Chlorocresol and its sodium salt: Human health tier II assessment

05 February 2016

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, 4-chloro-3-methyl-	59-50-7
Phenol, 4-chloro-3-methyl-, sodium salt	15733-22-9

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemical, phenol, 4-chloro-3-methyl-, sodium salt (CAS No. 15733-22-9), results from phenol, 4-chloro-3-methyl- (CAS No. 59-50-7; referred to as chlorocresol in this report) reacting with sodium hydroxide. Chlorocresol and its salt have been grouped together for assessment due to their similar toxicological properties and uses.

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 the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; 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 Organisation for Economic Co-operation and Development High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the Natural Health Products Ingredients Database; and the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011).

The chemicals have reported cosmetic uses as antimicrobial agents and preservatives. However, there is currently no documented use of the salt in cosmetic products in the USA, and chlorocresol had reported use in only one product (CIUCUS, 2011).

The chemicals have reported domestic uses, including in:

- adhesives and binding agents;
- cleaning or washing agents;
- colouring agents;
- paints, lacquers and varnishes; and
- surface treatments.

Chlorocresol has reported commercial use in cutting fluids.

The chemicals have reported non-industrial uses, including in:

- non-agricultural pesticides and preservatives; and
- pharmaceuticals.

Restrictions

Australian

Chlorocresol and, as the entry does not specifically exclude it, the sodium salt, are listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2015) in Schedule 5 as follows:

'CHLOROCRESOL **except** in preparations containing 3 per cent or less of chlorocresol.'

Schedule 5 chemicals are labelled with 'Caution'. These are '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.' (SUSMP, 2015).

International

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

Chlorocresol may be used in cosmetics and personal care products at a maximum concentration of 0.2 % and is 'not to be used in products applied on mucous membranes' (CosIng).

No known restrictions have been identified for the salt.

Existing Worker Health and Safety Controls

Hazard Classification

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

- Xn; R21/22 (acute toxicity);
- Xi; R41 (irritation); and
- Xi; R43 (sensitisation).

The salt is not listed on the HSIS (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for chlorocresol (Galleria Chemica).

An exposure limit of 22 mg/m^3 (5 ppm) time weighted average (TWA) in Canada, Denmark, Egypt, Iceland, Malaysia, South Africa, Taiwan, Turkey and the US, and 9 mg/m^3 (2 ppm) short-term exposure limit (STEL) in Sweden.

No specific exposure standards are available for the salt.

Health Hazard Information

The hazards of both chlorocresol (phenol, 4-chloro-3-methyl-; CAS No. 59-50-7) and its salt (phenol, 4-chloro-3-methyl-, sodium salt; CAS No. 15733-22-9) were assessed together using the available toxicological data (CIR, 1997; US EPA, 1997; CIR, 2006; ECHA, 2015; HSDB; REACH). No toxicological data are available for the salt. Therefore, the data available for chlorocresol are considered relevant for the hazard assessment due to the structural similarity of the two chemicals. However, the sodium salt could have different properties from chlorocresol with respect to local effects.

Toxicokinetics

In a published study, rats (species and number of animals unspecified) were orally administered 300 mg/kg bw of chlorocresol. Most of the chemical was metabolised by the liver and excreted rapidly by the kidneys, with trace amounts excreted by the lungs. In a separate study, five Wistar rats were administered 300 mg/kg bw of chlorocresol by gavage. Up to 95 % of the chemical administered was excreted via the urine and 0.4 % was recovered in the faeces within 24 hours. The bioaccumulation potential of chlorocresol is expected to be low (CIR, 1997; CIR, 2006; HSDB; REACH).

In order to determine the in vivo bioavailability of chlorocresol, it was applied occlusively for 24 hours to female albino guinea pigs (three animals/preparation) in the following preparations: (a) a suspension of 5 % in water containing 0.15 % Carbomer 941 as gelling agent; (b) a saturated aqueous solution at 0.38 % concentration; (c) 5 % in olive oil/acetone; or (d) 5 % in propylene glycol. The animals were euthanised after 96 hours and the patch test skin areas were excised for analysis. The bioavailability of chlorocresol was 75, 54, 34 and 35 % for preparations (a), (b), (c) and (d), respectively, indicating that the aqueous preparations were more bioavailable than the preparations in olive oil/acetone or propylene glycol (CIR, 1997; CIR, 2006; HSDB; REACH).

