2-Imidazolidinethione, 1,3-bis(hydroxymethyl)-: Human health tier II assessment

25 November 2016

CAS Number: 15534-95-9

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.

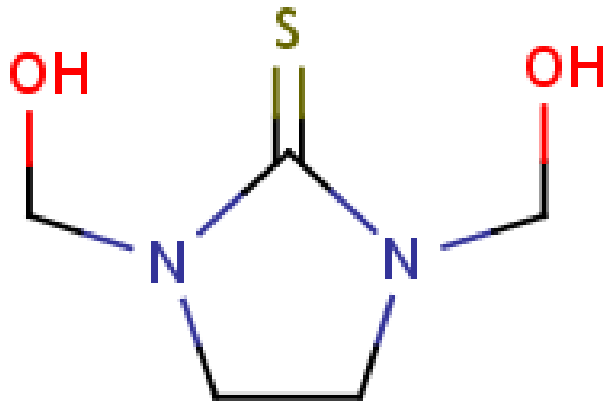
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	dimethylol ethylene thiourea 1,3-bis(hydroxymethyl)-2-imidazolidinethione
Structural Formula	
Molecular Formula	C5H10N2O2S
Molecular Weight (g/mol)	162.2
Appearance and Odour (where available)	White crystalline powder
SMILES	C1(=S)N(CO)CCN1CO

Import, Manufacture and Use

Australian

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

International

The following international use has been identified through: the European Commission Cosmetic Ingredients and Substances (CosIng) database; Galleria Chemica; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency (EPA) Aggregated Computer Toxicology Resource (ACToR); and the US EPA Chemical and Product Categories (CPCat) database.

The chemical dimethylol ethylene thiourea has reported cosmetic use as a preservative (antimicrobial) in personal care products (hair conditioning and nail products).

Restrictions

Australian

There are no restrictions specific to this chemical in Australia; however, this chemical is a known formaldehyde donor under aqueous conditions.

Formaldehyde (CAS No. 50-00-0) is listed in Schedule 6 and Schedule 10 of the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons) (SUSMP, 2016) as follows:

- in Schedule 6:

'FORMALDEHYDE (excluding its derivatives) in preparations containing 0.05 per cent or more of free formaldehyde **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde;

(d) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the statement: PROTECT CUTICLES WITH GREASE OR OIL;

(e) in all other cosmetic preparations; or

(f) in other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Schedule 6 chemicals are labelled with 'Poison' and are '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'.

- in Schedule 10:

'FORMALDEHYDE (excluding its derivatives):

(a) in oral hygiene preparations containing more than 0.1 per cent of free formaldehyde;

(b) in aerosol sprays for cosmetic use containing 0.005 per cent or more of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde; or

(d) in all other cosmetic preparations containing 0.05 per cent or more of free formaldehyde **except** in preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement: CONTAINS FORMALDEHYDE.'

Schedule 10 chemicals are 'substances, other than those included in Schedule 9, of such danger to health as to warrant prohibition of sale, supply and use'.

Formaldehyde donors are mentioned in the definition of free formaldehyde in Part I of the *Poisons Standard* (SUSMP, 2016) as follows:

Free formaldehyde includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol and formaldehyde released from formaldehyde donors.

International

The chemical dimethylol ethylene thiourea is listed on the following (Galleria Chemica):

- Association of Southeastern Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

These international restrictions allow for the use of the chemical in cosmetic products (hair and nail care preparations) up to a concentration of 2 %. The substance is also prohibited from being used in aerosols (sprays), and the pH of the substance containing the chemical is to be less than 4. This restriction is based on the release of formaldehyde from the chemical.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The chemical, dimethylol ethylene thiourea (CAS No. 15534-95-9), has reported use as an antimicrobial agent in personal care products. The biocidal mechanism involves formaldehyde release into aqueous solutions. The degree of completeness of formaldehyde release will depend on the concentration of the preservative in the product, the percentage of water in the product, the rate of formaldehyde release from the specific preservative (usually pH dependent), and the length of time since formulation. The hydrolysis reaction also generates the cyclic thiourea, 2-imidazolidinethione (or ethylene thiourea, CAS No. 96-45-7).

