Chemica (Galleria), the European Commission Cosmetic Ingredients and Substances (CosIng) database, the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary, the US Household Products database (US HPD), the Cosmetics to Optimise Safety (COSMOS) database, the International Fragrance Association (IFRA) transparency list (IFRA, 2011) and various international assessments (NTP, 1983; IARC, 1985; SCCNFP, 1999; Api et al., 2016):

The chemical has reported cosmetic uses, including as a:

- denaturant;
- perfuming agent; and
- toning agent.

The chemical has reported domestic uses, including in:

- air fresheners; and
- household cleaning products.

The chemical has reported commercial use in the manufacture of specially denatured alcohols.

The chemical has reported site-limited uses, including as:

- a chemical intermediate; and
- an antioxidant in inks.

The chemical has reported non-industrial uses, including:

- as a flavouring agent, food additive, and in food contact materials;
- in pharmaceuticals (e.g. analgesic);

- as components of dental products (e.g. disinfectant, dental cements, impression pastes, surgical pastes);
- as a pet cleaner; and
- as fungicide, insecticide, and pesticide.

Restrictions

Australian

The chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 5 and 6 (SUSMP, 2017).

Schedule 6:

'EUGENOL except:

(a) when included in Schedule 5;

(b) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 15 mL or less fitted with a restricted flow insert and compliant with the requirements of the Required Advisory Statements for Medicine Labels;

(c) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and a child-resistant closure and compliant with the requirements of the Required Advisory Statements for Medicine Labels;

(d) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 15 mL or less fitted with a restricted flow insert and labelled with the warnings: KEEP OUT OF REACH OF CHILDREN; and NOT TO BE TAKEN;

(e) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and a child-resistant closure and labelled with the warnings: KEEP OUT OF REACH OF CHILDREN; and NOT TO BE TAKEN; or

(f) in preparations containing 25 per cent or less of eugenol.'

Schedule 5:

‘EUGENOL for topical use in the mouth in a pack containing 5 mL or less of eugenol except in preparations containing 25 per cent or less of eugenol.'

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2017).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution’ (SUSMP, 2017).

International

The chemical is listed on the following (Galleria):

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: 'the presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products'; and

- Europe Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys - allergenic fragrances toys shall not contain. 'However, the presence of traces of these fragrances shall be allowed provided that such presence is technically unavoidable under good manufacturing practice and does not exceed 100 mg/kg'.

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

The chemical is also referred to as eugenol in this assessment. Eugenol is principally extracted from clove oil and is contained in various plants and derived oils (NTP, 1983; IARC, 1985; Api et al., 2016).

Toxicokinetics

Based on the available information, the chemical is rapidly absorbed in humans via the oral route, poorly absorbed in mice via the dermal route, widely distributed in organs of rats, metabolised to eugenol-glucuronide and sulfate, and rapidly eliminated in humans and rodents.

In a human study, healthy individuals (n=4/sex) were administered three capsules each containing 50 mg eugenol. Urine and blood samples were collected at various time points up to 24 hours and 120 minutes, respectively. Rapid absorption of the chemical was reported (rate of absorption not specified). The majority (approximately 95 %) of the applied dose was recovered in the urine within 24 hours wherein > 99 % consisted of phenolic conjugates (eugenol-glucuronide and sulfate) (REACH).

In an in vitro absorption study of human skin, approximately 18% of the dose (mean) of radiolabelled eugenol was found to be absorbed into the skin under unoccluded conditions for 72 hours, with approximately 4% of the dose remaining in the skin (Api et al., 2016).

Minimal amounts of the chemical were detected in blood samples of female Swiss mice exposed by inhalation to several fragrances, including eugenol, for one hour at unspecified doses (REACH). The chemical did not penetrate the skin of mice following dermal application. No other details were specified (IARC, 1985).

In an in vitro metabolism study, liver and lung microsomes from humans, Sprague Dawley (SD) rats, and ICR/CD-1 mice were incubated with the radiolabelled chemical at doses up to 250 µM. Results indicate that the allylic side chain was oxidised to form 1'-hydroxy-eugenol through phenoxy glucuronidation and that the clearance was similar in humans and mice (REACH). Another in vitro study in SD rat microsomes exposed to radiolabelled eugenol showed cytochrome P450 activation, in the presence of either NADPH or cumene hydroperoxide, to a minimum of three distinct gluthathione conjugates (REACH). In another in vitro

study in SD rat hepatocytes, the chemical was reported to be metabolised to form conjugates with glucuronic acid, sulfate, and glutathione (REACH).

