3-Isothiazolone, 2-methyl-: Human health tier II assessment

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CAS Number: 2682-20-4

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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	2-methyl-3-isothiazolone Methylisothiazolinone N-methylisothiazolin-3-one

Structural Formula	 Structural formula of 3-Isothiazolone, 2-methyl-
Molecular Formula	C4H5NOS
Molecular Weight (g/mol)	115.16
Appearance and Odour (where available)	Colourless, clear with a mild odour.
SMILES	C1(=O)C=CSN1C

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information:

- The chemical has reported domestic use including in car wash soap and protection and finish coatings.
- The chemical has reported commercial use in industrial coatings.

However, the chemical has now been reported to have domestic use as a preservative in paint formulations.

The Medical Journal of Australia has reported the use of the chemical as a preservative in baby wipes (Cahill et al., 2014).

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use in:

- baby products such as shampoos, soaps, detergents, bubble baths, lotions, oils, powders and creams, baby wipes;
- eye makeup such as eyeliners, removers;
- makeup blushers and face powders;
- fragrances;
- hair care products conditioners, sprays/aerosol fixatives, straighteners, rinses, shampoos, tonics, dressings, and wave sets;
- hair colouring products (dyes and colours), bleaches, and tints;
- nail cream and lotion;
- underarm deodorants;
- aftershave lotions, shaving cream, shaving soap; and
- skin care products such as skin cleansing creams, lotions, powder and sprays, depilatories, face and neck creams, body and hand cream, moisturisers, night creams, paste masks/mud packs, skin fresheners, suntan gels, and indoor tanning preparations.

The maximum use concentration in both leave-on and rinse-off cosmetic products is reported to be 0.01 % (CIR, 2014).

The chemical is also used as a preservative in adhesives, coatings, fuels, metalworking fluids, resin emulsions and paints (Burnett et al., 2010).

The chemical has reported domestic use including:

- dishwashing liquid;
- laundry detergents;
- stain remover;
- glass and surface cleaner;
- home odour neutraliser;
- linen spray;

- wood floor cleaner;
- shoe cleaning gel; and
- antimicrobial agent.

The chemical concentrations used in products are typically reported to be <1 % (US Department of Health and Human Services, Household Products Database (HHPD).

Restrictions

Australian

The chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6 (SUSMP, 2019). The restrictions are based on the recommended changes to the *Poisons Standard* from the IMAP assessment published in Tranche 9.

METHYLISOTHIAZOLINONE except:

a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.01 per cent or less of methylisothiazolinone; or

b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone.

However, as of **1 October 2019**, the Schedule 6 entry for methylisothiazolinone will change to the following (TGA, 2017):

METHYLISOTHIAZOLINONE except:

a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing **0.0015** per cent or less of methylisothiazolinone; or

b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone

Schedule 6 chemicals are described as 'Poison – 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'.

International

The Cosmetic Ingredient Review (CIR) expert panel concluded that MI is 'safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave on products when formulated to be non-sensitising, which may be determined based on a quantitative risk assessment (QRA)' (CIR, 2014).

The Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) is also of the opinion that 'for leave on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the induction of contact allergy' (SCCS, 2015).

Existing Work Health and Safety Controls

Hazard Classification

Methylisothiazolinone is classified as hazardous with the following hazard categories and hazard statement for human health in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia). This classification is based on the recommended amendment to the hazard classification in the HSIS (Hazardous Substance Information System–the Safe Work Australia online classification database at the time) from the IMAP assessment published in Tranche 9.

Acute toxicity – Category 3; H301 (Toxic if swallowed)

Acute toxicity – Category 3; H311 (Toxic in contact with skin)

Acute toxicity – Category 2; H330 (Fatal if inhaled)

Skin corrosion/irritation – Category 1B; H314 (Causes severe skin burns and eye damage)

Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction)

The reaction mass of of methylchloroisothiazolinone and methylisothiazolone (CAS No. 55965-84-9) is also classified as hazardous with the following hazard categories and hazard statement for human health in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia).