The permeability of chlorocresol was determined using the abdominal skin (whole skin and skin that had stratum corneum stripped) from SKH-hr-1 mice. The apparent permeability coefficients in whole and stripped skin were 119 ± 1.8 x 10^{-3} and 241 ± 22 x 10^{-3} cm/h, respectively. The estimated permeability coefficients in viable tissue and stratum corneum were 302 x 10^{-3} and 235 x 10^{-3} cm/h, respectively. The results of this in vitro permeability study indicate that chlorocresol has a high tendency to penetrate the skin (CIR, 1997; CIR, 2006; HSDB).

Acute Toxicity

Oral

Chlorocresol is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data indicate that the chemicals in this group have low to moderate acute oral toxicity in rats and mice, supporting the extension of this classification to both chemicals in this group.

The oral median lethal dose (LD50) values for chlorocresol were 1830 and 600 mg/kg bw/day in male Wistar rats and mice (species unspecified), respectively. Reported signs of toxicity included diuresis, sedation, respiratory disturbance, tremor, tonic cramps and somnolence (CIR, 1997; CIR, 2006; ECHA, 2015; HSDB; REACH; RTECS).

In an acute oral toxicity study, groups of male Wistar rats (number of animals unspecified) were administered a single oral dose of chlorocresol at a concentration of 400 mg/kg bw. The animals were euthanised 60 hours after dosing. Effects on the liver, including slightly enlarged liver, as well as distinct dilation of the sinusoids with an activation of the Kupffer cells and irregular bile canaliculi, were observed (CIR, 1997; CIR, 2006; ECHA, 2015; HSDB).

In another acute oral toxicity study, the LD50 for chlorocresol in Sprague Dawley (SD) rats was 5129 mg/kg bw for males and 3636 mg/kg bw for females. Effects included ataxia, wheezing, muscle twitching, tremors, convulsions and salivation. These reported values were higher than those for Wistar rats. The reason for the strain difference observed is not clear (CIR, 1997; US EPA, 1997; CIR, 2006; ECHA, 2015; HSDB; REACH).

Dermal

Chlorocresol is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). The available data do not support the existing classification.

Chlorocresol has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in Wistar rats and rabbits was >5000 mg/kg bw. Observed sub-lethal effects included anorexia, slight depression, soft faeces, red staining around the anal region and necrosis at the application site (US EPA, 1997; ECHA, 2015; HSDB; REACH). In a proposal for harmonised classification and labelling, the dermal acute toxicity classification for the parent base is recommended to be removed due to its low order of toxicity (ECHA, 2015).

Inhalation

The chemicals in this group are expected to have low acute toxicity based on results from an animal test following inhalation exposure. The median lethal concentration (LC50) in Wistar rats was >2.8 mg/L (dust) in a study conducted according to the OECD Test Guideline (TG) 403. No mortalities were observed in the study. Observed sub-lethal effects included corneal opacity, cyanosis and tremor, oedema and necrosis in the nose, reddened nostrils with red encrustations, nasal discharge and abundant secretions in the trachea (ECHA, 2015; REACH).

Corrosion / Irritation

Corrosivity

Chlorocresol is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in the HSIS (Safe Work Australia). The available data indicate that the chemicals in this group are corrosive to the skin, supporting an amendment of the existing classification.

In an acute skin irritation study conducted similarly to the OECD TG 404, 0.5 g of chlorocresol was applied occlusively onto the shaved skin of a female New Zealand White rabbit. Severe necrosis to the epidermal layer at the application site was observed four hours after patch removal. The complete layer of necrotic tissue was sloughed after one week. No other clinical signs of toxicity were observed throughout the study. Chlorocresol was concluded to be corrosive to the skin of New Zealand White rabbits when applied dermally (REACH).

In a skin irritation study, 0.5 g of chlorocresol was applied occlusively onto the shaved skin of six New Zealand White rabbits for four hours. Skin reactions were recorded at four, 24, 48 and 96 hours after exposure. Marked epidermal and dermal necrosis was observed in all animals at the end of the observation period. The average dermal irritation score was 1.9/4 for erythema and 0.5/4 for oedema. Although the duration of the observation period (96 hours) and the irritation scores were not sufficient to lead to classification, the lack of data on reversibility and the severity of the effects were concerning. Chlorocresol was concluded to be a skin irritant in this study (ECHA, 2015; HSDB).

