Additional mercaptoacetate salts: Human health tier II assessment

10 March 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Acetic acid, mercapto-, compound with 2-aminoethanol (1:1)	126-97-6
Acetic acid, mercapto-, monolithium salt	22535-44-0

Preface

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

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

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

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

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to

human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

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

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

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of two chemicals consists of monoethanolamine mercaptoacetate (CAS RN 126-97-6) and lithium mercaptoacetate (CAS RN 22535-44-0), both of which are salts of mercaptoacetic acid (otherwise known as thioglycolic acid; CAS RN 68-11-1). These salts dissociate in solution to form the mercaptoacetate anion and their respective cations (2-aminoethanol or lithium). The 2-aminoethanol and lithium cations have been assessed by NICNAS (NICNAS a; NICNAS b; NICNAS c) and are not considered to significantly contribute to systemic toxicity at the doses where mercaptoacetate toxicity occurs. Based on an assessment of a group of mercaptoacetate salts conducted by NICNAS (NICNAS d), any significant toxicity is expected to result from the presence of the mercaptoacetate anion.

Where data are unavailable for the specific chemicals in this group, relevant supporting information from the related assessments, mentioned above, have been included in this report.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for either of the chemicals.

International

While no specific international use information has been identified for lithium mercaptoacetate, the following international uses have been identified for monoethanolamine mercaptoacetate through the European Union (EU) Registration, Evaluation,

Authorisation and Restriction of Chemicals (REACH) dossiers; the Substances and Preparations in Nordic countries (SPIN) database; and the European Commission Cosmetic Ingredients and Substances (CosIng) database.

Monoethanolamine mercaptoacetate (CAS RN 126-97-6) has reported cosmetic uses in:

- hair perming/hair waving products;
- hair straightening products; and
- depilatory/hair removal creams and liquids.

Restrictions

Australian

The two chemicals in this group are covered by the following listing in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 5 and 6 (SUSMP, 2016).

Schedule 6:

'MERCAPTOACETIC ACID and its salts, but excluding its derivatives, in cosmetic preparations **except**:

a) when included in Schedule 5; or

b) in preparations containing 5 per cent or less of mercaptoacetic acid or its salts (as mercapturic acid).'

Schedule 5:

‘MERCAPTOACETIC ACID and its salts, but excluding its derivatives, in cosmetic preparations containing 20 per cent or less of mercaptoacetic acid or its salts (as mercapturic acid), **except** in preparations containing 5 per cent or less of mercaptoacetic acid or its salts (as mercapturic acid).'

Schedule 6 chemicals are described as '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'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2016).

Schedule 5 chemicals are described as '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.' Schedule 5 chemicals are labelled with 'Caution’ (SUSMP, 2016).

International

The two chemicals are covered under the following listings:

- EU Cosmetic Directive 88/233/EEC Annex III: List of substances which cosmetic ingredients must not contain except subject to the restrictions laid down (reference 2a; thioglycolic acid and its salts) (CosIng); and
- New Zealand: Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down (Galleria).

According to these directives, the maximum allowable concentration of the mercaptoacetates (measured as mercaptoacetic acid) in preparations is limited according to the type of cosmetic product:

- Hair products for waving or straightening:

(a) General use (= 8 %; pH 7 to 9.5);

(b) Professional use (= 11 %; pH 7–9.5);

- Depilatories (= 5 %; pH 7–12.7); and
- Hair rinse-off products (= 2 %; pH 7–9.5).

Labelling requirements are specified for all these uses.

Additionally, monoethanolamine thioglycolate (CAS RN 126-97-6), is covered under the following listing:

- EU Cosmetic Directive 88/233/EEC Annex III: List of substances which cosmetic ingredients must not contain except subject to the restrictions laid down (reference 61; monoalkylamines, monoalkanolamines and their salts) (CosIng)

Under this directive, the maximum use concentration of the chemical is limited by a maximum allowable secondary amine content of 0.5 % in ready for use preparations.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemicals 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

Acute Toxicity

Oral

No specific data are available for lithium mercaptoacetate; however, monoethanolamine mercaptoacetate has high acute toxicity based on results from animal tests following oral exposure. Therefore, the chemicals in this group are expected to have high acute oral toxicity warranting hazard classification (see **Recommendation** section).

