

3(2H)-Isothiazolone, 2-methyl-, hydrochloride: Human health tier II assessment

08 March 2019

CAS Number: 26172-54-3



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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.

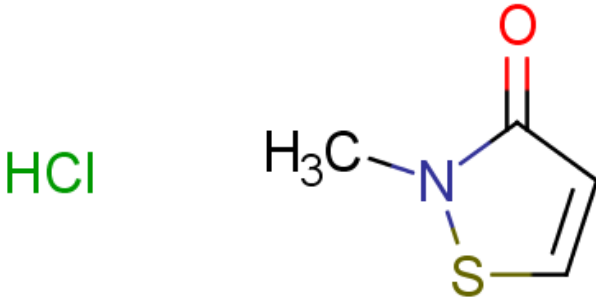
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Acronyms & Abbreviations

Chemical Identity

Synonyms	2-methyl-4-isothiazolin-3-one, hydrochloride methylisothiazolinone hydrochloride
Structural Formula	
Molecular Formula	C ₄ H ₅ NOS.ClH
Molecular Weight (g/mol)	151.60
Appearance and Odour (where available)	powder/particulate
SMILES	C1(=O)C=CSN1C.Cl

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the chemical in voluntary or mandatory calls for information.

The chemical is a salt of methylisothiazolinone (MI, CAS No. 2682-20-4). Methylisothiazolinone is commonly used in cosmetics to the extent allowed under the *Poisons Standard* (SUSMP, 2019). It also has reported domestic use in car wash soap and finish coatings, and as a preservative in paint formulations. The parent chemical, MI, is often used as a 3:1 mixture of methylchloroisothiazolinone and methylisothiazolinone (MCI/MI, CAS No. 55965-84-9) (NICNAS, 2014). It is expected that the chemical may be used in similar products.

International

The chemical has industrial uses as adhesives, binding agents, fillers, and in paints lacquers and varnishes (Substances and Preparations in the Nordic countries (SPIN) database). The chemical has also reported use as disinfectant or a biocide (REACH).

The CAS No. is not listed in the US Personal Care Products Council, International Nomenclature of Cosmetic Ingredients (INCI) directory (Personal Care Products Council), the European Commission Cosmetic Substances and Ingredients (CosIng) database, or in the United States Household Products Database (US HPD).

The uses identified for the parent chemical are considered relevant to the chemical. The parent chemical, MI, has reported use in a range of cosmetic and domestic products (NICNAS, 2014).

Restrictions

Australian

The chemical is not individually listed in *the Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP). However, it is covered under the entry for the parent chemical methylisothiazolinone (MI) in Schedule 6, as its salt (SUSMP, 2019).

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

No restrictions were identified for the chemical.

The Cosmetic Ingredient Review (CIR) expert panel concluded that the parent chemical, MI, is 'safe for use in rinse-off cosmetic products at concentrations up to 100 ppm (0.01 %) 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

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

There is very limited health hazard information available for the chemical. The chemical is the salt of methylisothiazolinone (MI, CAS No. 2682-20-4). Using read-across principles (OECD, 2007), toxicity data from the parent chemical was used for this risk assessment. This report should be read in conjunction with the Tier II assessment of the parent chemical, MI, which can be accessed at https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1062.

Toxicokinetics

Toxicokinetic studies in rats using MI show that MI is readily absorbed and metabolised. It is widely distributed to all tissues in the body, with the highest level seen in the liver and lowest in the bone. The parent 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 MI 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 is highly toxic based on results from animal tests following acute oral exposure. The median lethal dose (LD50) in rats (female Wistar) is 175 mg/kg bw. The chemical is recommended for hazard classification (see **Recommendation** section).

The chemical (>99.9 %) was administered according to OECD Test Guideline 425 - Acute Oral Toxicity: Up-and-Down Procedure, as a single dose through gavage at doses of 55, 175, 550 mg/kg bw. Observed sub-lethal effects included piloerection, shortness of breath (dyspnoea), decreased activity, hunched posture and ataxia (REACH). This is consistent with data for MI, for which MI also has high acute toxicity in animal tests following oral exposure. The LD50 in rats (CrI:CD@BR strain) is 209 mg/kg bw (235 mg/kg bw for males and 183 mg/kg bw for females) (NICNAS, 2014).

