Soluble manganese compounds: Human health tier II assessment

29 June 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Ethanedioic acid, manganese(2+) salt (1:1)	640-67-5
Acetic acid, manganese(2+) salt	638-38-0
Sulfuric acid, manganese(2+) salt (1:1)	7785-87-7
Nitric acid, manganese(2+) salt, hexahydrate	17141-63-8
Acetic acid, manganese(2+) salt, tetrahydrate	6156-78-1
D-Gluconic acid, manganese salt (2:1)	6485-39-8
Manganese chloride (MnCl2)	7773-01-5
Manganese bromide (MnBr2), tetrahydrate	10031-20-6
Sulfuric acid, manganese(2+) salt (1:1), monohydrate	10034-96-5
Phosphinic acid, manganese(2+) salt (2:1)	10043-84-2
Sulfuric acid, manganese(2+) salt (1:1), tetrahydrate	10101-68-5
Nitric acid, manganese(2+) salt	10377-66-9
Manganese chloride (MnCl2), tetrahydrate	13446-34-9
Phosphoric acid, manganese(2+) salt (2:1)	18718-07-5
Propanoic acid, manganese(2+) salt	21129-18-0
Manganese, bis[2-(hydroxy-.kappa.O)propanoato-.kappa.O]-	74051-88-0
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, manganese(2+) sodium salt	85169-06-8

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**

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are assessed together as they are all soluble in water and release manganese (II) ions following systemic absorption. Any hazard arising from these chemicals is therefore related to the bioavailability of manganese (II) ions. The anions in these chemicals are expected to have similar, and minimal, systemic toxicological properties.

Import, Manufacture and Use

Australian

Manganese sulfate is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 1000–9999 tonnes.

The following Australian uses for chemicals in this group were identified through the HVICL, National Pollutant Inventory (NPI), Therapeutic Goods Administration (TGA) and Food Standards Australia New Zealand (FSANZ).

Manganese chloride and manganese sulfate have reported domestic uses in paints (as a drying agent), glazes and varnishes.

Manganese acetate, manganese chloride and manganese sulfate have reported commercial uses in:

- soil fertilisers; and
- dry-cell batteries.

Manganese acetate, manganese chloride, manganese nitrate and manganese sulfate have reported site-limited uses in:

- manufacturing other chemicals;
- textile dyeing;
- purifying natural gas; and
- ceramics and ore flotation.

Manganese chloride, manganese gluconate and manganese sulfate (including hydrated forms) have reported non-industrial uses:

- as nutritional supplements;
- in fungicides;
- in medicines (TGA, 2007);
- as processing aids (*Australia New Zealand Food Standards Code*, Standard 1.3.3);
- as a nutrient or trace mineral in animal feeds; and
- in food packaging.

Although no specific Australian use, importation, or manufacturing information has been identified for the chemicals manganese acetate tetrahydrate, manganese chloride tetrahydrate and manganese nitrate hexahydrate, for regulatory purposes, hydrated forms of chemicals are considered identical to the anhydrous form and so the uses identified above for the anhydrous forms of these chemicals may also apply.

No specific Australian use, importation, or manufacturing information has been identified for the chemicals manganese bromide tetrahydrate, manganese dipropionate, manganese hypophosphite, manganese lactate, manganese oxalate, manganese phosphate and manganese sodium citrate.

Manganese has reported non-industrial use as a substance (a component) that may be used in listed medicines in conjunction with an approved source. The approved sources are manganese compounds (TGA, 2007).

As a nutrient, no estimated average requirement (EAR) or upper level of intake (UL) has been established for manganese due to a lack of suitable data. An adequate intake (AI) of 0.6–5.5 mg manganese/day has been estimated based on median intakes from different age–gender groups reported in the 23rd Australian Total Diet Study. Specifically, for children 7–12 months of age, the AI is 0.6 mg/day; for children 2–18 years of age, the AI is 2.0–3.5 mg/day; and for adults over 19 years of age the AI is 5.0–5.5 mg/day (FSANZ, 2011).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation and Authorization and Restrictions of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR) and ChemView; and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB) and Household Products Database.

Manganese chloride, manganese gluconate, manganese sulfate and manganese sulfate monohydrate have reported cosmetic use as skin conditioning agents (CosIng; no concentration limits indicated).