In an acute oral toxicity study in Wistar rats, conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 423, the median lethal dose (LD50) for monoethanolamine mercaptoacetate in rats is reported to be 181 mg/kg body weight (bw) in females and 318 mg/kg bw in males (REACH). Observed sub-lethal effects included reduced activity, abnormal gait and posture, and decreased respiratory rate.

In another acute oral toxicity study in Wistar rats, conducted according to OECD TG 401, the LD50 for monoethanolamine mercaptoacetate was reported to be 71 mg/kg bw in females and >200 mg/kg bw (highest dose tested) in males (REACH).

Based on data available for two other mercaptoacetate salts, ammonium mercaptoacetate (CAS RN 5421-46-5) and sodium mercaptoacetate (CAS RN 367-51-1), hazard classification is recommended for both the chemicals in this assessment.

Two oral gavage studies testing the acute oral toxicity of ammonium mercaptoacetate (71 % solution) on Wistar rats established an LD50 of 35–142 mg/kg bw. In these studies, all rats died at the highest dose of either 142 or 200 mg/kg bw, but no mortalities were observed at lower doses of 25 or 35 mg/kg bw. The signs of toxicity included hair loss (alopecia), discolouration of the stomach and intestine, emphysema and black discolouration of the lungs, discolouration and excessive fluid in the bladder and dilation of the bladder (NICNAS d).

Two other oral gavage studies (using methodology similar to OECD TG 423) with sodium mercaptoacetate have been reported. In the first, administering sodium mercaptoacetate (98 % purity) resulted in an LD50 of 50–200 mg/kg bw. In the second, the salt (45.9 % purity) resulted in an LD50 of 92–229 mg/kg bw. Clinical observations in the second test included lung haemorrhage, and discolouration of the liver and kidneys (NICNAS d).

All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as acutely toxic – Category 3, with the hazard statement 'Toxic if swallowed' (H301) in the HCIS (Safe Work Australia).

Dermal

In an acute dermal toxicity study in Sprague Dawley (SD) rats, conducted according to OECD TG 402, the LD50 for monoethanolamine mercaptoacetate was reported to be >2000 mg/kg bw (REACH). Reduced body-weight gain was the only sub-lethal effect observed.

No specific data are available for lithium mercaptoacetate. However, considering the availability of the mercaptoacetate anion for both chemicals in this group when in solution (see **Group justification** section), and based on an assessment of a group of mercaptoacetate salts conducted by NICNAS (NICNAS d), hazard classification is recommended for the two chemicals in this group (see **Recommendation** section).

In guideline studies (OECD TG 402), the dermal LD50 for a related mercaptoacetate salt, sodium mercaptoacetate (CAS RN 367-51-1), was 1000–2000 mg/kg bw. Additionally, dermal absorption of the analogue ^{35}S-labelled sodium mercaptoacetate was tested in male rabbits. When a dose of 330 mg/kg bw was applied to the skin of five rabbits, no mortalities occurred. When a higher dose of 660 mg/kg bw was applied to three rabbits, all of the animals died, i.e. LD50 330–660 mg/kg bw (NICNAS d).

All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as hazardous, as acutely toxic – Category 3, with the hazard statement 'Toxic in contact with skin' (H311) in the HCIS (Safe Work Australia).

Inhalation

No data are available for the two chemicals in this group. However, based on an assessment conducted by NICNAS (NICNAS d), and available data for mercaptoacetic acid (CAS RN 68-11-1) (LC50 < 2 mg/L/4-h), a hazard classification for acute inhalational toxicity is recommended for both chemicals in this group (see **Recommendation** section).

Free mercaptoacetic acid is classified as acutely toxic – Category 2, with the hazard statement 'Fatal if inhaled' (H330) in the HCIS (Safe Work Australia).

The inhalation median lethal concentration (LC50) (4 hours) for mercaptoacetic acid was established as 1094 mg/m^3 (1.09 mg/L/4-h) in female rats and 1981 mg/m^3 (1.98 mg/L/4-h) in male rats, in a test with the chemical as a vapour, according to OECD TG 403 (NICNAS d). Clinical signs of toxicity included irregular and laboured breathing, irritation of the respiratory tract, ruffled coat, reduced mobility, leg tremors and paralysis.

Another inhalation toxicity study with seven hours exposure in rats resulted in no mortalities at a concentration of 2.4 mg/L (600 ppm) (NICNAS d).