There are limited toxicological data available for the chemical; however, the hydrolysis products, formaldehyde (CAS No. 50-00-0) and 2-imidazolidinethione (CAS No. 96-45-7), are considered the critical drivers for toxicity due to their likely formation under physiological conditions. The toxicology of these chemicals has previously been assessed by NICNAS, and has been considered in this assessment (NICNASa; NICNASb). Where appropriate, data for these chemicals are read across to fill data gaps in the assessment, as hydrolysis of the chemical can occur in biological systems to generate both compounds.

Toxicokinetics

There are no toxicokinetic data available for the chemical.

The chemical is expected to be unstable in dilute aqueous solutions at neutral pH. Under these conditions, the methylol groups are expected to be cleaved to generate formalin (the aqueous form of formaldehyde) and 2-imidazolidinethione.

Due to release of formaldehyde from the chemical, formaldehyde is generally present in low concentrations when products containing the chemical are administered. Formaldehyde is an endogenous metabolic product in many biochemical pathways in humans, and is rapidly metabolised to formate and is excreted in urine, or oxidised to carbon dioxide and exhaled (NICNASa).

The hydrolysis product, 2-imidazolidinethione, can be absorbed by the oral and dermal routes, and is widely distributed. Accumulation of the chemical was observed in the thyroid, independent of the administration route and species. The chemical is metabolised via different pathways in rats and mice, to give different metabolic products that are primarily eliminated in urine. In mice, the chemical is rapidly metabolised preferentially via the flavin-dependent mono-oxygenase (FMO) system to give 2-imidazolin-2-yl sulfenate as the major metabolite. In rats, the metabolites were identified as imidazoline, ethylene urea and 4-imidazoline-2-one (NICNASb).

Acute Toxicity

Oral

There are no data available for the chemical. The chemical is expected to have low acute oral toxicity as used in cosmetics.

The hydrolysis products, formaldehyde and 2-imidazolidinethione, are known to cause harmful effects via the oral route (NICNASa; NICNASb); however, neither chemical is expected to be hazardous at the concentrations of dimethylol ethylene thiourea used in cosmetic products.

Dermal

There are no data available for the chemical. The chemical is expected to have low acute dermal toxicity as used in cosmetics.

Formaldehyde has been found to be moderately toxic in rabbits exposed via the dermal route (NICNASa); however, it is not expected to be hazardous at the concentrations of dimethylol ethylene thiourea used in cosmetic products.

The hydrolysis product, 2-imidazolidinethione, is not considered to be acutely toxic via the dermal route (NICNASb).

Inhalation

There are no data available for the chemical. The chemical is expected to have low acute inhalation toxicity as used in cosmetics.

Formaldehyde has been found to be moderately toxic in rodents exposed via the inhalation route (NICNASa). Given that formaldehyde is unlikely to be volatile from aqueous solutions at low concentration, it is not expected to be hazardous at the concentrations of dimethylol ethylene thiourea used in consumer products.

Corrosion / Irritation

Skin Irritation

There are no data available for the chemical. The chemical is not expected to be a skin irritant as used in cosmetics.

Formaldehyde is a known skin irritant (NICNASa), although at low reported concentrations of the chemical anticipated in cosmetic products, skin irritation is not expected to occur.

The hydrolysis product, 2-imidazolidinethione, is not irritating to skin (NICNASb).

Eye Irritation

There are no data available for the chemical. The chemical is not expected to cause eye irritation as used in cosmetics.

Sensory irritation from formaldehyde vapour release is not expected from products containing the chemicals, given that formaldehyde is unlikely to be volatile from aqueous solutions at low concentrations. However, if the chemicals are applied directly to the eye, irritation could occur due to the severe irritancy of formaldehyde (NICNASa).

