Phenol, 4-chloro-3,5-dimethyl-: Human health tier II assessment

21 April 2016

CAS Number: 88-04-0

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.

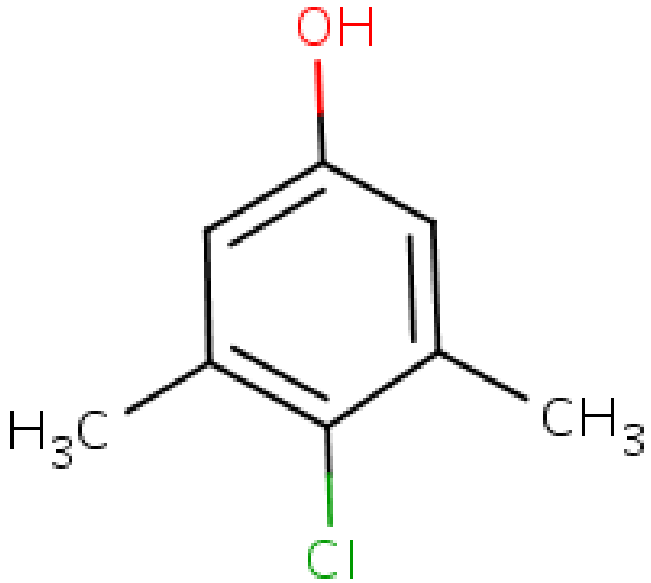
For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	chloroxylenol p-chloro-m-xylenol 2-chloro-5-hydroxy-1,3-dimethylbenzene 2-chloro-5-hydroxy-m-xylene dettol
Structural Formula	

	
Molecular Formula	C8H9ClO
Molecular Weight (g/mol)	156.611
Appearance and Odour (where available)	White to off-white crystalline powder with a faint, characteristic phenolic odour
SMILES	c1(C)c(Cl)c(C)cc(O)c1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; 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 Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); Household Products Database; and Natural Health Products Ingredients Database (NHPID).

The chemical has reported cosmetic uses, including as:

- an antimicrobial agent;
- a deodorising agent; and
- a preservative.

The chemical is listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011), indicating its use in 58 cosmetic products.

The chemical has reported domestic uses, including in:

- cleaning/washing agents;
- colouring agents; and
- paints, lacquers and varnishes.

The chemical has reported non-industrial uses in non-agricultural pesticides and as a preservative in a therapeutic antiseptic.

Restrictions

Australian

The chemical is listed in Appendix B (Part 3) of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2016).

The chemicals in Appendix B (Part 3) are substances that are considered not to require control by scheduling due to 'low toxicity, or where other factors suggest that the potential public health risk would be minimal' (SUSMP, 2016).

International

The chemical is listed on the European Union (EU) Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products (Galleria Chemica).

The chemical may be used in cosmetics and personal care products at a maximum concentration of 0.5 % (CosIng).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R22 (acute toxicity);
- Xi; R36/38 (irritation); and
- Xi; R43 (sensitisation).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The majority of the toxicity studies on the chemical have been conducted using a commercial disinfectant formulation for therapeutic use. The commercial disinfectant formulation contains 4.8 % of the chemical as an active ingredient, 10 % alcohol and 20 % terpineol in a castor oil soap base. Due to possible contributory effects from the vehicle, the toxicity profile of the chemical can be difficult to interpret. However, the general conclusion is that the chemical is of a low order of toxicity (Guess & Bruch, 1986).

Toxicokinetics

The available toxicokinetic studies indicate that the chemical is well absorbed following dermal exposure and rapidly metabolised and eliminated.

The chemical was applied to the shaved backs of mice (species and number of animals unspecified) as a single or repeated dose (dosage unspecified). For repeated dosing, the chemical was applied once daily for 14 or 28 days. Twenty-four hours after application, approximately 50 % of the applied dose was absorbed following a single dose, and approximately 65 % was absorbed following 14 or 28 days of dosing. Tissue concentrations were highest in the kidney, liver and brain. The concentration of the chemical was increased in the tongue following repeated dosing, suggesting continued oral ingestion of the dermally applied dose. Therefore, the absorbed doses reported were indications of both oral and dermal exposures (ACI, 2014).