All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as acutely toxic – Category 2, with the hazard statement 'Fatal if inhaled' (H330) in the HCIS (Safe Work Australia).

Corrosion / Irritation

Respiratory Irritation

While no specific data are available for the chemicals in this group, based on the limited data available for some salts of mercaptoacetate, hazard classification for respiratory tract irritation is recommended for both chemicals (see R**ecommendation** section).

Ammonium mercaptoacetate (CAS RN. 5421-46-5) and sodium mercaptoacetate (CAS RN 367-51-1) have been reported to cause respiratory tract irritation in rats exposed to a high concentration of a vapour/aerosol mixture, but not when exposed to saturated vapour only. However, no further details are given on these studies (NICNAS d).

Irritation of the respiratory tract was observed in rats exposed to the vapours of mercaptoacetic acid (CAS RN 68-11-1). However, mercaptoacetic acid is of limited value as an analogue due to its corrosive properties.

All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as Category 3 single exposure specific target organ toxins, with the hazard statement 'May cause respiratory irritation' (H335) in the HCIS (Safe Work Australia).

Skin Irritation

The available data for methanolamine mercaptoacetate indicate that the chemical is not a potential skin irritant. This is likely due to the monoethanolamine cation being acidic, compensating for the basicity of the mercaptoacetic anion. In regards to lithium mercaptoacetate, the lithium cation is non-acidic, therefore, the skin irritation results for monoethanolamine mercaptoacetate cannot be read across to lithium mercaptoacetate. No specific data are available for lithium mercaptoacetate. Based on the data available for other salts of mercaptoacetate, hazard classification for skin irritation is recommended for lithium mercaptoacetate, but not for monoethanolamine mercaptoacetate (see **Recommendation** section).

In a skin irritation study, conducted according to OECD TG 404, 0.5 mL of monoethanolamine mercaptoacetate (83.4 % concentration) was applied to the clipped skin of three New Zealand White (NZW) rabbits, for an exposure period of four hours under semiocclusive conditions. Skin reactions were measured at 24, 48 ad 72 hours after exposure. The only effect observed was slight erythema (grade 1) in all animals at 24 hours, which persisted in one animal for up to four days and another animal for up to six days after exposure. Mean scores for erythema were $\leq$1 in all three animals. No effects of oedema were observed, and erythema was reported to be reversed in all animals by day six. However, dryness of the skin was still observed in one animal at the end of six-day study observation period.

Most reliable data on skin irritation are for ammonium mercaptoacetate (CAS RN 5421-46-5), but data are also available for calcium di(mercaptoacetate), potassium and sodium mercaptoacetate (CAS RN. 814-71-1, 34452-51-2 and 367-51-1, respectively) (NICNAS d).

A study conducted according to OECD TG 404 found that ammonium mercaptoacetate (71 % solution) was only slightly irritating to rabbit skin after a four hour exposure (mean erythema and oedema scores of 0.66 and 0, respectively). However, a second study conducted with exposure to ammonium mercaptoacetate for 24 hours (according to a national guideline 16 CFR 1500.41) found it to be highly irritating (erythema and oedemas scores were 3 and 2.33 respectively, on intact skin after 72 hours) (NICNAS d).

Calcium di(mercaptoacetate) (99.8 % purity) and sodium mercaptoacetate (98 %) were found to be moderately irritating to rabbit skin. Potassium mercaptoacetate (43 %) was found to be mildly irritating to rabbit skin. Erythema and oedema scores are not available (NICNAS d).

All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as Category 2 skin irritants, with the hazard statement 'Causes skin irritation' (H315) in the HCIS (Safe Work Australia).

Eye Irritation

Data available for methanolamine mercaptoacetate indicate that the chemical is not a potential eye irritant. This is likely due to the monoethanolamine cation being acidic, compensating for the basicity of the mercaptoacetic anion. In regards to lithium mercaptoacetate, the lithium cation is non-acidic, therefore, the eye irritation results for monoethanolamine mercaptoacetate cannot be read across to lithium mercaptoacetate. No specific data are available for lithium mercaptoacetate. Based on the data available for ammonium mercaptoacetate (CAS RN 5421-46-5) and calcium di(mercaptoacetate) (CAS RN 814-71-1), hazard classification for eye irritation is recommended for lithium mercaptoacetate only (see **Recommendation** section).