Dermal

No data are available for the chemical. However, MI has high acute toxicity in animal tests following dermal exposure. The LD50 in rats (CrI:CD@BR strain) is 242 mg/kg bw for both sexes (NICNAS, 2014). Based on the read across principles, the chemical is recommended for hazard classification (see **Recommendation** Section).

Inhalation

No data are available for the chemical. However, MI has high acute toxicity in animal tests following inhalation exposure. The median lethal concentration (LC50) for aerosol in two independent studies in rats after four-hour exposure is 0.11 mg/L and 0.33 mg/L (NICNAS, 2014). Based on the read across principles, the chemical is recommended for hazard classification (see **Recommendation** section).

Corrosion / Irritation

Corrosivity

Based on the available information, the chemical is corrosive and recommended for hazard classification (see **Recommendation** section).

In an in vitro skin irritation study (according to OECD Test Guideline 431), reconstructed human epidermis (RHE) were treated with the chemical (99.9 %) for three minutes and one hour. The mean relative tissue viability was <50 % following both treatments (22 % after 3 minutes and 5.6 % after 1 hour exposure) indicating that the chemical is corrosive (REACH).

Sensitisation

Skin Sensitisation

No data are available for the chemical. However, based on the potential for MI to cause skin sensitisation in both animals and in humans (NICNAS, 2014), the chemical is recommended for hazard classification (see **Recommendation** section).

The critical effect for MI is sensitisation. Positive results were reported in animal tests (guinea pig maximisation test, Buehler test and local lymph node assays). Results from a number of clinical reports indicated that MI is a strong sensitiser in humans. A mixture of methylchloroisothiazolinone and methylisothiazolinone (3:1 MCI/MI) are reported to be sensitisers at low concentrations when used in both cosmetic and occupational settings with a strong potential to cause sensitisation in human patch tests (NICNAS, 2014).

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

Repeated Dose Toxicity

Oral

No data are available for the chemical. Based on available data on MI, the chemical is not expected to cause serious damage to health from repeated oral exposure (NICNAS).

Dermal

No data are available for the chemical. Based on available data on MI, the chemical is not expected to cause serious damage to health from repeated dermal exposure (NICNAS).

Inhalation

No data are available for the chemical. Based on available data on MI, the chemical is not expected to cause serious damage to health from repeated inhalation exposure (NICNAS).

Genotoxicity

No data are available for the chemical. Based on available data on MI, the chemical is not expected to be genotoxic (NICNAS).

Carcinogenicity

No data are available for the chemical. Based on available data on MI, the chemical is not likely to be a carcinogen (NICNAS).

Reproductive and Developmental Toxicity

No data are available for the chemical. Based on available data on MI, the chemical is not likely to have specific reproductive and developmental toxicity (NICNAS).

Risk Characterisation

Critical Health Effects

Based on information available for the salt and for MI, the critical health effect for risk characterisation is skin sensitisation. The chemical may also cause systemic acute toxicity (by all routes of exposure) and local effects (skin corrosion and possibly serious eye damage).

Public Risk Characterisation

The chemical is currently listed (as a derivative of methylisothiazolinone) on Schedule 6 of the Poisons Standard (SUSMP, 2019).

Direct exposure to paint formulations containing the chemical and several other isothiazolinones have resulted in allergic reactions (see **Skin sensitisation** 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 preservatives in water-based paint formulations should be undertaken. There is an existing control of 0.1 %;

however, whether this control is sufficiently protective should be further evaluated. 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 maintaining of equipment. Worker exposure to the chemical at lower concentrations can 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 chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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.

The data available support an amendment to the hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) (see **Recommendation** section).

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

The chemical falls within the scope of the listing of methylisothiazolinone on Schedule 6 of the Poisons Standard. Therefore, 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 recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS) ^a	GHS Classification (HCIS) ^b
Acute Toxicity	Not Applicable	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Fatal if inhaled - Cat. 2 (H330)

Hazard	Approved Criteria (HSIS) ^a	GHS Classification (HCIS) ^b
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 instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral/dermal/ocular/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 that could 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[s], 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 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[s] 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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