The hydrolysis product, 2-imidazolidinethione, is considered a mild eye irritant; however, the effects do not warrant hazard classification (NICNASb), especially at the low concentrations of dimethylol ethylene thiourea expected in cosmetic products.

Sensitisation

Skin Sensitisation

There are no data available for the chemical.

Based on the available data for the hydrolysis product, formaldehyde, the chemical is expected to be a skin sensitiser, warranting hazard classification (see **Recommendation** section). The release of formaldehyde—a known skin sensitiser (NICNASa)—from the chemical under aqueous conditions is expected on structural grounds.

The hydrolysis product, 2-imidazolidinethione, is not considered a skin sensitiser (NICNASb).

Repeated Dose Toxicity

Oral

There are no data available for the chemical.

Based on the lack of systemic toxicity of formaldehyde in oral studies (NICNASa), repeated oral exposure to the chemical is not considered to cause serious damage to health.

The hydrolysis product, 2-imidazolidinethione, is considered to cause thyroid effects in rats following repeated oral exposure to the chemical at low doses (NICNASb). However, it is not expected to be hazardous at the concentrations of dimethylol ethylene thiourea used in consumer products.

Dermal

There are no data available for the chemical.

Based on the lack of evidence of systemic toxicity of formaldehyde in relevant dermal studies (NICNASa), the chemical is not considered to cause serious damage to health from repeated dermal exposure.

No data are available for the hydrolysis product, 2-imidazolidinethione.

Inhalation

There are no data available for the chemical.

Although the hydrolysis product, 2-imidazolidinethione, has been demonstrated to cause thyroid effects in rats following repeated inhalation exposure (NICNASb), it is not expected to be hazardous at the concentrations of dimethylol ethylene thiourea used in cosmetic products.

Based on the lack of conclusive evidence of systemic toxicity of formaldehyde in inhalation studies (NICNASa), and the low volatility of formaldehyde from dilute aqueous solutions, the chemical is not expected to be harmful due to repeated inhalation exposure to the formaldehyde released from products containing the chemical.

Genotoxicity

Limited data are available. The chemical was not reported mutagenic in studies detecting sex-linked recessive lethal mutations, or chromosomal aberrations in mouse bone-marrow cells. Positive results were found in two strains of *Salmonella typhimurium*. In the absence of further information, hazard classification is not warranted.

In a bacterial gene mutation assay, *S. typhimurium* strains TA1535A, TA1535B, TA100, TA1538, TA98 and TA1537 were treated with dimethylol ethylene thiourea at concentrations of 0, 4, 8 and 12 µmoles per plate. No mutagenic activity was observed in the majority of strains tested; however, a positive result was seen in strain TA1535A without metabolic activation, and strain TA100 with metabolic activation (Gocke et al., 1981).

In a bone marrow micronucleus test, Naval Medical Research Institute (NMRI) mice were administered doses of 0, 649, 1298 and 1964 mg/kg bw of the chemical via intraperitoneal (i.p.) injection. No increases in the frequency of micronuclei in erythrocytes were observed (Gocke et al., 1981).

In a sex-linked recessive lethal mutation test in *Drosophila melanogaster*, no effects were observed following oral feeding of the chemical (100 mM) (Gocke et al., 1981).

Formaldehyde will generally be present in products containing the chemical. While some in vivo studies showed positive results for genotoxicity, formaldehyde was not classified as mutagenic in the Priority Existing Chemical (PEC) assessment report (NICNASa). The chemical 2-imidazolidinethione was predominantly non-mutagenic in vitro and in vivo (NICNASb).

Carcinogenicity

There are no data available for the chemical.

While formaldehyde is classified hazardous (Category 2 carcinogenic substance) with the risk phrase 'May cause cancer by inhalation' (T; R49) in HSIS (Safe Work Australia), this applies to inhaled formaldehyde at high concentrations (NICNASa). Formaldehyde is not likely to be volatile from aqueous solutions at the low concentrations present in products containing the chemical. Therefore, there are no carcinogenicity concerns expected relating to the role of the chemical as a formaldehyde releaser in cosmetic products.