In an eye irritation study, conducted according to OECD TG 405, 0.1 mL of monoethanolamine mercaptoacetate (83.4 % in water) was instilled into one eye of three NZW rabbits. Eye irritation reactions were measured at one, 24, 48 and 72 hours after exposure. Mild conjunctival reactions, including chemosis (grade 1), redness of the conjunctivae (grade 1 or 2) and a clear discharge from the eyes, were observed in all animals on days one and two. No other ocular reactions were observed. Mean scores for all eye irritation effects were <1 in all three animals.

A study conducted according to OECD TG 405 on three rabbits with ammonium mercaptoacetate (71 % solution), gave mean (24, 28 and 72 h) eye irritation scores of 0, 0, 0.9 and 0.7 for corneal irritation, iritis, redness of the conjunctivae and chemosis, respectively. All the effects were fully reversible within 72 hours (NICNAS d). In a similar test (in accordance with the US CFR 1500.42 guideline), the mean eye irritation scores were 0, 0 and 2.6 for cornea, iritis and redness of the conjunctivae, respectively. Discharge was also noted in 3/6 animals. In a literature review of eye irritation studies with ammonium mercaptoacetate at likely concentrations in consumer products (5.0–17.5 % solutions), effects ranged from no irritation to moderate irritation. These studies imply that the ammonium salt is slightly irritating to the eye (NICNAS d).

Calcium di(mercaptoacetate) (CAS RN 814-71-1) in its pure powder form was found to be an extreme eye irritant, while a 10 % solution only produced very mild irritation. No data are available on the eye irritant scores (NICNAS d).

All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as Category 2A eye irritants, with the hazard statement 'Causes serious eye irritation' (H319) in the HCIS (Safe Work Australia).

Observation in humans

While no data are available for the chemicals in this group, a number of human skin irritation and sensitisation (repeated insult patch testing on the skin of the arm or back) studies have been conducted with another mercaptoacetate salt, ammonium mercaptoacetate (CAS No. 5421-46-5), at concentrations from 14.4–18 % in solution, and one study with a hair waving/perming product containing ammonium mercaptoacetate at 4.4 % (NICNAS d).

A number of people had to be withdrawn from these studies due to skin reactions within the first few applications in the induction phase. The majority of reactions were slight with just noticeable redness or erythema (which scored > 0 or < 1 out of 4). However, there were usually also a number of cases of mild erythema (score 1/4) or moderate erythema (score 2/4) (NICNAS d).

When patients with asthma were exposed to mists of ammonium mercaptoacetate (71 %) at various dilutions (1:10 to 1:100000), 13/14 exhibited signs of respiratory irritation (NICNAS d). The irritation of the throat (pharyngeal irritation) lasted from 0.5–2 hours. Eight non-asthmatic patients (control group who had not suffered previously from hayfever or eczema) exposed to the same scenarios did not suffer from respiratory irritation.

Sensitisation

Skin Sensitisation

No specific data are available for lithium mercaptoacetate; however, monoethanolamine mercaptoacetate was demonstrated to be a skin sensitiser in one animal test. All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as hazardous, as Category 1 skin sensitisers, with the hazard statement 'May cause an allergic skin reaction' (H317) in the HCIS (Safe Work Australia). Therefore, hazard classification is recommended for both the chemicals in this assessment (see **Recommendation** section).

In a skin sensitisation test (mouse local lymph node assay (LLNA)), conducted according to OECD TG 429, monoethanolamine mercaptoacetate was tested for skin sensitisation reactions at concentrations of 0.25, 0.5, 1, 2.5, 5, 10 or 25 % w/v in propylene glycol (REACH). The chemical was reported to be a skin sensitiser based on a stimulation index > 3 being produced at application concentrations of 25 %. The EC3 (concentration required to produce a three-fold increase in the proliferation of lymph node cells) value was calculated to be 5.89 %.

Other mercaptoacetate salts have also demonstrated to be skin sensitisers. LLNA conducted in mice (OECD TG 429) reported positive results for skin sensitisation for the following salts (NICNAS d):

- ammonium mercaptoacetate (CAS RN 5421-46-5; 70 % solution): EC3 of 0.65 %;
- calcium di(mercaptoacetate) (CAS RN 814-71-1; original purity not reported): EC3 not calculated, sensitisation at 30 %;
- potassium mercaptoacetate (CAS RN 34452-51-2; 43 % solution): EC3 not calculated, sensitisation at 25 %; and
- sodium mercaptoacetate (CAS RN 367-51-1; 98 % purity): EC3 of 6 %.