In an excretion study, similar to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 417 (toxicokinetics), the radiolabelled chemical was administered by gavage to female Wistar rats (number not specified) at doses of 0.5, 5, 50, or 1000 mg/kg bw. The applied dose was mainly detected in the urine and faeces at rates of 75-80 and 10 %, respectively. The excreted products in the urine were conjugated eugenol (50-60 % of the applied dose), and the metabolites 3,4-dihydroxy-propylbenzene (1-15 % of the applied dose) and 3-methoxy-4-hydroxy-propylbenzene (1-3 % of the applied dose) (REACH).

In a pharmacokinetics study, male SD rats (n=6/dose) were dosed with eugenol intravenously (i.v.) at 0, 5, 10, 20, 40 or 60 mg/kg bw. The chemical was distributed to peripheral tissues and elimination was rapid in blood and plasma with half-life values of 7.05 and 12.6 minutes, respectively. Sulfate and glucuronide conjugated metabolites were observed in the urine (REACH).

Radiolabelled chemical applied intraperitoneally to male Wistar rats was widely distributed in organs. The recovered radioactivity from the tissues was mainly the unchanged chemical. After 24 hours, 1 % of the applied dose recovered was carbon dioxide (NTP, 1983).

The following information is also available (IARC, 1985):

- the metabolites observed from cultured epithelial cells derived from rat livers were 2,3-epoxyeugenol and 2,3-dihydroxy-2,3-dihydroeugenol;
- incubation in the presence of microsomes derived from the livers of female mice produced 2,3-epoxide;
- rat urinary metabolites detected were 3-piperidyl-1-(3-methoxy-4-hydroxyphenyl)-1-propanone and 3-pyrrolidinyl-1-(3-methoxy-4-hydroxyphenyl)-1-propanone; and
- glucuronidation reactions in liver slices incubated with different doses of eugenol were inhibited.

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The median lethal doses (LD50s) are >2000 mg/kg bw in rats, and between 1500 and 3000 mg/kg bw in mice.

Two separate studies equivalent or similar to OECD TG 423 (acute toxic class method) were conducted in Fischer 344 rats (5/sex/dose) and B6C3F1 mice (5/sex/dose). The rodents were administered a single dose of eugenol (purity is 99 %; vehicle 1 % solution of carboxymethylcellulose in saline) by gavage. The doses used ranged from 150 to 2000 mg/kg bw in rats and 150 to 3000 mg/kg bw in mice. One female rat died in the 2000 mg/kg bw dose. Mortalities in mice occurred at the 750 mg/kg bw (one male mouse) and 3000 mg/kg bw (two male and five female mice) doses. No clinical signs or other findings were reported in both studies (REACH).

Several other oral LD50 values were reported (IARC, 1995; RTECS) as follows:

- 1930 mg/kg bw in rats;
- 2680 mg/kg bw in rats;
- 2130 mg/kg bw in guinea pig; and
- 3000 mg/kg bw in mice.

Dermal

No data are available.

Inhalation

The chemical has low acute toxicity in animal tests following inhalation exposure. No mortalities were observed and the 4-hour median lethal concentration (LC50) was reported as >2.6 mg/L.

In a study equivalent or similar to OECD TG 403 (acute inhalation toxicity), SD rats (5/sex/concentration) were exposed (whole body) to aerosolised eugenol (purity 99 %) for 4 hours at nominal concentrations of 0, 0.77, 1.37, or 2.58 mg/L. Observed clinical signs, which disappeared in all treated rats at the end of the observation period, include increased salivation and restlessness, lethargy, wet snouts, and red-brown staining of furs. No significant histopathological effects were detected in the lungs of the treated rats (REACH).

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate when administered to rabbit skin. The effects and skin irritation scores were not sufficient to warrant hazard classification for the chemical.