The chemical was administered to rats and dogs as the commercial disinfectant formulation (25 % dilution) at doses of 4 mL/kg and 1 mL/kg, respectively, either by the oral route or by dermal application. The chemical was well absorbed and excreted in the urine within 24 hours after oral dosing in both rats and dogs. Absorption through the skin was approximately half of the oral absorption. The majority of the chemical was distributed to the kidney, with a small amount observed in the brain. Metabolites observed included hydroxylated chloroxylenol, as well as sulfate and glucuronide conjugates (CIR, 1985; Guess & Bruch, 1986; US EPA, 1994).

In a separate dermal toxicokinetic study in rats, the chemical was found in the kidney, liver and brain in increasing concentrations with repeated dosing. A minor metabolite of the chemical, hydroxylated chloroxylenol, was identified as 10–15 % of the metabolites found in the urine. Excretion was mostly completed in 24 hours after a single dermal application (ACI, 2014).

The dermal absorption of the chemical from the commercial disinfectant formulation was studied in four human subjects following single and repeated bathing (approximately 120 mg of the chemical, 10 minutes daily for 1–10 days) and following a single 30-minute occlusive exposure (46 mg of the chemical) to the back of one subject. The calculated total amount of the chemical absorbed and excreted in the urine was approximately 0.5 % following bathing exposure. In the single subject exposed occlusively, approximately 10 % of the applied dose was absorbed by the skin (Guess & Bruch, 1986; ACI, 2014).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS (Safe Work Australia). While the available data do not support this classification, in the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend this classification.

An acute oral toxicity study was conducted in Dublin strain male albino rats at doses of 1000, 1470, 2150, 3160, 4640 or 6810 mg/kg bw by oral gavage. The median lethal dose (LD50) was established as 3830 mg/kg bw. Reported signs of toxicity included diarrhoea, mild depression, emaciation, corneal reflexes, ataxia, excessive salivation, piloerection and coma (CIR, 1985; Guess & Bruch, 1986; US EPA, 1994; HSDB; RTECS).

In an acute oral toxicity study using the commercial disinfectant formulation, the LD50 values were 84 and 76 mg/kg bw (calculated chemical content) in female and male rats (species unspecified), respectively. These data showed the significant contributory effects of all the ingredients of the commercial disinfectant formulation (Guess & Bruch, 1986).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rats (species unspecified) was >2000 mg/kg bw. Sub-lethal effects were not reported (US EPA, 1994; HSDB).

Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation exposure. The median lethal concentration (LC50) in male albino rats following a one-hour inhalation exposure to the chemical as aerosol was >205 mg/L. Observed sub-lethal effects included reddened extremities, nasal discharge, sneezing, squinting, slight ataxia and unkempt fur (Guess & Bruch, 1986). In a separate study, the LC50 in rats (species unspecified) was >6.29 mg/L. Sub-lethal effects were not reported (US EPA, 1994).

Corrosion / Irritation

Skin Irritation

The chemical is classified as hazardous with the risk phrase ‘Irritating to skin’ (Xi; R38) in the HSIS (Safe Work Australia). There are no available data using test conditions consistent with classification criteria. However, the chemical causes skin irritation at high concentrations under the reported test conditions, supporting this classification.

In a skin irritation test, the chemical was applied onto the skin of rabbits (strain unspecified; three animals/group with abraded skin; six animals/group with intact skin) at concentrations of 0, 1.8 or 18 %. The animals with abraded and intact skin were exposed to 15 and 65 repeated applications, respectively. Minimal skin irritation with mild erythema and desquamation were observed in the control group and at 1.8 %. Moderate to extreme irritation with erythema, desquamation, fissuring and leatheriness were observed at 18 %. No difference in the effects was observed between the animals with abraded or intact skin (Guess & Bruch, 1986).

In a skin irritation test, 0.1 mL of 1 % aqueous solution of the chemical was applied occlusively to the shaved skin of nine albino rabbits for 24 hours. No skin reactions were observed in the study (CIR, 1985).