Repeated Dose Toxicity

Oral

While no specific data are available for these two chemicals, based on the data available for another mercaptoacetate salt, sodium mercaptoacetate (CAS RN 367-51-1), the chemicals in this group may cause serious damage to health from repeated oral exposure. Hazard classification, category 2 (H373), is warranted under GHS to indicate specific target organ toxicity from repeated oral exposure.

A 90-day oral gavage repeated dose toxicity study (OECD TG 408) exposed rats to sodium mercaptoacetate daily (7 mg/kg bw/d or 20 mg/kg bw/day, n = 10/sex/dose; 60 mg/kg bw/day, n = 16/sex/dose). The no observed adverse effect level (NOAEL) was 20 mg/kg bw/day based on mortalities at 60 mg/kg bw/day (1/16 males died, 1/16 females had to be euthanised). The liver of each of these animals was discoloured. Other signs of toxicity at the highest dose included higher mean absolute and relative liver weights (accompanied by histopathological changes, particularly microscopic vacuolation in the area near the portal vein of the liver), microscopic vacuolation of the heart and kidneys, excessive salivation and piloerection (raised fur) (NICNAS d). In blood plasma, there were dose-related increases in the concentration of fatty acids (36–178 % increase), urea (60–70 % increase) and lactate (80–107 % increase), and dose-related decreases in both glucose (17–32 % decrease) and β-hydroxybutyrate (78–80 % decrease). Changes were significant in blood plasma at 60 mg/kg bw/day in male rats and from 20 mg/kg bw/day in female rats. These observations of blood biochemical changes, in conjunction with microscopic histopathological changes in the liver, are consistent with a mode of toxic action where β-oxidation of fatty acids is inhibited, leading to higher concentrations of triglycerides in the liver (NICNAS d).

In an oral gavage study, rats were dosed with sodium mercaptoacetate during the 10-week premating phase of a reproductive toxicity study. No effects were seen for male or female adult rats at doses of 10 and 20 mg/kg bw/day (n = 25/sex/dose). The lowest observed effect level (LOEL) was 40 mg/kg bw/day based on microscopic observation of vacuolation in the liver in 2/25 males and 6/25 females. Biochemical observations showed significant decreases in urea in males and decreases in fatty acids in females at this dose. As the reproductive test continued, 4/6 (pregnant) females with the microvacuolation of the liver were found dead and 2/6 had to be euthanised (NICNAS d).

In a similar oral gavage test (premating phase of a reproductive toxicity test), rats were administered sodium mercaptoacetate at doses of 20, 40 or 80 mg/kg bw/day (14 animals/sex/dose). A NOAEL of 40 mg/kg bw/d and a lowest observed adverse effect level (LOAEL) of 80 mg/kg bw/d were established based on mortalities at 80 mg/kg bw/d (1/14 female, 2/14 male) in the 10-week premating period (NICNAS d).

All chemicals in the group of mercaptoacetate salts assessed by NICNAS (NICNAS d) are classified as Category 2 repeated exposure specific target organ toxins, with the hazard statement 'May cause damage to organs through prolonged or repeated exposure' (H373) in the HCIS (Safe Work Australia).

Dermal

While no specific data are available for the two chemicals in this group, based on the data available for sodium mercaptoacetate (CAS RN 367-51-1), neither chemical is considered to cause serious damage to health from repeated dermal exposure.

In two, 13-week studies (similar to OECD TG 411), sodium mercaptoacetate was applied to the skin of rats (Fischer) and mice (B6C3F1) for five days/week (five dose levels, 10 animals/sex/dose). NOAELs for systemic toxicity were established as 180 mg/kg bw/day and 360 mg/kg bw/day for rats and mice, respectively, which was the highest dose tested in each case. No mortalities occurred. In rats, no weight or histopathological changes in major organs were seen. Changes were only observed in a few animals at the highest dose in mice. Local effects were observed at the site of application. Skin irritation was noted in all rats at all treatment levels, including at the lowest dose of 11.25 mg/kg bw/day. Skin thickening and ulceration were also observed, but major effects were only seen at higher doses. In mice, microscopic changes at the treatment site resulted in hyperplasia at doses of 45 mg/kg bw/day (NICNAS d).