In an acute eye irritation study conducted according to the OECD TG 405, 0.1 g of chlorocresol moistened with distilled water was instilled in the conjunctival sac of one eye of each New Zealand White rabbit (three animals) for 24 hours. The other eye was left untreated and served as a control. The eyes were examined at one, 24, 48 and 72 hours after instillation. Translucent cornea, slightly obscured iris and unresponsiveness to light, reddened conjunctivae, drooping eyelid and excess eye discharge, with an irritation score of 58/110 were reported. No details of the mean scores for corneal opacity and iritis for each animal were provided in the study. The effects were fully reversed within the 21-day observation period and no clinical signs of toxicity were observed (REACH).

In a published study, the irritation potential of chlorocresol as a preservative used in eye drops was determined. Rabbits (species and number of animals not specified) were dosed with 0.05 % or 0.1 % of the chemical in physiological saline for 10 minutes. At 0.05 %, reddened cornea was observed four hours after application and the effect was reversed after 24 hours. At 0.1 %, inflamed eyes were observed after 48 hours and the effect was reversed after 106 hours. Chlorocresol was concluded to be irritating to rabbit eyes when applied at concentrations of 0.05 % and 0.1 % for 10 minutes (CIR, 2006; HSDB; REACH).

Soft lenses that were stored in bactericidal-strength solution containing 0.1 % of chlorocresol were applied to the eyes of 13 rabbits for six hours/day. Severe eye irritation was observed after a few days (CIR, 1997; CIR, 2006; HSDB).

The sodium salt is expected to be a moderately strong base and form significant concentrations of chlorocresol when in contact with skin and eyes. Therefore, the corrosivity of the salt is not expected to be lower than that of chlorocresol.

Observation in humans

A study was conducted to determine the skin irritation potential of chlorocresol in 1462 eczema patients, when the chemical was applied at a concentration of 2 % for a period of three years. The frequency of application was not stated in the study. Irritant reactions were observed in 6/1462 patients (CIR, 1997; CIR, 2006; HSDB; REACH).

Respiratory Irritation

Based on the available data, the chemicals in this group are expected to cause respiratory irritation, warranting hazard classification.

In an acute inhalation toxicity study conducted according to the OECD TG 403 (refer to **Acute Toxicity - Inhalation** section), Wistar rats (five animals/sex/group) were exposed nose-only to chlorocresol as dust at concentrations of 0, 1.34 or 2.87 mg/L for four hours and the animals were observed for two weeks post-exposure. At both treatment levels, bloated abdomen, salivation, giddiness, cyanosis and tremor were observed. Corneal opacity was also observed at 2.87 mg/L. Signs of upper respiratory irritation, including oedema/necrosis in the nose, reddened nostrils with red encrustations and nasal discharge, were observed in the treated animals. Most of the animals showed evidence of recovery by the end of the observation period. Chlorocresol is concluded to be irritating to the respiratory system (ECHA, 2015).

Sensitisation

Skin Sensitisation

Chlorocresol is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the HSIS (Safe Work Australia). The available data support the extension of this classification to both chemicals in this group.

In a modified local lymph node assay (LLNA), chlorocresol was applied onto the dorsal part of the ears of Naval Medical Research Institute (NMRI) mice (six females/group) at concentrations of 0, 1, 10 or 50 % for three consecutive days. The

stimulation indices (SIs) for weights were 1, 1.07, 0.97 and 1.34, and the SIs for cell counts were 1, 0.99, 0.71 and 1.28 for the 0, 1, 10 and 50 % concentrations, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) could not be calculated. Chlorocresol was concluded to have a weak sensitising potential in mice following dermal application (ECHA, 2015).

In a guinea pig maximisation test, female albino guinea pigs were given intradermal induction exposures with a 5 % solution in propylene glycol and a patch of 0.5 mL of 10 % chlorocresol in yellow petrolatum. The animals were then challenged occlusively with 0.5 mL of 1 % chlorocresol in petrolatum on days 21 and 35. Positive reactions were observed in 16/19 animals on challenge day 21 and 4/19 animals on challenge day 35. Chlorocresol was concluded to be extremely sensitising to the skin of guinea pigs (CIR, 1997; CIR, 2006; HSDB; REACH).