Acute toxicity – Category 3; H301 (Toxic if swallowed)

Acute toxicity – Category 3; H311 (Toxic in contact with skin)

Acute toxicity – Category 3; H331 (Toxic if inhaled)

Skin corrosion/irritation – Category 1B; H314 (Causes severe skin burns and eye damage)

Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

In this section, the health hazards of methylisothiazolinone (CAS No. 2682-20-4) have been reported and, where data are not available, data on the analogues 3(2H)-Isothiazolone, methylchloroisothiazolinone (CAS No. 26172-55-4) and 3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone (CAS No. 55965-84-9) were used in accordance with the read-across principles (OECD, 2007).

Toxicokinetics

Toxicokinetic studies in rats using the chemical and its analogue (CAS No. 55965-84-9) show that it is readily absorbed and metabolised. The major metabolic products of the chemical are N-methyl malonamic acid (NMMA) and the 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl-propionamide. These studies did not report accumulation of the chemical or its metabolites in tissues. It is widely distributed to all tissues in the body, with the highest level seen in the liver and lowest in the bone. The chemical is eliminated within 24 hours through urine > bile > faeces. In an in vitro human skin absorption study conducted in accordance with OECD Test Guideline (TG) 428, aqueous solutions of products containing the chemical were applied by occlusion for 24 hours at doses of 52.2, 104.3 or 313 µg/mL. Potential systemic bioavailability was estimated as a maximum of 75.5 % of the applied dose (SCCS, 2009).

Acute Toxicity

Oral

The chemical had high acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats (Crl:CD®BR strain) was 209 mg/kg bw (235 for male and 183 mg/kg bw for female rats). The chemical (99.7 %) was administered as a single dose through gavage at concentrations of 75, 150, 180, 225 and 300 mg/kg bw. Observed sub-lethal effects included passivity, ataxia, scant or no faeces, mucus in faeces, yellow or brown stained anogenital area, red-stained muzzle and/or lacrimation. Additionally, at necropsy reddened intestines and/or stomach mucosa, reddened glandular portion of the stomach, and distended stomachs were observed (CIR, 2010; SCCNFP, 2003).

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia).

Dermal

The chemical had high acute toxicity in animal tests following dermal exposure. The median lethal dose (LD50) in rats (Crl:CD®BR strain) was 242 mg/kg bw for both sexes. The chemical (97.5 %) was administered undiluted at a single 24-hour occluded topical application on shaved intact skin. Observed sub-lethal effects included decrease in body weight in both sexes at higher dose groups (200 mg/kg and above). Local effects included blanching, oedema, erythema, desiccation, darkened or reddened areas, scabs, eschar, and/or sloughing (CIR, 2010).

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia).

Inhalation

The chemical had high acute toxicity in animal tests following inhalation exposure. The median lethal concentration (LC50) for aerosol in rats (Crl:CD®BR strain, 6 animals/group) after four-hour exposure was 0.11 mg/L. The necropsy showed signs of slight to severe redness in all lobes of the lung in all treatment groups (CIR, 2010).

In another study, the LC50 in rats (Crl:CD®BR strain, 5 animals/group) after four-hour aerosol exposure was reported at 0.33 mg/L. Observed sub-lethal effects included body weight reduction in females at higher dose groups (0.25 mg/kg and above). Signs of pale and/or reddened lungs, distended intestines, and/or wet muzzles were observed at necropsy (CIR, 2010).

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Very toxic by inhalation’ (T; R26) in HSIS (Safe Work Australia).

Corrosion / Irritation

Corrosivity

Based on the available data, the chemical is recommended for classification as hazardous with the risk phrase ‘Causes burns’ (R34) in HSIS (Safe Work Australia).

The chemical was applied undiluted as a single semi-occluded application of 0.5 mL to shaved intact skin of New Zealand White rabbits for three minutes, one hour, and four hours. The three-minute exposure resulted in a very slight to well-defined erythema through to day seven and slight oedema at 1- and 48-hours observations. At 1 and 4 hour exposures to the chemical, skin irritation indicative of corrosivity (concave eschar) was observed on days 7 and 14, respectively (CIR, 2010; SCCNFP, 2003). In an in vitro study with skin constructs, exposure to 1.7 % of the chemical for three or 60 minutes was not corrosive to the skin. However, the chemical was corrosive at higher concentration of 51.1 % at an exposure period of 60 minutes (CIR, 2010).