Inhalation

No data are available for the two chemicals in this group, or for other relevant mercaptoacetate salts or mercaptoacetic acid.

Genotoxicity

While no specific data are available for the two chemicals in this group, based on the weight of evidence from available, well-conducted in vitro and in vivo genotoxicity studies using ammonium mercaptoacetate (CAS RN 5421-46-5), sodium mercaptoacetate (CAS RN 367-51-1) and mercaptoacetic acid (CAS RN. 68-11-1), the chemicals in this group are not considered genotoxic.

Negative results were reported for ammonium mercaptoacetate in a number of in vitro genotoxicity tests (bacterial reverse mutation assay—Ames test; and mammalian cell gene mutation assay with mouse lymphoma cells). No in vivo tests are reported for this salt (NICNAS d).

Negative results were reported for sodium mercaptoacetate in an in vitro genotoxicity test (Ames test) and for some in vivo genotoxicity tests (chromosome aberration study using a micronucleus assay on mouse bone marrow at doses up to and including 250 mg/kg bw (OEC TG 474); and sex-linked recessive lethal mutation test with Drosophila melanogaster) (NICNAS d).

In a micronucleus assay in mouse bone marrow (similar to OECD TG 474), following administration of the chemical at a single dose, negative results were reported at all doses up to and including 360 mg/kg bw, in males and at doses between 22.5–280 mg/kg bw, for females. However, positive results were reported for females at the highest dose of 360 mg/kg bw (NICNAS d).

Negative results were reported for the analogue mercaptoacetic acid in an in vitro mammalian chromosome aberration test (OECD TG 473) with human lymphocytes. Additionally, negative results were reported in an in vivo chromosome aberration study at single doses up to and including 1000 mg/kg bw for males and 500 mg/kg bw for females (micronucleus assay on mouse bone marrow; NICNAS d).

Carcinogenicity

No specific data are available for the two chemicals in this group, and only limited data are available for one other mercaptoacetate salt (sodium mercaptoacetate—CAS RN 367-51-1). Therefore, it is not possible to make a conclusion on the carcinogenic potential of the chemicals in this group.

In a non-guideline study, sodium mercaptoacetate was non-carcinogenic in mice when dermally administered in solution at 1 % or 2 % in acetone, twice weekly from seven weeks of age until their death. The average lifespan and the incidence of tumours in the mice were similar for control and treated groups (50 mice/sex/dose) (NICNAS d).

Reproductive and Developmental Toxicity

While no specific data are available for the two chemicals in this group, based on the data available for sodium mercaptoacetate (CAS RN 367-51-1) and ammonium mercaptoacetate (CAS RN 5421-46-5), the chemicals in this group are not considered to have reproductive or developmental toxicity.

A two-generation reproductive study (OECD TG 416) exposed rats to sodium mercaptoacetate via oral gavage doses of 10, 20 or 40 mg/kg bw/day (25 rats/sex/dose). Doses were given daily to the parental (F0) males and females throughout a 10-week premating period, the mating period (up to three weeks), gestation and lactation (up to 21 days). The F0 generation was sacrificed once the litters had weaned. At 22 days of age, eight male and eight female F1 generation animals were selected for further study and doses applied as above. They were mated after 9–11 weeks. The no observed effect level (NOEL) for F0 parental toxicity was established as 20 mg/kg bw/d, based on microscopic vacuolation of the liver in the region of the portal vein in 2/25 male and 6/25 female rats at the highest dose of 40 mg/kg bw/day. Four of these females died. Fatty acid concentrations in the blood were also significantly lower in this highest dose group for females. It is stated that 'sodium thioglycolate is known to induce fatty liver via an inhibition of the β-oxidation of fatty acids' (NICNAS d). The NOEL for fertility and gestation was 20 mg/kg bw/day in females. The NOEL for male fertility and mating was 40 mg/kg bw/day (no effects at the highest dose). The NOEL for developmental toxicity was 20 mg/kg bw/day. At the higher dose, the pregnant female rats did not nest or nurse properly, which may have caused pups to die (NICNAS d).