Groups of 15 Pirbright White guinea pigs each were used in two maximisation tests. In the first study, intradermal and topical inductions at 25 % chlorocresol were applied to the males. The animals were then challenged with 25 % and 12.5 % of the chemical on the right and left flank, respectively. In the second study, female animals were administered intradermal and topical inductions at 1 % chlorocresol. The animals were then challenged with 50 % and 25 % of the chemical on the right and left flank, respectively. In both studies, the topical induction exposures were 48 hours in duration and the challenges were performed two weeks after induction and lasted six hours. Positive reactions were observed in 13/15 and 4/15 animals in the first and second study, respectively. Chlorocresol was concluded to be a skin sensitiser (ECHA, 2015).

In a separate maximisation test, 36 guinea pigs were induced by intradermal administration of 1 % chlorocresol on day 0 and topical administration of 10 % chlorocresol on day 7. The animals were challenged occlusively on day 21 at 0.1 and 1 % chlorocresol. Forty-eight hours after the challenge, 28/36 animals showed positive reactions. Chlorocresol was concluded to be a skin sensitiser in this study (CIR, 1997; CIR, 2006; HSDB).

In a Magnusson and Kligman test, Stamm Pirbright White guinea pigs (30 animals/sex) were induced intradermally (concentration not specified), followed by a topical application of 1 % and 25 % chlorocresol at different application sites a week later. The animals were challenged two weeks later with topical applications of 12.5, 22, 50 and 100 % chlorocresol. It was concluded that a 1 % solution was ‘weakly sensitising’ and a 25 % solution ‘strongly sensitising’. No further details were provided (CIR, 1997; CIR, 2006; HSDB).

In the toxicokinetic study to determine the in vivo bioavailability of chlorocresol (refer to **Toxicokinetics** section), female albino guinea pigs were subjected to a cumulative contact enhancement test with the same treatments using topical induction patches on days 0, 3, 7 and 9. Challenge reactions were recorded 48 and 72 hours after the last application. Positive reactions were observed in 12/19 animals treated with 5 % chlorocresol in water, 11/20 animals treated with 5 % chlorocresol in olive oil/acetone, and 4/20 animals treated with 5 % chlorocresol in propylene glycol. Chlorocresol was concluded to be sensitising to the skin of guinea pigs (CIR, 1997; CIR, 2006; HSDB; REACH).

In an epicutaneous test, 35 female Stamm Pirbright White guinea pigs were induced by two open applications of 1, 3, 10 and 30 % chlorocresol. The animals were then challenged at 3, 10, 30 and 100 % chlorocresol. No sensitisation reaction was observed in this study. No further details were provided (CIR, 1997; CIR, 2006; HSDB).

Observation in humans

Chlorocresol is a strong skin sensitiser in animal tests, but human skin sensitisation has been reported to be fairly rare. Several cases of skin sensitisation were reported due to cosmetic products or occupational contact (CIR, 2006; ECHA, 2015).

A Draize test was conducted to determine the sensitisation potential of chlorocresol in humans. Thirty-one male subjects aged between 21–50 years were given ten daily topical induction exposures at 5 % chlorocresol in petrolatum to the upper lateral portion of the arm. The subjects were challenged at the same application sites with the same concentration of the chemical two weeks after induction. No positive reactions were observed and chlorocresol was concluded to be non-sensitising to the skin of humans at 5 % concentration (CIR, 1997; CIR, 2006; HSDB; REACH).

In a separate Draize test, groups of 98, 88 and 66 male subjects were given ten daily topical induction exposures at 5, 10 or 20 % chlorocresol in petrolatum to the upper lateral portion of the arm for 3–5 weeks. Approximately two weeks later, the subjects were challenged with a 72-hour patch containing 5 % of the chemical in petrolatum. No positive reactions were observed (CIR, 1997; CIR, 2006; HSDB).

A patch test study was conducted in 1462 eczema patients (refer to **Corrosion/Irritation** section). Positive reactions were observed in 5/1462 patients (CIR, 1997; CIR, 2006; HSDB; REACH).