In a separate skin irritation test, a foot powder containing 0.25 % of the chemical was applied non-occlusively to the shaved skin of nine albino rabbits (final concentration of the chemical was 0.125 %). The test material was applied daily for four consecutive days and graded for irritation 24 hours after each application. The chemical was concluded to be a slight skin irritant with an irritation score of 1/4 (CIR, 1985).

Two skin irritation tests were conducted in the abraded and intact skin of rabbits (strain unspecified) using the commercial disinfectant formulation. In one study, test patches (concentrations not specified) were applied for 24 hours and the application sites were evaluated 72 hours after application. The formulation was concluded to be a moderate skin irritant with an irritation index of 3.38. In another study, initial screening of the formulation at dilutions of 10–100 % were regarded as too irritating for testing. A test dilution of 2.5 % of the formulation resulted in some erythema in the animals and the formulation was concluded to be a mild irritant (Guess & Bruch, 1986).

In a primary skin irritation test performed in rabbits (strain unspecified), undiluted and 40 % of the commercial disinfectant formulation caused severe necrosis, 10 and 20 % of the formulation caused severe irritation, and 2.5 % of the formulation caused only slight irritation. The primary irritation score for 2.5 % of the formulation in rabbits was 0.125 (mild irritant). In the same test performed in guinea pigs, no irritation was observed for 2.5 % of the formulation. The primary irritation score for 2.5 % of the formulation in guinea pigs was 0.46 (mild irritant) (Guess & Bruch, 1986).

Skin irritation was observed in several repeated dose toxicity studies following dermal exposures to high concentrations of the chemical (refer to **Repeat dose toxicity - Dermal** section).

Eye Irritation

The chemical is classified as hazardous with the risk phrase ‘Irritating to eyes’ (Xi; R36) in the HSIS (Safe Work Australia). The available data support this classification.

In a modified Draize test, 0.1 mL of the chemical was instilled into the conjunctival sac of one eye of each of six albino rabbits. The average irritation scores were 28, 31, 30, 28 and 34 on days 1, 2, 3, 4 and 7, respectively (maximum score of 110). No further information was available. The chemical was concluded to be a ‘moderate’ eye irritant in this study (CIR, 1985).

In a separate eye irritation test, 0.1 mL of the chemical (30 % w/v in propylene glycol) was instilled into one eye of each of six albino rabbits. Marked corneal opacity, iritis and conjunctivitis were observed 24 hours after treatment. Signs of eye irritation, including erythema, oedema and discharge, were not fully reversed over the 72-hour observation period in the majority of the animals. The chemical was concluded to be a severe eye irritant in this study. A similar test using a foot powder containing the chemical at a concentration of 0.25 % produced average irritation scores of 2, 6 and 0 on days 1, 2 and 3, respectively. The chemical was concluded to be a ‘mild’ eye irritant in this study (CIR, 1985; US EPA, 1994; HSDB).

In a standard Draize test, the commercial disinfectant formulation was instilled undiluted into the eyes of nine rabbits separated into three groups. In the first group, one eye of each rabbit remained unwashed after instillation. The eyes of three animals in the second group were washed with 20 mL warm water two seconds after instillation and in the third group the eyes were washed four seconds after instillation. The formulation produced lesions of the cornea and iris that persisted for seven days. In the washed eyes, no effects were observed at the end of the 14-day observation period. The formulation was concluded to be a severe eye irritant, while eye-washing after instillation greatly reduced the effects observed (Guess & Bruch, 1986).

In an eye irritation study, a formulated scrub product containing 3 % of the chemical was instilled into the eyes of six rabbits. The eyes of three animals were washed immediately after instillation and the eyes of the remaining three animals were washed 30 seconds after instillation. Conjunctival redness was observed at 24 hours but no other effects were observed at other observation timepoints. The product was concluded to not be an eye irritant (Guess & Bruch, 1986).

Observation in humans

In a 24-hour patch test, an aqueous paste of a foot powder containing 0.25 % of the chemical was applied to the forearms or upper arms of 18 human subjects. No primary skin irritation was observed in the study (CIR, 1985).