Manganese acetate (including hydrated forms), manganese chloride, manganese dipropionate, manganese oxalate, manganese sulfate and manganese sulfate monohydrate have reported domestic uses including:

- as paint and varnish driers; and
- in cleaning or disinfecting products.

Manganese acetate (including hydrated forms), manganese chloride, manganese nitrate (including hydrated forms) and manganese sulfate (including hydrated forms) have reported commercial uses:

- as ingredients in plant and lawn soil fertilisers; and
- in dry-cell batteries.

Manganese acetate, manganese chloride, manganese nitrate and manganese sulfate (all including their hydrated forms), as well as manganese phosphate and manganese oxalate have reported site-limited uses including in:

- alloy manufacture;
- metal surface treatment products;
- plastics manufacturing;
- dyeing (textiles and porcelain);
- leather manufacturing and tanning;
- glass making; and
- purifying natural gas.

Manganese chloride and manganese sulfate (both including their hydrated forms), as well as manganese gluconate have reported non-industrial uses including as:

- nutrients or trace minerals in animal feeds;

- water treatment agents;
- intermediates in producing fungicides and pharmaceuticals; and
- an ingredient in whitening toothpaste (gluconate compound only).

No specific international use, importation, or manufacturing information has been identified for the chemicals manganese bromide tetrahydrate, manganese hypophosphite, manganese lactate and manganese sodium citrate.

Restrictions

Australian

No known restrictions associated with industrial use have been identified for the chemicals.

Manganese bromide tetrahydrate has a maximum residue limit (MRL) of 20–400 mg/kg in particular foods, according to the *Australia New Zealand Food Standards Code* (Standard 1.4.2) under the levels specified for inorganic bromide (bromide ion).

International

No known international restrictions associated with industrial use have been identified for the chemicals in this group.

Manganese compounds are limited to 60 mg/kg (as Mn) as polymerisation aids for plastics intended to come into contact with food (Council of Europe Resolution AP (92) 2).

Manganese chloride and manganese hypophosphite are listed as additives or polymer production aids for plastic materials and articles intended to come into contact with food, with a migration limit restriction of 0.6 mg Mn/kg food or food simulant (Europe Commission Regulation No 10/2011).

Existing Worker Health and Safety Controls

Hazard Classification

Manganese sulfate (CAS No. 7785-87-7) is classified as hazardous, with the following hazard category and hazard statement for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Specific target organ toxicity (repeated exposure) – category 2; H373 (May cause damage to organs through prolonged or repeated exposure)

The routes of exposure are not specified, but are considered to be oral and inhalation.

The other chemicals are not listed on the HCIS (Safe Work Australia).

Exposure Standards

Australian

Manganese, dust and compounds (as Mn), has an exposure standard of 1 mg/m³ time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica) for manganese acetate (including hydrated forms), manganese dipropionate, manganese gluconate, manganese lactate, manganese oxalate and manganese sodium citrate:

- TWA of 0.1–5 mg/m³ in different countries such as Bulgaria, Canada (Quebec, Yukon), Chile, Egypt, Greece, Ireland, Japan, Singapore, South Africa, Switzerland and the United States of America (USA) (California, Hawaii, Minnesota, Vermont); and
- a short term exposure limit (STEL) of 3 mg/m³ in different countries such as Chile, Egypt, South Africa and the USA (Hawaii, Minnesota, Vermont).

The following exposure standards are identified (Galleria Chemica) for manganese bromide, manganese chloride, manganese nitrate, manganese sulfate (all including their hydrated forms), as well as manganese phosphate and manganese hypophosphite:

- TWA of 0.02–5 mg/m³ in different countries such as Bulgaria, Canada (Alberta, British Columbia, Quebec, Saskatchewan, Yukon), Chile, China, Denmark, Egypt, France, Germany, Greece, Hungary, Iceland, Indonesia, Ireland, Japan, Latvia, Malaysia, Mexico, Norway, Poland, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, the United Kingdom, and the USA (California, Hawaii, Minnesota, Tennessee, Vermont, Washington); and
- a STEL of 0.6–20 mg/m³ in different countries such as Bulgaria, Canada (Saskatchewan), Egypt, Hungary and the USA (Minnesota, Vermont, Washington).

Based on Western diets, a tolerable UL of 11 mg/day has been set for manganese (IOM, 2002).