Repeated Dose Toxicity

Oral

The available data suggest that chlorocresol has low repeated dose toxicity based on results from animal tests following oral exposure. The effects observed were not sufficient to warrant hazard classification.

In a repeated dose oral toxicity study, Wistar rats (10 animals/sex/group) were administered chlorocresol at 0, 50, 200 or 400 mg/kg bw/day by gavage for 28 days. A significant reduction in body weight gain was observed at 400 mg/kg bw/day during the last week of treatment. No other adverse effects were observed. A no observed adverse effect level (NOAEL) of 200 mg/kg bw/day was established in this study (CIR, 1997; CIR, 2006; HSDB; REACH).

In a separate repeated dose oral toxicity study, specific-pathogen-free (SPF) rats (20 animals/sex/group) were administered chlorocresol in diet at 0, 150, 500 or 1500 ppm (approximately 0, 12, 41 or 120 mg/kg bw/day for males and 0, 17, 54 or 167 mg/kg bw/day for females, respectively) for 90 days. Growth retardation was observed at 500 and 1500 ppm. No other adverse effects were observed. A no observed effect level (NOEL) of 150 ppm (approximately 12 mg/kg bw/day) was established in this study (CIR, 1997; US EPA, 1997; CIR, 2006; HSDB).

In a chronic oral toxicity study, Wistar rats (60 animals/sex/group) were administered chlorocresol in diet at 0, 400, 2000 or 10000 ppm (approximately 0, 21, 103 or 559 mg/kg bw/day for males and 0, 28, 134 or 744 mg/kg bw/day for females, respectively) for two years. Ten animals/sex from each group were euthanised after 53 weeks for interim pathological examinations. Significant reductions in body weights were observed in all treated females. At 10000 ppm, significant reductions in body weights were observed in the males, a significant increase in the frequency of poor general condition was observed in the females, reductions in total protein excretion and serum potassium and phosphate concentrations were observed in both sexes, and deformation of the kidneys was observed in 6/44 surviving males. Pathological examinations showed increased incidences of papillary necrosis, cortical tubular dilations and cortical fibrosis of the kidneys in the males at 10000 ppm. A NOEL of 2000 ppm (approximately 103 or 134 mg/kg bw/day for males and females, respectively) was established in this study (CIR, 1997; US EPA, 1997; CIR, 2006; HSDB).

Dermal

The available data suggest that chlorocresol has low repeated dose toxicity based on results from an animal test following dermal exposure. The effects observed were not sufficient to warrant hazard classification.

In a 21-day dermal toxicity study, chlorocresol was applied to New Zealand White rabbits (10 animals/sex/group) at doses of 0, 10, 40 or 160 mg/kg bw/day, five days/week for a total of 15 applications. Dermal irritation was observed in all treatment groups, including erythema, oedema, thickened skin, scaling, blanching, raw areas, necrosis, brown scab-like areas and sloughing. Inflammation and proliferation of bile ducts in the liver were observed at 160 mg/kg bw/day. A systemic NOAEL of 40 mg/kg bw/day was established in this study (US EPA, 1997; CIR, 2006; HSDB; REACH).

Inhalation

No data are available for the chemicals in this group.

Genotoxicity

Based on the available data from in vitro and in vivo studies, the chemicals in this group are not considered to be genotoxic.

In vitro studies

Several bacterial gene mutation assays were conducted in up to seven *Salmonella typhimurium* strains (TA97, TA98, TA100, TA102, TA1535, TA1537 and TA1538) up to a maximum concentration of 12.5 mg/plate of chlorocresol, in the absence or presence of a rat liver metabolic activation system. Negative findings were reported in these studies (CIR, 1997; US EPA, 1997; CIR, 2006; HSDB; REACH).

A modified SOS chromotest (simple bacterial colorimetric assay) was conducted in *Escherichia coli* strain PQ37. At concentrations of 0.1–4 mM, chlorocresol induced SOS-DNA repair synthesis in the absence of metabolic activation. The presence of metabolic activation system reduced the genotoxicity of chlorocresol (CIR, 1997; CIR, 2006; HSDB).