In a study equivalent or similar to OECD TG 404 (acute dermal irritation/corrosion), the clipped skin of female New Zealand White (NZW) rabbits (n=4) was treated (semiocclusive) with 0.5 mL of undiluted eugenol (purity not specified) for 4 hours. The mean irritation scores observed at the 24-, 48-, and 72-hour observation periods were 1.9 for erythema and 1.0 for oedema (REACH).

Eye Irritation

The chemical is reported to be irritating when instilled in rabbit eyes, warranting hazard classification (see **Recommendations**).

In a study equivalent or similar to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of undiluted eugenol (purity not specified) was instilled in the eyes of female NZW rabbit (n=6) eyes were instilled . Effects (not specified) were reportedly observed after one day of application and decreased over the seven-day observation period. The eye irritation scores were based on the standard Draize scale (110-point rating scale). Based on the overall score, the chemical was found to be severely irritating after 24 hours exposure, mildly irritating after 24 and 72 hours exposure, and non-irritating after seven days.

Sensitisation

Skin Sensitisation

The chemical is considered to be a skin sensitiser based on human data (see **Observation in Humans**), and positive results seen in a guinea pig maximisation test (GPMT) and local lymph node assays (LLNA) (EC3 is 5.4). Hazard classification is warranted (see **Recommendations**).

In a LLNA study conducted in accordance with OECD TG 429 with deviations (positive control not reported, group housing instead of individual housing, and period of acclimatisation not reported), female CBA/Ca mice (4/dose) were exposed to eugenol (purity is 99.9 %; vehicle 1:3 ethanol:diethyl phthalate) at 0, 2.5, 5, 10, 25 or 50 %. The chemical was administered topically on both ears for three days. All animals were injected intravenously with radiolabelled thymidine to label proliferating cells. The animals were euthanised and cell suspensions were prepared five hours post-injection. The mean stimulation indices (SI) were 1.2, 2.7, 6.0, 14.3, and 19.4 at 2.5, 5, 10, 25, and 50 % concentrations, respectively. An EC3 (estimated concentration needed to produce a three-fold increase in lymphocyte proliferation) of 5.4 % was determined (REACH). In another LLNA study equivalent or similar to OECD TG 429, eugenol (purity > 95 %) in acetone/olive oil (4:1 v/v) was tested in female CBA/JN mice

(4/dose) at 1, 6, 15 or 30 %. The reported SI were 1.7, 1.5, 2.3, and 3.3 at 1, 6, 15, and 30 % concentrations, respectively (REACH).

In a GPMT study equivalent or similar to OECD TG 406, female Hartley guinea pigs (n=10) were exposed to 5 % eugenol (purity is >95 %) in olive oil. This concentration was used in the induction (both intradermal and epicutaneous routes) and challenge phases. The positive response rate, evaluated 24 hours following challenge application was 20 % (REACH).

The IFRA Standards provide limits in the finished products containing eugenol of 0.14 to 4.9 % for products requiring skin contact (IFRA, 2020). The Research Institute for Fragrance Materials (RIFM) Expert Panel (Api et al., 2016), indicate that the chemical has a weak skin sensitisation potency with a no expected sensitisation induction level (NESIL) of 5900 µg/cm^2.

The MAK evaluation for eugenol (MAK Value Documentation, 2003) included several skin sensitisation studies in guinea pigs (GPMT and Buehler) and mice (mouse ear swelling test). The evaluation concluded that the chemical has skin sensitising potential.

Observation in humans

Eugenol is listed as one of the most frequently reported allergens in consumer products (SCCNFP, 1999).

The chemical is an ingredient (at 1 % concentration) in the fragrance mix that is used to diagnose fragrance contact allergy and is available in the standard patch test kits (SCCNFP, 1999; MAK Value Documentation, 2003). Clinical patch testing studies from the use of the fragrance mix showed positive results in up to 1.8 % of population-based groups and up to 10.6 % of eczema patients (SCCNFP, 1999).

The chemical induced skin reactions following patch tests of patients with contact dermatitis or suspected contact allergy. The positive reactions were observed in 1.2 to 14.6 % of the patients tested (MAK Value Documentation, 2003).