Health Hazard Information

Soluble manganese compounds contain manganese (II) ions, a highly bioavailable form of manganese. The chemicals are considered appropriate analogues for each other since it is expected that the manganese cations will be responsible for the toxicity of these chemicals. The anions have minimal systemic toxicity. Therefore, when data for any of the chemicals in this group are lacking, available data from other chemicals in the group are considered appropriate to use (read-across) in assessing potential risks associated with the use of these chemicals.

The IMAP report on manganese (NICNAS) provides human epidemiological data to complement this report.

Toxicokinetics

Manganese is a trace dietary nutrient, with an important role in the biological processes of carbohydrate, cholesterol and amino acid metabolism, as well as bone formation (SCOEL, 2011). It is maintained at relatively stable levels in human tissues via regulated absorption by the gut and excretion by hepatobiliary transport (SCOEL, 2011; ATSDR, 2012). The chemical can be absorbed following inhalation and oral exposure, but it does not readily penetrate the skin following dermal exposure (EPA, 2004).

Following oral or inhalation exposure, the bioavailability of manganese (II) ions is dependent on the solubility of these chemicals. Water solubility permits greater lung absorption, and both water and acid solubility permit absorption from the gastrointestinal tract. Mucociliary clearance from the respiratory tract can generate oral exposure following inhalation, as particles can be returned from the lungs to the back of the throat and swallowed (ATSDR, 2012).

Acute Toxicity

Oral

Based on the available data, the chemicals in this group are considered to have moderate oral acute toxicity in animals, warranting hazard classification (see **Recommendation** section).

The following median lethal dose (LD50) values were available (ATSDR, 2012; REACHa; REACHb; REACHc; REACHd; REACHe; REACHf):

- 1082 mg/kg bw in Wistar rats for manganese acetate;
- 3730 mg/kg bw in male Carworth-Wistar rats for manganese acetate tetrahydrate;
- 236 mg Mn/kg bw in female rats (strain not specified) for manganese chloride;
- 331 mg/kg bw in female Wistar rats for manganese chloride;
- 342, 351 and 412 mg/kg bw in male Wistar, Albino and Sprague-Dawley (SD) rats, respectively, for manganese chloride;
- 619 and 850 mg/kg bw in 54- and 18-week old, respectively, female albino rats for manganese chloride;
- 804–1860 mg/kg bw in 2- to 6-week old albino rats for manganese chloride;
- 1470 mg/kg bw in Wistar rats for manganese chloride;
- 1484 mg/kg bw in male SD rats for manganese chloride tetrahydrate;
- 1330 mg/kg bw in male Swiss mice for manganese chloride;
- 782 mg/kg bw in male Swiss albino rats, 2150 mg/kg bw in Wistar rats and 2330 mg/kg bw in male Swiss mice for manganese sulfate;
- between 300 and 2000 mg/kg bw in female Wistar rats for manganese nitrate (adjusted to the anhydrous equivalent);
- >1597 mg/kg bw in female Wistar rats for manganese oxalate (adjusted to the anhydrous equivalent); and
- 2000 mg/kg bw in female Wistar rats for manganese phosphate.

Dermal

Only limited data are available and only for one chemical in this group.

The dermal LD50 for manganese oxalate was reported to be >2000 mg/kg bw in Wistar rats exposed (semi-occlusive) to the chemical in arachis oil vehicle for 24 hours (REACHe).

Inhalation

Only limited data are available and only for one chemical in this group.

The median lethal concentration (LC50) for manganese sulfate was reported to be >4.45 mg/L in Wistar rats exposed (nose only) to the chemical dust for four hours (REACHc).

Corrosion / Irritation

Corrosivity

Based on the available data for manganese nitrate, this chemical is considered to be corrosive, warranting hazard classification (see **Recommendation** section).

In an acute dermal irritation / corrosion study (according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 404), New Zealand White (NZW) rabbits (n = 3 males) were exposed (semi-occlusive) to 500 mg of the chemical on shaved skin for four hours, and observed for up to 14 days. In one rabbit, haemorrhage was observed immediately at the test site, there was skin blanching surrounding this lesion at the 1 hour and 24 hour observation time-points, and a hardened scab formed after 48 hours. Oedema was also observed in this animal immediately. These effects were not reversible by 14 days. Discolouration and desquamation were reported in the other two rabbits, with effects reversed by 14 days (REACHd).