Eye Irritation

The chemical is recommended for classification as corrosive. It is expected that undiluted chemical will be severely damaging to the eyes.

The chemical (undiluted) was found to be an irritant in a bovine cornea study measuring opacity and permeability. Eye irritation studies using formulations containing the chemical at 100 ppm (body lotion, shampoo and sunscreen) were found non-irritating (CIR, 2010).

Sensitisation

Skin Sensitisation

The chemical produced skin sensitisation effects in several animal and human studies. Although the potency of these effects varied across the studies, skin sensitisation was sufficiently noted across all the studies to support the classification (refer to **Recommendation** section) (SCCS, 2009; CIR, 2010; Lundov et al., 2011; Yazar et al., 2011; Boyapati et al., 2013; Cahill et al., 2014; SCCS, 2013; Lammintausta et al., 2014).

Methylisothiazolinone, in combination with methylchloroisothiazolinone (MCI) in a ratio of 1:3, has been used in industrial and consumer products as a preservative since the beginning of the 1980s. The first cases of contact allergy caused by these chemicals were published in 1985. Although MCI has been considered a more potent sensitiser than MI, this chemical is still classified as a strong sensitiser. As a result of the sensitising potential of these chemicals, the maximum permitted concentration in the EU of the mixed preservative in cosmetics in the ratio of 1:3 (MI:MCI) is 15 ppm (0.0015 %); the allowed concentration of MI in the mixture is 3.75 ppm. Following a review of the safety of MI, the chemical was allowed in cosmetic products in the EU at a maximum concentration of 100 ppm in 2005 (see **Restrictions**) (SCCNFP, 2003; Lundov et al., 2011). The CIR expert panel recommended that the United States cosmetic manufacturers use the chemicals at the same concentrations as allowed in the EU (CIR, 2010).

Following its approval for use as a preservative in cosmetic products in 2005 at a maximum concentration of 100 ppm, several reports have indicated the emergence of the issue of contact allergy to the chemical (see **Sensitisation: observation in humans**). The permitted use of the chemical at 100 ppm in cosmetic products is approximately 25-fold the permitted concentration of the chemical in the MI/MCI combination (3.75 ppm MI in 15 ppm of MI/MCI).

The chemical, in a combination with MCI (1:3 ratio), is also used as a preservative in industrial products and there are no restrictions on the use of this chemical in industrial products. The chemical-induced occupational contact allergy and dermatitis were also reported after contact with wall covering glue and in a paint factory (Lundov et al., 2011; Boyapati et al., 2013; SCCS, 2013).

Although several reports on the sensitisation potential of the mixture (MI:MCI) are available in animals, the most comprehensive studies conducted on the chemical (MI) are reported below.

The potential for MI to cause skin sensitisation was investigated in an OECD Test Guideline (TG) 406 study (Buehler test). In this study, four groups of Hartley guinea pigs (five/sex/group) were treated with the chemical in the form of 6 hours' induction with three doses each week for 3.5 weeks under an occlusive condition. The chemical was administered at 0.4 mL/dose containing concentrations of 1000, 5000, 15000 and 30000 ppm suspended in distilled water on shaved intact skin. The animals were allowed to rest for two weeks before the challenge application. During the challenge phase, the animals were patched with the chemical at doses 1000, 5000, or 15000 ppm in distilled water. The treated animals were monitored for erythema for 24 or 48 hours following the application. Appropriate controls were also used in this study. The results showed no erythema reactions in the non-induced control animals at any challenge concentration. However, incidences of erythema were observed in animals induced and challenged with the chemical at 1000 ppm or higher (Burnett et al., 2010; SCCS, 2013).

In another study (maximisation test), 60 female Hartley guinea pigs received six intradermal injections containing induction doses of 500 ppm or 800 ppm of the chemical. After a week, the treated animals were given a single 24-hour topical exposure to 0.1 mL of the chemical under occlusive conditions. The animals were challenged with 500 ppm or 800 ppm after two weeks and were evaluated for reactions at 24 and 48 hour periods. The animals were also subjected to rechallenge with 1000 ppm. The results showed that 550 ppm did not cause dermal reactions. Only one reaction was noted at 800 ppm dose challenge after the 48-hour observation. During the rechallenge, less than 30 % of the animals displayed grade one erythema. Based on these results, the chemical was not considered a sensitiser at concentrations up to 800 ppm (Burnett et al., 2010).