The commercial disinfectant formulation applied undiluted to the forearms of eight human subjects for six hours caused transient erythema that was reversed within 24 hours (Guess & Bruch, 1986).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in the HSIS (Safe Work Australia). While the limited available animal data do not support this classification, there is limited human evidence of sensitisation.

The chemical did not produce skin sensitisation in guinea pigs. No further details were provided (US EPA, 1994; HSDB).

Observation in humans

In three separate repeated insult patch test, the chemical was applied occlusively to the skin of human subjects at concentrations up to 1 %. Challenge applications did not result in skin reactions in these studies (CIR, 1985).

The North American Contact Dermatitis Group reported that the incidence of skin sensitisation was <1 % in 1752 dermatitis patients (13 positive reactions) exposed to 1 % of the chemical (CIR, 1985).

The chemical was reported to be the second highest cause of medicinal contact allergic dermatitis in the United Kingdom, with 53/220 reported skin allergy cases to antibacterial agents caused by the chemical. Other case reports also suggested that cross-reactions with chlorocresol (CAS No. 59-50-7), a structurally-related compound used in cosmetic products, occurred in individuals sensitive to the chemical (CIR, 1985).

Repeated Dose Toxicity

Oral

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

In an oral toxicity study, the chemical was administered to rats (species unspecified; 20 animals/sex/group) at doses of 0, 8, 24 or 75 mg/kg bw/day by gavage daily for 30 or 90 days. No significant dose-dependent effects were observed in the study (Guess & Bruch, 1986; ACI, 2014).

In an oral toxicity study, the commercial disinfectant formulation was administered to Specific Pathogen-Free (SPF) rats (five animals/sex/group) at concentrations of 0, 25, 50 or 100 % solution with a constant volume of 5 mL/kg (equivalent to 0, 60, 120 or 240 mg/kg bw/day of the chemical) by gavage, daily for four weeks. At 240 mg/kg bw/day, increased salivation and resistance to handling were observed in both sexes, decreased body weight gain and reduced food intake were observed in the females, and increased liver weights were observed in the males. Increased kidney weights were observed in all treated males compared with the controls, but the effect was not dose-related (Guess & Bruch, 1986). The no observed adverse effect level (NOAEL) was 120 mg/kg bw/day.

In an oral toxicity study, CFY rats (15 animals/sex/group) were administered the commercial disinfectant formulation as an emulsion in water at doses of 0, 0.5 mL/kg/day of a 5 % emulsion, 5 mL/kg/day of a 25 % emulsion or 5 mL/kg/day of a 50 % emulsion (equivalent to 0, 1.1, 55 or 110 mg/kg bw/day of the chemical, respectively), seven days a week for 13 weeks. Salivation and increased absolute and relative liver weights were observed with 50 % emulsion. The males in this dose group also had increased kidney weights, increased volume of diluted urine, lower packed cell volume and haemoglobin values, and higher total leukocyte and lymphocyte counts. Salivation was observed in a few rats and increased absolute and relative liver and kidney weights were observed in males with 25 % emulsion. Increased absolute and relative liver weights were also observed in males with 5 % emulsion (CIR, 1985; ACI, 2014).

In a separate oral toxicity study, Beagle dogs (three animals/sex/group) were administered the commercial disinfectant formulation at doses of 0, 0.5 mL/kg/day of a 5 % solution, 5 mL/kg/day of a 25 % solution or 5 mL/kg/day of a 50 % solution (equivalent to 0, 1.2, 60 or 120 mg/kg bw/day of the chemical, respectively), seven days a week for 13 weeks by oral gavage. The mean liver weights in all treated groups were significantly increased compared with the controls. No other effects were observed in this study (CIR, 1985; Guess & Bruch, 1986; ACI, 2014).