A mammalian cell gene mutation assay was conducted in Chinese hamster ovary (CHO) cells (hypoxanthine-guanine phosphoribosyl transferase (hprt) locus). Chlorocresol was tested up to a maximum concentration of 300 µg/mL in the absence or presence of a metabolic activation system. Negative findings were reported in this study (US EPA, 1997; HSDB; REACH).

In an unscheduled DNA synthesis (UDS) test in rat primary hepatocytes, chlorocresol was tested at dose levels of 0.25, 0.5, 2.5, 7.5, 10 or 20 µg/mL and 2.53, 5.06, 7.58, 10.1, 15.2 or 20.2 µg/mL. Chlorocresol did not cause any DNA damage or inducible repair in the study (US EPA, 1997; HSDB).

In vivo studies

In an in vivo micronucleus assay in bone marrow cells in mice (species and number of animals unspecified), chlorocresol was administered as a single intraperitoneal (i.p.) injection at a dose of 125 mg/kg. Bone marrow cells were collected 24, 48 and 72 hours after administration and the polychromatic erythrocytes (PCEs) from each mouse were examined. No increases in micronucleated PCEs were found; thus, the chemical was concluded to be non-mutagenic in this study (US EPA, 1997; HSDB).

Carcinogenicity

Based on the available data, the chemicals in this group are not considered to be carcinogenic.

In a chronic oral toxicity study (refer to **Repeat dose toxicity - Oral** section), Wistar rats (60 animals/sex/group) were administered chlorocresol in diet at 0, 400, 2000 or 10000 ppm (approximately 0, 21, 103 or 559 mg/kg bw/day for males and 0, 28, 134 or 744 mg/kg bw/day for females, respectively) for two years. Significant increases in pituitary adenomas were observed in the females at 2000 ppm (approximately 134 mg/kg bw/day) and in the males at 400 ppm (approximately 21 mg/kg bw/day) without a dose response. A significant increasing trend in testicular interstitial cell tumours was also observed in the males. However, the incidences of these tumours were reported to be within the historical control range. Therefore, the tumour incidences were not considered to be treatment-related and the chemical was concluded to be not classifiable as a carcinogen (CIR, 1997; US EPA, 1997; CIR, 2006; HSDB).

Reproductive and Developmental Toxicity

Based on the available data, the chemicals in this group are not expected to cause reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a one-generation reproductive toxicity study, pregnant Wistar rats (25 animals/group) were administered chlorocresol at doses of 0, 30, 100 or 300 mg/kg bw/day by gavage on gestational days (GD) 6–15. The animals were euthanised on GD 20. Significant reductions in body weight, food intake and water consumption, and clinical signs of toxicity, including extreme exhaustion, convulsions and laboured breathing, were observed in the animals treated at 300 mg/kg bw/day. Significant reductions in body weight and laboured breathing were also observed at 100 mg/kg bw/day. No significant effects were observed in the number of corpora lutea, implantations, live foetuses and live foetuses per sex. A significant reduction in the mean foetal weight and a significant increase in early resorptions were observed at 300 mg/kg bw/day. Significant skewing of the normal sex ratio (from 55.6 % males in the controls to 45.6 % males at 100 mg/kg bw/day) was observed without a dose response. A developmental NOAEL of 30 mg/kg bw/day was established in this study (US EPA, 1997; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation is skin sensitisation. At higher exposures, the chemicals cause systemic acute effects (acute toxicity from oral exposure) and local effects (corrosivity).

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemicals are reported to be used in cosmetic products overseas as preservatives (CosIng). Therefore cosmetic use is not expected to expose the public to high concentrations. Chlorocresol was reported to be used in a cosmetic product (skin barrier cream) overseas at a concentration of ≤1 %, while the salt was not identified in any cosmetic product (CPCat). There were no identified domestic products containing the chemicals on the US Household Product Database.

The chemicals are currently listed on Schedule 5 of the SUSMP for preparations containing more than 3 % chlorocresol (SUSMP, 2015). The characterised critical health effects have the potential to pose an unreasonable risk under the uses identified at concentrations lower than 3 %. The risks could be mitigated by implementation of concentration limits for use in cosmetic products, as supported by the EU Cosmetics Regulation 1223/2009 (CosIng).