Furthermore, several mouse local lymph node assay (LLNA) studies have reported evidence suggesting that the chemical is a potential skin sensitiser. In one study, female CBA/Ca mice were treated with the chemical (19.7 % purity in water) at the concentrations of 0.049, 0.099, 0.197, 0.493, 0.985 % in acetone and olive oil (4:1; v/v) and also at the concentrations of 0.99, 1.97, 4.93, 9.85 % in propylene glycol (PG). The induction phase consisted of applying the chemical, positive controls (formaldehyde, glutaraldehyde, MCI/MI mixture) or vehicles over the ears (25 µL/ear) for three consecutive days (days one, two and three). After two rest days, the proliferation of lymphocytes in the lymph node draining the application site was measured by incorporating tritiated methyl thymidine (day six) for five hours. A linear interpolation of the dose response data was used to estimate concentrations required to induce stimulation indices (SI) of 3, relative to concurrent vehicle-treated controls (the EC3 value). The EC3 values of 0.4 and 2.2 % were calculated for the chemical for acetone and olive oil (4:1; v/v) and PG solutions, respectively. It was concluded that the chemical has strong sensitising potential, with potency being comparable to that of the formaldehyde although much lower than the mixture of the chemical with MCI in 1:3 ratio. Similar findings were noted in another study, indicating that the chemical is a sensitiser at concentrations greater than 0.76 % in acetone/olive oil (4:1) with a reported EC3 value of 0.86 % (SCCS, 2013).

Overall, these data suggest that the chemical is a potential skin sensitiser.

Observation in humans

Contact allergy to the chemical and the mixed preservative (MI:MCI) has been commonly reported following its approval for use in cosmetics in 2005 with MI being allowed to be used at up to 0.01% (100 ppm) (SCCS, 2003; CIR, 2010). Increased incidence of clinical sensitisation to MI was more evident following the introduction of patch test for MI alone. The prevalence of sensitisation increased from 1.94 % of all dermatological clinic patients in 2009 to 6.02% in 2012 in Germany. This increase was mainly stated to be driven by female patients aged ≥40 years, patients with face dermatitis, and the use of cosmetics. Additionally, the chemical was named the 2013 "Contact Allergen of the Year" by the American Contact Dermatitis Society, indicating increased incidence of the chemical-induced contact dermatitis (Cahill et al., 2014). Painters, beauticians, and patients with ano-genital dermatitis were identified as being potentially at risk for sensitisation to the chemical (Lundov et al., 2011; Uter et al., 2013; Gameiro et al., 2014; Lammintausta et al., 2014).

In a series of repeat insult patch tests (RIPT) in human volunteers, exposure to the chemical at doses 200, 300, 400, 500, or 600 ppm did not cause dermal sensitisation (CIR, 2010; Burnett et al., 2010). Conversely, cases of allergic contact dermatitis were also reported in patients who had come into contact with coolant solutions containing biocides and those who were exposed to paint additives containing 7-10 % of the chemical. In addition, a lowest eliciting dose of 1.47 µg of the chemical (49 ppm) was observed in a sensitisation studies conducted in 11 MI-allergic patients (CIR, 2010).

Airborne allergic contact dermatitis following non-occupational exposures to isothiazolinones in water-based paints has also been reported (Lundov et al., 2014; Aerts et al., 2017; Amsler et al., 2017).

The chemical has been reported to be an emerging and important allergen in both cosmetic and occupational settings in Australia. Baby wipes and facial wipes containing the chemical were reported to be an important cause of hand dermatitis in carers. Facial dermatitis in children was also noted following the use of moist wipes containing the chemical. It was concluded that the continued use of the chemical in baby wipes and facial wipes will lead to increased rates of allergy to these preservatives in adults. The present study also noted three cases of contact allergy as occupational exposure from hand cleansers containing the chemical (Boyapati et al., 2013). Based on the results of a series of patch test conducted from 2011-2013, the Medical Journal of Australia reported a significant increase in the incidence of contact dermatitis in adult patients from the use of the baby wipes which contain the chemical (Cahill et al., 2014). In this report, the authors highlighted this remarkable rise of contact dermatitis from 3.5 % in 2011 to 11. 3 % in 2013 among their patient population. The authors also noted that the chemical is now the most common cause of allergic contact dermatitis in their patient population (Cahill et al., 2014).