Repeated Dose Toxicity

Oral

Based on the available information, repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a study conducted similarly to OECD TG 408 (repeated dose 90-day oral toxicity), Fischer 344 (F344) rats (n=10/sex/dose) were administered eugenol (purity >99 %) in the diet at doses of 0, 800, 1500, 3000, 6000 or 12500 ppm (equivalent to 0, 80, 150, 300, 600 or 1250 mg/kg bw/day) daily for 90 days. Decreased bodyweight gain (12.4 and 5.9 % in males and females, respectively) was observed at the highest dose. There were no observed effects on mortality, gross pathology, and histopathology (NTP, 1985; REACH).

In a similar study in B6C3F1 mice administered 0, 400, 800, 1500, 3000 or 6000 ppm eugenol (equivalent to 0, 60, 120, 225, 450 or 900 mg/kg bw/day), no effects were observed on bodyweight, mortality, gross pathology, and histopathology (NTP, 1985; REACH).

A NOAEL of 300 mg/kg bw/day has been reported (REACH) based on reduced bodyweight gain as well as notable decreases in food consumption at doses above 300 mg/kg in female rats in a two-year carcinogenicity study in rats (NTP, 1983).

Slight liver enlargement with yellow discolouration, moderate to severe hyperplasia, and hyperkeratosis associated with focal ulceration in the forestomach were observed in rats (strain, sex, and number not specified) orally administered the chemical (purity not specified) at doses of up to 4000 mg/kg bw/day for 34 days (IARC, 1983). No other details were specified.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available information from well-conducted in vitro and in vivo genotoxicity studies, the chemical is not considered genotoxic.

The chemical was found to be negative in the following in vitro genotoxicity tests (NTP, 1983; IARC, 1985; Api et al., 2016; REACH):

- a bacterial reverse mutation assay (equivalent or similar to OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *Escherichia coli* WP2 with and without metabolic activation at concentrations up to 600 µg/plate;
- a bacterial reverse mutation assay (equivalent or similar to OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation at concentrations up to 2000 µg/plate;
- a bacterial reverse mutation assay (equivalent or similar to OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without metabolic activation at concentrations up to 333 µg/plate;
- an unscheduled DNA synthesis assay (equivalent or similar to OECD TG 482) in F344 rat hepatocytes at concentrations up to 1 mM; and
- an unscheduled DNA synthesis assay (equivalent or similar to OECD TG 482) in B6C3F1 mouse hepatocytes at concentrations up to 1 mM.

The chemical was found to be negative in the following in vivo genotoxicity tests (NTP, 1983; IARC, 1985; Api et al., 2016; REACH):

- a chromosome aberration assay (equivalent or similar to OECD TG 475) in human blood erythrocytes;
- a bone marrow micronucleus assay (equivalent or similar to OECD TG 474) in female SD rats administered the chemical by gavage at doses of 0, 335, 670 or 1340 mg/kg bw/day;
- a micronucleus assay (equivalent or similar to OECD TG 474) in male SD rats administered the chemical by gavage at doses of 0, 1340 or 2690 mg/kg bw/day;
- a bone marrow micronucleus assay (equivalent or similar to OECD TG 474) in male B6C3F1 mice administered the chemical intraperitoneally at doses of 0, 150, 300 or 600 mg/kg bw/day;
- a bone marrow micronucleus assay (equivalent or similar to OECD TG 474) in male Swiss-Webster mice administered the chemical in the diet at concentrations of 0, 0.4 or 0.6 %; and
- an unscheduled DNA synthesis assay (equivalent or similar to OECD TG 486) in male SD rats administered the chemical by gavage at doses of 0, 1340 or 2680 mg/kg bw/day.

Carcinogenicity

Based on the available information, eugenol is not considered carcinogenic.

The International Agency for Research on Cancer (IARC) has evaluated and concluded that eugenol is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1985). The US National Toxicology Program (NTP) concluded that eugenol presented no evidence of carcinogenicity in rats and equivocal evidence of carcinogenicity in mice (NTP, 1983).