In another oral toxicity study, Beagle dogs (one animal/sex/group) were administered the commercial disinfectant formulation at doses of:

- 2 mL/kg/day of undiluted solution (equivalent to 96 mg/kg bw/day of the chemical) for four weeks;
- 4 mL/kg/day of undiluted solution (equivalent to 192 mg/kg bw/day of the chemical) for four weeks followed by 5 mL/kg/day of a 50 % solution (equivalent to 120 mg/kg bw/day of the chemical) for four weeks; or
- 8 mL/kg/day of undiluted solution (equivalent to 384 mg/kg bw/day of the chemical) for up to 3.5 weeks.

Weight loss, oedema of the pancreas, congestion of the kidneys, and reduced thymus, spleen and pancreas weights were observed in the animals administered 8 mL/kg/day of the test solution (384 mg/kg bw/day of the chemical) (CIR, 1985; Guess & Bruch, 1986; ACI, 2014).

Dermal

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

In a dermal toxicity study, the chemical was applied occlusively to the back of rabbits (species unspecified; 12 animals/group) at doses of 0, 48, 112, 360 or 1200 mg/kg bw/day, daily for 30 days. Due to extreme skin irritation at the application site, the dose of 1200 mg/kg bw/day had to be halved to 600 mg/kg bw/day after the tenth dose. Apart from skin irritation observed at the high dose, no significant toxic effects were observed in the study (Guess & Bruch, 1986).

In a separate dermal toxicity study, the chemical was applied to the skin of albino rabbits (nine animals/group) at doses of 0, 18 or 180 mg/kg bw/day. The chemical was either applied onto the abraded skin of three animals/group, five times a week for three weeks, or onto the intact skin of six animals/group, five times a week for 13 weeks. Moderate to

extreme skin irritation, including erythema, desquamation and fissuring, was observed at 180 mg/kg bw/day. No systemic toxicity was observed in this study (CIR, 1985; US EPA, 1994; ACI, 2014; HSDB).

In a range-finding dermal toxicity study, the chemical was applied onto the shaved skin of CD1 mice (number of animals per group not specified) at initial concentrations of 0, 0.2, 0.4, 0.8 or 1.6 % for 49 consecutive days. The dosages were increased weekly until consistent dermal irritation was observed during week five of the study at concentrations of 19.2, 25.6, 38.4 and 51.2 %. Dermal irritation including desquamation, oedema, erythema, cracking and/or thickening was observed in all treatment groups. No systemic effects were observed (ACI, 2014).

In a subchronic dermal study, the chemical was applied to the skin of CD1 mice (number of animals per group not specified) at concentrations of 0, 15, 30 or 60 % (equivalent to 0, 250, 500 or 1000 mg/kg bw/day, respectively) for an unspecified period of time. Very slight erythema and oedema were observed in all treatment groups, and thickened and scabbed skin was observed at 1000 mg/kg bw/day. Granulocytic hyperplasia of the bone marrow and lymphocytic hyperplasia of the mesenteric lymph nodes were observed at 1000 mg/kg bw/day. A NOAEL of 500 mg/kg bw/day for systemic toxicity was established in this study (ACI, 2014).

In a combined dermal toxicity and carcinogenicity study (refer to **Carcinogenicity** section), the chemical was applied to Slc/ddY SPF female mice (70 animals for control group and 50 animals/treated group) at concentrations of 0, 1 or 10 %, twice weekly for 18 months. An additional 10 animals were allocated to all the groups for the concurrent chronic toxicity study and were sacrificed at six and 12 months. Significant dose-dependent decrease of free fatty acids and increase of alkaline phosphatase were observed in the 10 % treatment group at 12 months. No other significant findings of systemic toxicity were reported at 12 months. In the 18-month study, decreases in the absolute spleen weight were observed in both treatment groups, and significant decreases in the absolute and relative liver weights were observed at 10 %. Significant increases in red blood cells, haemoglobin and mean corpuscular haemoglobin concentration (MCHC) were observed at 1 %, and in haemoglobin and MCHC at 10 %. These increases were considered to be minimal by the authors when compared with background data. (ACI, 2014).