Another reproductive study is available using sodium mercaptoacetate (according to OECD TG 421; single generation) in rats dosed at 20, 40 and 80 mg/kg bw/day. The NOEL for parental toxicity (F0) was 20 mg/kg bw/day based on deaths of pregnant rats in the gestation phase, due to late delivery at 40 mg/kg bw/day and above. At the highest dose 2/12 males died during the prebreeding phase; and 7/12 females died or had to be sacrificed early in the prebreeding, late gestation or early lactation stages. The NOEL for pups (F1 generation) was 40 mg/kg bw/day, based on the death of an entire litter of pups at 80 mg/kg bw/day, which may or may not have been related to adverse maternal effects (NICNAS d).

In a developmental toxicity study (OECD TG 414), ammonium mercaptoacetate was administered to pregnant rats at concentrations of 3, 15 or 75 mg/kg bw/day (gestation days 6–15). The NOAEL for maternal toxicity was 15 mg/kg bw/day based on two mortalities on gestation day 20 at the highest dose. The NOAEL for developmental toxicity was 75 mg/kg bw/day based on lack of teratogenic effects in pups, even at maternal toxic doses (NICNAS d).

Sodium mercaptoacetate was administered to the skin of pregnant rats (6 hours/day, gestation days 6–19 at doses of 50, 100 or 200 mg/kg bw/day) or rabbits (6 hours/day; gestation days 6–29 at doses of 10, 15, 25 or 65 mg/kg bw/day). In rabbits, the NOAEL for maternal toxicity was 65 mg/kg bw/day (no systemic toxicity at any dose tested; skin irritant effects at all doses at the application site). In rats, a NOAEL for maternal toxicity could not be established due to local effects observed at the lowest dose. At 200 mg/kg bw/day there was one mortality and a reduction in the mean body weight gain. At all doses there were changes in feeding habits, water intake and local irritant effects at the application site. A LOAEL for maternal toxicity in rats was established as 50 mg/kg bw/day. The NOAEL for developmental toxicity was > 65 mg/kg bw/day in rabbits (no teratogenic effects at highest dose) and 100 mg/kg bw/day in rats based on lower body weight of foetuses (NICNAS d).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation of the two mercaptoacetate salts in this group include acute toxicity; skin, eye and respiratory tract irritation; skin sensitisation; and harmful effects following repeated oral exposure. The monoethanolamine salt appears less irritating than other mercaptoacetate salts.

Public Risk Characterisation

Although use in cosmetic/domestic products in Australia is not known, the chemicals are reported to be used in cosmetic products overseas.

Both chemicals are currently listed on Schedules 5 and 6 of the SUSMP (refer to **Restrictions**: **Australia** section) for cosmetic preparations containing >5 % (calculated as mercapturic acid). A number of warning statements, first aid instructions and safety directions, relating to use of the either of the chemicals in cosmetic or domestic products at any concentration, also apply.

The current controls are considered adequate to minimise the risk to public health posed by domestic and cosmetic products containing the chemicals; therefore, the chemicals are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure of workers to these chemicals 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. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemicals in this group may pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation exposure to the chemical are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU), e.g. employer, at a workplace, has adequate information to determine appropriate controls.

Based on the available data, all chemicals in this group are recommended to be classified as hazardous.

NICNAS Recommendation

Assessment of these chemicals 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

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2016).

Work Health and Safety

The chemicals are 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. The skin and eye irritation classifications listed in the table below do not apply to the monoethanolamine salt.

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) Harmful in contact with skin - Cat. 4 (H312) Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)

[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 or 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.

References

European Commission Cosmetic Ingredients and Substances (CosIng) database. Accessed November 2016 at **http://ec.europa.eu/growth/tools-databases/cosing/**

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at **http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html**

NICNAS a. National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II assessment for Ethanol, 2-amino- (CAS RN 141-43-5). Australian Government Department of Health and Ageing. Available at **http://www.nicnas.gov.au/**

NICNAS b. NICNAS IMAP Human Health Tier II assessment for Lithium hydroxide. Australian Government Department of Health and Ageing. Available at **http://www.nicnas.gov.au/**

NICNAS c. NICNAS IMAP Human Health Tier II assessment for Carbonic acid, dilithium salt (CAS RN 554-13-2). Australian Government Department of Health and Ageing. Available at **http://www.nicnas.gov.au/**

NICNAS d. NICNAS IMAP Human Health Tier II assessment for Mercaptoacetate salts. Australian Government Department of Health and Ageing. Available at **http://www.nicnas.gov.au/**