The following results were reported in several long-term oral administration studies conducted to evaluate the carcinogenic potential of eugenol:

- No significant increased incidences of tumours were observed in male Fischer 344 rats (n=50) administered eugenol (purity >99 %) in the diet at 3000 or 6000 ppm (equivalent to 150 or 300 mg/kg bw/day) for 103 weeks (NTP, 1983; IARC, 1985; REACH).
- Increased incidence of endometrial stromal polyps was observed in female Fischer 344 rats (n=50) administered eugenol (purity >99 %) in the diet at 6000 or 12500 ppm (equivalent to 300 or 625 mg/kg bw/day) for 103 weeks (statistically significant at the low dose group only) (NTP, 1983; IARC, 1985; REACH).
- Increased incidences of hepatocellular adenomas and carcinomas (statistically significant in females only) were observed in groups of B6C3F1 mice (n=50/sex/dose) administered eugenol (purity >99 %) in the diet at a dose of 0, 3000, or 6000 ppm (equivalent to 0, 450 or 900 mg/kg bw/day) for 103 weeks (NTP, 1983; IARC, 1985; REACH).
- No increased incidence in tumours was observed in female Charles River CD-1 mice (n=30) fed a diet containing 0.5 % eugenol (purity >98 %) for 12 months and observed for 8 months following administration (NTP, 1983; IARC, 1985).

In a dermal administration study, female ICR/Ha Swiss mice (n=20) were applied a single initiating dose of 150 µg 7,12-dimethylbenz[a]anthracene (DMBA) in 0.1 mL acetone. After two to three weeks, 5 mg eugenol (purity not specified) in 0.1 mL acetone was applied three times per week for 63 weeks. Three papillomas were observed in treated mice. In a similar application regime with eugenol only, no skin tumours were reported (IARC, 1983).

Reproductive and Developmental Toxicity

No data are available for the chemical.

Two structurally similar chemicals have been identified: isoeugenol (phenol, 2-methoxy-4-(1-propenyl)-; CAS No. 97-54-1) and methyl eugenol (benzene, 1,2-dimethoxy-4-(2-propenyl)-; CAS No. 93-15-2). Isoeugenol does not exhibit specific reproductive or developmental toxicity and any reproductive and developmental effects observed from the administration of isoeugenol in rats were reported as secondary to maternal toxicity (NICNASb). Methyl eugenol is not expected to cause developmental toxicity (NICNASa).

In rats fed by gavage, a NOAEL of 500 mg/kg/day for developmental toxicity and a NOAEL of 230 mg/kg/day for reproductive toxicity have been reported for isoeugenol (Api et al., 2016). The developmental NOAEL was based on intrauterine growth retardation and delayed skeletal ossification, which occurred at maternally toxic doses. The reproductive NOAEL was determined based on decreased number of male pups per litter in F0 and decreased pup weights (both sexes) in F1.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include eye irritation and skin sensitisation.

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that may contain the chemical, the main route of public exposure is expected to be through the skin and inhalation from products applied as aerosols.

The chemical is currently listed on Schedules 5 and 6 of the SUSMP (see **Restrictions: Australian**). At concentrations greater than 25 %, a number of warning statements, first aid instructions and safety directions relating to the use of the chemical apply.

The chemical is reported to be used in cosmetic and domestic products in Australia and overseas. Concentrations up to 0.001 % in leave-on products and 0.01 % in rinse-off products have been identified overseas. The concentration cutoff for cosmetic preparations containing the chemical is recommended to be reduced (see **Recommendations**).

Occupational Risk Characterisation

During product formulation, dermal and inhalation 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 effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and 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 HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

It is recommended that an amendment to the current listing of the chemical in the SUSMP be considered. Given the risk characterisation, it is recommended that the concentration cut-off for cosmetic use of the chemical listed in Schedule 6 be reduced.

Matters to be taken into consideration include that the chemical:

- has reported uses in cosmetic and domestic products in Australia and overseas;
- is widely available as a component of essential oils;
- is a skin sensitiser and an eye irritant;
- is frequently reported as an allergen in consumer products, with documented skin reactions in humans (see **Skin sensitisation: Observation in humans**);
- is likely to induce a significant proportion of the population and therefore labelling requirements to control elicitation are appropriate; and
- has restrictions on the domestic or cosmetic uses overseas. The restrictions on the use of the chemical in cosmetic products and toys in the European Union (see **International restrictions**) are considered appropriate to mitigate the risk.

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]
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (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 chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal and 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:

- 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

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