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. 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 chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure are implemented. The chemicals 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 HSIS (Safe Work Australia) (refer to **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 chemicals in cosmetics and/or domestic products be managed through changes to the Poisons Standard, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemicals 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

Given the risk characterisation, it is recommended that an ammendment to the current listing of the chemicals in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons) be considered with an appropriate concentration cut-off for use in cosmetic products.

Consideration should be given to the following:

- the chemicals are skin sensitisers;
- the chemicals are corrosive; and
- overseas restrictions for use of chlorocresol in cosmetics and personal care products where the maximum concentration allowed is 0.2 % and that the chemical is 'not to be used in products applied on mucous membranes' (CosIng).

Work Health and Safety

The chemicals are 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. Available data give rise to questions about the relevance of the existing acute dermal toxicity classification. Safe Work Australia is recommended to take note of the current EU harmonised classification assessment and remove this classification if considered appropriate in this assessment.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Harmful in contact with skin (Xn; R21)	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Causes burns (C; R34)	May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335) Causes severe skin burns and eye damage - Cat. 1C (H314)
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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

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

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;

- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

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

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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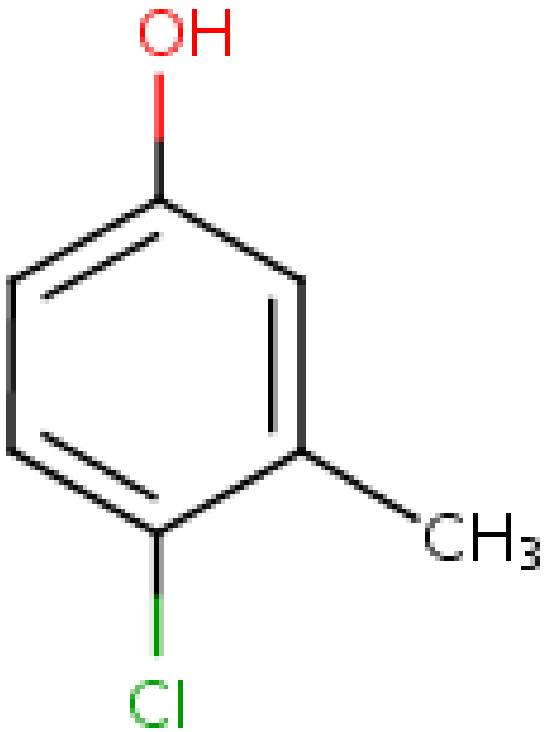
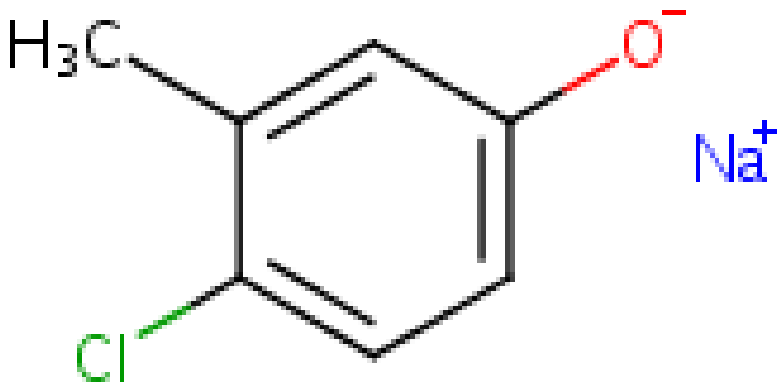
Last Update 05 February 2016

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, 4-chloro-3-methyl-** p-chloro-m-cresol chlorocresol 2-chloro-5-hydroxytoluene 4-chloro-1-hydroxy-3-methylbenzene parachlorometacresol
CAS Number	59-50-7
Structural Formula	

	
Molecular Formula	C7H7ClO
Molecular Weight	142.5843

Chemical Name in the Inventory and Synonyms	**Phenol, 4-chloro-3-methyl-, sodium salt** p-chloro-m-cresol, sodium salt chlorocresol sodium sodium 4-chloro-3-methylphenolate sodium 4-chloro-3-methylphenoxide sodium 4-chloro-m-cresolate
CAS Number	15733-22-9
Structural Formula	

	
Molecular Formula	C7H7ClO.Na
Molecular Weight	164.566

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