REACH. REACH Dossier for (2-hydroxyethyl)ammonium mercaptoacetate (CAS RN 126-97-6). Accessed November 2016 at **https://echa.europa.eu/information-on-chemicals/registered-substances**

Safe Work Australia. Hazardous Chemicals Information System (HCIS). Accessed February 2017 at **http://hcis.safeworkaustralia.gov.au/HazardousChemical**

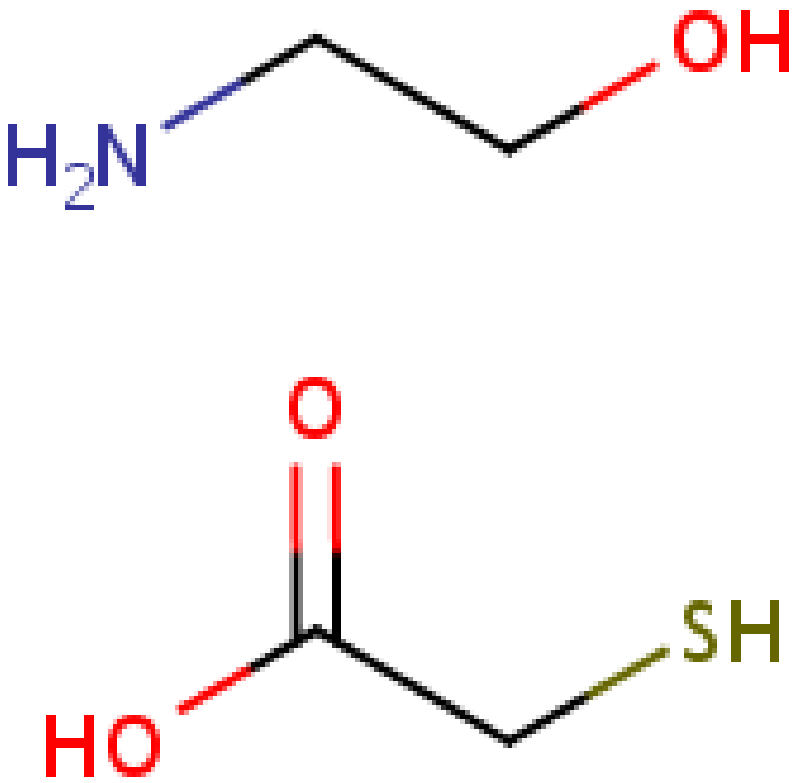
Substances in Preparations in Nordic Countries (SPIN) Database. Accessed November 2016 at **http://195.215.202.233/DotNetNuke/default.aspx**

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2016. Available at **https://www.tga.gov.au/publication/poisons-standard-susmp**

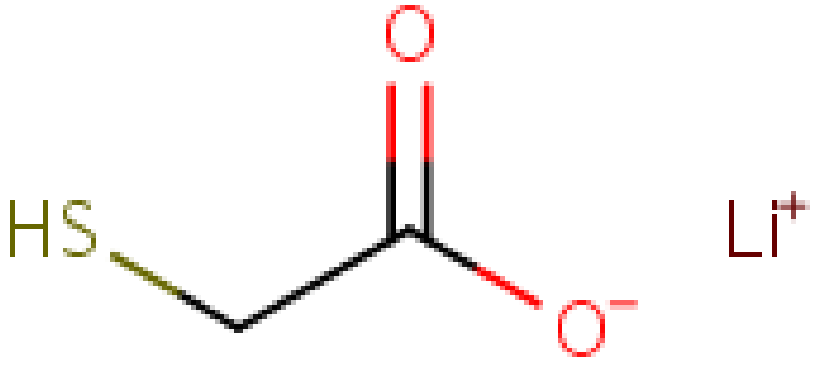
Last Update 10 March 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Acetic acid, mercapto-, compound with 2-aminoethanol (1:1)** monoethanolamine mercaptoacetate monoethanolamine thioglycolate

	(2-hydroxyethyl) ammonium mercaptoacetate
CAS Number	126-97-6
Structural Formula	
Molecular Formula	C2H7NO.C2H4O2S
Molecular Weight	153.20

Chemical Name in the Inventory and Synonyms	**Acetic acid, mercapto-, monolithium salt** lithium mercaptoacetate lithium thioglycolate
CAS Number	22535-44-0
Structural Formula	

	
Molecular Formula	C2H4O2S.Li
Molecular Weight	98.05

Share this page