The chemical 2-imidazolidinethione caused thyroid tumours in rats, and tumours of the liver, thyroid and pituitary gland in mice. The relevance of thyroid tumours in rodents to humans was considered to be questionable, as the thyroid hormone effects that result in tumourigenesis are more pronounced in rodents compared with humans. Therefore, the hydrolysis product is not expected to cause thyroid tumours in humans at concentrations that do not alter thyroid hormone homeostasis. The tumours observed in the liver and pituitary gland in mice were considered poorly characterised and insufficient to allow for hazard classification (NICNASb).

Reproductive and Developmental Toxicity

There are no data available for the chemical.

Based on the available data for the hydrolysis product, 2-imidazolidinethione (NICNASb), the chemical has the potential to cause developmental toxicity, warranting hazard classification (see **Recommendation** section).

The chemical 2-imidazolidinethione was found to be teratogenic in rats, but not in other tested species including mice, guinea pigs and hamsters. Rats also showed sensitivity to effects on the brain and central nervous system, which are also considered developmental toxicity effects. Most studies also

showed teratogenicity occurred at low doses that did not appear to cause maternal toxicity (NICNASb).

The hydrolysis product, formaldehyde, is not expected to cause reproductive or developmental toxicity (NICNASa).

Other Health Effects

Neurotoxicity

The hydrolysis product, 2-imidazolidinethione, was reported to induce central nervous system (CNS) and brain defects in rat foetuses (NICNASb) (see **Reproductive and Developmental Toxicity** section).

Endocrine Disruption

The hydrolysis product, 2-imidazolidinethione, is a known endocrine disruptor (NICNASb). This is in relation to thyroid hormone activity in animals. The chemical is listed in the European Commission Endocrine Disruptors Priority List under Category I classification (evidence of endocrine disrupting activity in at least one species using intact animals) (EC, 2015).

Risk Characterisation

Critical Health Effects

In general, the critical health hazards relate to the release of formaldehyde and 2-imidazolidinethione from products containing the chemical. In cosmetic products, the chemical is used as a preservative; therefore, the critical health hazard is considered to be skin sensitisation from the release of formaldehyde. There is also a risk of developmental toxicity resulting from the formation of the hydrolysis product, 2-imidazolidinethione.

For workers, health hazards can arise from the presence of formaldehyde gas and 2-imidazolidinethione during formulation of products containing the chemical (NICNASa).

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic products overseas. In these instances, the general public may be exposed to low concentrations of the chemical via the dermal route. The potential risk of sensitisation and developmental toxicity relates to the release of formaldehyde and 2-imidazolidinethione from products containing the chemical, respectively. However, the presence of formaldehyde and 2-imidazolidinethione are not expected to pose unreasonable risk to public health at the low concentration of the chemical used in cosmetic products. The SUSMP also specifies limits for the levels of formaldehyde in cosmetic products (SUSMP, 2016). This will limit the concentrations of the chemical in these products.

The current controls are considered adequate to minimise the risk to public health posed by cosmetic products containing the chemical.

Occupational Risk Characterisation

Where this chemical is handled in a pure or highly concentrated form during formulation, formaldehyde and 2-imidazolidinethione could be present, and pose unreasonable risks to workers unless adequate control measures to minimise dermal and inhalation exposure to these chemicals are implemented.

The chemical should be appropriately classified and labelled, and the appropriate risk management measures for formaldehyde and 2-imidazolidinethione (NICNASa; NICNASb) should be applied in these cases.

The data available support an amendment to the hazard classification in the Hazardous Substances Information System (HSIS) (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

The chemical falls within the scope of the listing of 'formaldehyde' in Schedule 6 and Schedule 10 of the SUSMP. Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)	May damage the unborn child - Cat. 1B (H360D)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal and 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, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

References

Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

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