The Scientific Committee on Consumer Safety (SCCS) presented its opinion on the safety of the chemical (methylisothiazolinone) in consumer products. The committee concluded that, on the basis of current clinical data, the use of the chemical at 100 ppm in cosmetic products is not safe for the consumer. The committee also concluded that, for leave-on cosmetic products (including wet wipes), safe concentrations of the chemical for induction of contact allergy or elicitation have not been adequately demonstrated. Although a concentration of 15 ppm (0.0015 %) of the chemical was considered safe for the consumer with respect to induction of contact allergy for rinse-off cosmetic products, no information was available for these products with respect to elicitation of contact allergy (SCCS, 2013).

Repeated Dose Toxicity

Oral

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

No treatment related effects were observed in rats (Crl:CD BR strain) exposed to the chemical (up to 1000 ppm, equivalent to 65.7 and 93.5 mg/kg bw/day in males and females, respectively) in drinking water for three months. Dogs fed with diets prepared with the chemical for three months had a NOAEL of 1500 ppm (41 mg/kg bw/day) (CIR, 2010; US EPA, 1998).

Dermal

No data were available for the chemical. Based on the available toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, CAS No. 55965-84-9), in which there was no evidence of toxicity, the chemical is not considered to cause serious damage to health from repeated exposure.

A formulation containing analogue chemical (2.55:1 ratio) was applied once daily for 91 days to the intact skin of Sprague Dawley (SD) rats by semi-occlusive dressing at doses of 0, 0.75, 3.75, or 18.75 mg/kg bw/day. Treatment-related skin reactions at all doses included slight to moderate erythema and desquamation, slight oedema and atonia, and eschar formation. Microscopic findings revealed treatment-related lesions such as inflammation, parakeratosis, and acanthosis at the treated sites. The LOAEL and NOAEL identified for local effects in this study, were = 0.104 and < 0.104 mg/kg bw/day (SCCS, 2009).

Inhalation

No data were available for the chemical. Based on the available inhalation toxicity study for the analogue chemical (3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone, CAS No. 55965-84-9), in which there was no evidence of inhalation toxicity, the chemical is not considered to cause serious damage to health from repeated exposure through this route.

In a study conducted in accordance with OECD TG 413, Charles River Crl: CD(SD) BR rats were exposed to an aerosol product containing 14% of the analogue chemical for 13 weeks (0, 0.34, 1.15, or 2.64 mg/m^3, at 6 hours/day, 5 days/week). At the top dose, effects included decreased bodyweight gain and signs consistent with sensory irritation such as chromorhinorrhoea, rhinorrhoea, eye squint, bradypnoea, and dyspnoea. Slight to moderate eosinophilic droplets in the anterior mucosa of the nasal turbinates and slight rhinitis in the lining of the nasal cavity were also reported at the top dose. At the mid-dose, slight incidence of rhinitis was observed. The study authors noted that eosinophilic droplets in the nasal turbinates and rhinitis were possibly reversible responses to upper respiratory tract inflammation. The lowest-observed-adverse-effect-concentration (LOAEC) and no-observed-adverse-effect-concentration (NOAEC) for this study were 2.64 and 1.15 mg/m^3, respectively (SCCS, 2009; US EPA, 1998).

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies the chemical is not considered to be genotoxic.

The chemical was not mutagenic in Ames tests in *Salmonella typhimurium*, with or without metabolic activation (CIR, 2010; SCCNFP, 2003). The chemical (0.5-40 µg/mL) was also negative in an in vitro chromosome aberration study using the Chinese hamster ovary (CHO) cells, both with and without metabolic activation. In another study using CHO cells, chromosomal aberrations (at 3.75 µg/mL without S-9 activation (28 % aberrant cells) and at 7.50 µg/mL with S-9 activation (34 % aberrant cells) were seen accompanied by significant cytotoxicity (29-48 % reductions).