In a dermal toxicity study, a test substance containing 0.25 % of the chemical was applied occlusively onto the shaved skin of albino rabbits (five animals/sex/group) for 6–8 hours at doses of 0 or 2000 mg/kg bw/day, five days a week for four weeks. Two males and two females received the test substance on abraded skin. No significant effects were observed in the study (CIR, 1985; ACI, 2014).

Inhalation

No data are available.

Genotoxicity

Based on the limited available data, the chemical is not expected to be genotoxic.

A bacterial gene mutation assay was conducted in six *Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537, TA1538 and TA1978) up to a maximum concentration of 1 µg/plate of the chemical, in the absence or presence of a rat liver metabolic activation system. Negative findings were reported in this study (CIR, 1985).

Negative findings were reported in an unscheduled DNA synthesis test in primary rat hepatocytes. Negative results were also reported in an in vivo mouse micronucleus assay. No further details were provided (US EPA, 1994; HSDB).

The chemical has no structural features that present an alert for binding to DNA, or alerts for genotoxicity, based on the profiling functionality of the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox v.3.3.0.152.

Carcinogenicity

Limited data are available. Based on the available data, the chemical is not expected to be carcinogenic.

In a combined dermal toxicity and carcinogenicity study (refer to **Repeat dose toxicity - Dermal** section), the chemical was applied to Slc/ddY SPF female mice (70 animals for control group and 50 animals/treated group) at concentrations of 0, 1 or 10 %, twice weekly for 18 months. No increase in carcinogenicity was observed in the study (ACI, 2014).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to cause reproductive or developmental toxicity.

In a developmental toxicity study, Sprague Dawley (SD) rats (25 mated females/group) were administered the chemical at doses of 0, 100, 500 or 1000 mg/kg bw/day by oral gavage on gestational day (GD) 6–15. Reductions in food consumption and consequently, body weight gains, were observed at 500 and 1000 mg/kg bw/day. No adverse effects on foetal development were observed in the study (US EPA, 1994; ACI, 2014; HSDB).

In a separate developmental toxicity study, Wistar rats (24–29 mated females/group) were administered the chemical at doses of 0, 100, 300 or 900 mg/kg bw/day by oral gavage on GD 0–19 (16–19 dams/group were sacrificed on GD 20) or from GD 0 until birth (8–10 dams/group were allowed to deliver). Significant reductions in food consumption were observed at 300 and 900 mg/kg bw/day. Clinical signs of toxicity including death in four animals, total litter resorptions, and reduction in body weight gains were observed at 900 mg/kg bw/day. Significant reduction in foetal body weights and delayed ossification of the sternebrae and vertebrae were observed in the dams at 900 mg/kg bw/day that were sacrificed on GD 20. However, no developmental effects were observed in the offspring of dams that were allowed to deliver, indicating that the effects observed prior to birth were due to developmental delay caused by maternal toxicity (ACI, 2014).

In a range-finding developmental study, SD rats were administered the chemical by oral gavage at doses of 0, 150, 300, 750 or 1000 mg/kg bw/day (duration of the study was not specified). The no observed effect level (NOEL) for maternal toxicity was 750 mg/kg bw/day based on reduced body weight gains and no observed developmental effects. No further details were provided (ACI, 2014).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include skin and eye irritation. There is evidence that the chemical is a skin sensitiser in humans.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic products overseas, but only as a preservative (CosIng). Therefore, cosmetic use is not expected to expose the public to high concentrations of the chemical. The chemical is reported to be used overseas in cosmetic products at a maximum concentration of 0.5% in skin cleansing products (CIR, 2006).

The chemical is currently listed in the Appendix B (Part 3) of the Poisons Standard (SUSMP, 2016) due to low toxicity. Provided that normal precautions are taken to avoid prolonged skin and eye contact, the public health risk posed by the products containing the chemical is expected to be minimal at the concentrations reported internationally (≤0.5 %). Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety. However, should better information become available on skin sensitisation, reassessment of the chemical may be warranted.

Occupational Risk Characterisation

During product formulation, oral, dermal and 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 systemic acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, 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.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

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]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	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 oral, 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:

- health monitoring for any worker who is at risk of exposure to the chemical, 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 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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