The chemical was reported to be negative in an in vivo mouse micronucleus assay (CIR, 2010; SCCNFP, 2003).

Carcinogenicity

No data are available for the chemical. Based on the weight of evidence from the available carcinogenicity study for the analogue chemical—3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone (CAS No. 55965-84-9), in which there was no evidence of carcinogenicity, the chemical is not likely to be a carcinogen.

In a two-year drinking water study on rats (CRL:CD BR) exposed to the analogue chemical, no treatment related neoplasms were observed upto the highest dose tested, 300 ppm (equivalent to 17.2 mg/kg bw/day). Hyperplasia of the forestomach was seen at mid and top doses. This was attributed to the corrosive nature of the chemical (CIR, 2010).

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity.

In a two-generation reprotoxicity study, no treatment related effects were noted in rats (Crl:CD IGS BR strain) exposed to the chemical (up to 86 mg/kg bw/day in males and 115 mg/kg bw/day in females) through drinking water (CIR, 2010; US EPA, 1998).

Two teratogenicity studies showed no treatment related effect in rats (Crl:CD(SD) IGS BR strain) and rabbits (New Zealand White) exposed to the chemical at concentrations up to 40 and 30 mg/kg bw/day respectively. Based on the results, the maternal NOAELs were 20 (rats) and 10 (rabbits) mg/kg bw/day and developmental NOAELs were 40 (rats) and 30 (rabbits) mg/kg bw/day (CIR, 2010; US EPA, 1998).

Other Health Effects

Neurotoxicity

An acute in vitro neurotoxicity study of the chemical using cultures of embryonic rat (SD) cortical neurons and glia observed widespread neuroronal cell death within 24 hours in the cortical cultures exposed to 100 and 300 µM (highest concentration tested) concentrations. Gliotoxicity was low. Another 14-hour in vitro neurotoxicity study of the chemical concluded that prolonged exposures to the chemical and related isothiazolones may damage developing nervous systems (based on cell death observed in cultures treated with 3 µM concentration of the chemical along with changes in signalling complexes normally found in developing neurons) (CIR, 2010). However, no evidence of neurotoxicity was observed in vivo in the repeat dose or reproductive and developmental animal studies.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation includes systemic acute toxicity (by all route of exposure) and local effects (skin sensitisation). The chemical may also cause skin corrosion and possibly serious eye damage.

Public Risk Characterisation

The use of the chemical in cosmetic products in Australia is not known;however, the chemical has been reported to have domestic use as a preservative in paint formulations. The chemical is reported to be used in cosmetic/domestic products overseas at concentrations up to 0.1 % and 1 % respectively (HHPD).

Considering the range of 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. Given the low concentrations expected in these products, health effects apart from skin sensitisation are not expected.

Direct exposure to paint formulations containing the chemical and several other isothiazolinones have resulted in allergic reactions (see **Skin sensitisation: Observation in humans** section). Currently, there are no restrictions in Australia on using the chemical and several other isothiazolinones in paint formulations. Further characterisation of the risks from the use of the chemical and other isothiazolinones as a preservative in water-based paint formulations should be examined. In the absence of any regulatory controls, the characterised critical health effect of skin sensitisation has the potential to pose an unreasonable risk when used as a preservative in paint formulations.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations may also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute and local health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical 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 appropriate controls.

NICNAS Recommendation

The chemical is recommended for Tier III assessment to further characterise the risks from its use in domestic products. The Tier III assessment would consider the risks and appropriate concentration limits to manage the risks from the use of the chemical and other isothiazolinones as preservatives in paint formulations.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2019).

The need for further regulatory control for public health will be determined as part of the Tier III assessment.

Work Health and Safety

The chemical is classified as hazardous for human health in the Hazardous Chemicals Information system (HCIS) (Safe Work Australia).

Note that the classification below was based on the recommended amendment to the hazard classification in the HSIS (Hazardous Substance Information System—the Safe Work Australia online classification database at that time) from the IMAP assessment published in Tranche 9, as discussed in the **Health Hazard Information** section of this report.

This updated assessment report does not change the recommended classifications (see Existing Work Health and Safety Controls). This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1B (H314)
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 instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular, and inhalation 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 which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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 assist with meeting 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.

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