Skin Irritation

Based on the data available for manganese chloride, manganese sulfate, manganese oxalate and manganese phosphate, the chemicals (excluding manganese nitrate; see **Corrosivity** section above) are not considered to be irritating to skin.

In a study conducted according to OECD TG 404, NZW rabbits (n = 3 males) were exposed to 0.5 g of manganese chloride (mixed with 0.5 mL of distilled water to create a paste) on a shaved site with semi-occlusive coverage for four hours. One rabbit showed erythema (score = 2) and oedema (score = 1) at 24 hours post-exposure, both of which were reversed by seven days post-exposure (REACHb).

In an in vitro skin irritation test (according to EU method B.46), reconstituted human epidermis (EPISKIN ™ model) was uniformly exposed to flakes (10 ± 2 mg) of manganese chloride for 15 minutes. No irritation was observed at 42 hours post exposure, measured by the mean viability of the reconstituted human epidermis, which was not significantly changed by chemical exposure compared with the control (REACHb).

In a skin irritation study (OECD TG 404), NZW rabbits (n = 3 males) were exposed to 0.5 g of manganese sulfate (mixed with 0.5 mL of distilled water to create a paste) on a shaved site with semi-occlusive coverage for four hours. No signs of irritation were observed at 24, 48 and 72 hours post exposure (REACHc).

In an in vitro skin irritation test (conducted according to EU method B.46), reconstituted human epidermis (EPISKIN ™ model) was uniformly exposed to flakes (10 ± 2 mg) of manganese sulfate for 15 minutes. No irritation was observed at 42 hours post exposure, measured by the mean viability of the reconstituted human epidermis, which was not significantly changed by chemical exposure compared with the control (REACHc).

Similar results were also observed using the above in vitro experimental protocol (according to OECD TG 439) with manganese oxalate and manganese phosphate (REACHe; REACHf).

Eye Irritation

Based on the weight of evidence from the in vivo data available for some of the chemicals in this group (excluding manganese nitrate; see **Corrosivity** section above), the remaining chemicals, apart from manganese oxalate, are considered to be eye irritants, warranting hazard classification (see **Recommendation** section).

In a eye irritation study conducted according to OECD TG 405, two male NZW rabbits were exposed to approximately 100 mg of manganese chloride for up to 72 hours. The maximum mean total score was 53/110 at 48 hours post-exposure, and corneal and conjunctival lesions were not reversible by 21 days post-exposure. The chemical was reported to be a severe eye irritant (REACHb).

In an eye irritation study (OECD TG 405), one male NZW rabbit was exposed to approximately 80 mg of manganese sulphate for up to 72 hours. The maximum mean total score was 36/110 at 48 hours post-exposure. Lesions were not reversible by seven days post-exposure. The rabbit was euthanised seven days post-exposure due to its moribund condition and the chemical was reported to be at least a moderate eye irritant (REACHc).

In an eye irritation study (OECD TG 405), three female NZW were exposed to 100 mg of manganese phosphate and observed for up to 10 days. It was reported that corneal opacity was minimal (average 0.33/4 for all animals over the 24, 48 and 72 hour time-points), but that it was not fully reversed within 72 hours in one rabbit (further details not available); and that there was no iritis in any rabbit over the duration of the study. The average score for conjunctival redness was 3/3 for all animals over the 24, 48 and 72 hour time-points, but this was fully reversible within 10 days. The average score for chemosis was 3/4 for all animals over the 24, 48 and 72 hour time-points and chemosis was not fully reversed within seven days in one rabbit (further details not available) (REACHf).

In an eye irritation study (OECD TG 405), NZW rabbits (n = 2 males and 1 female) were exposed to 100 mg of manganese oxalate and observed for up to seven days. It was reported that the chemical is not irritating, based on no corneal opacity or iritis; and minimal and reversible conjunctival redness (0.8/3) and chemosis (0.1/4) (REACHe).

Reports from in vitro eye irritation tests conducted with manganese chloride or manganese sulfate using reconstituted corneal epithelium (SkinEthic model) showed that these two chemicals were non-irritating in this model. (REACHb; REACHc). Using the ex vivo bovine corneal opacity and permeability test method (according to OECD TG 437) with manganese oxalate, it was reported that the chemical was not severely irritating or corrosive; whereas for manganese phosphate, it was reported that the chemical is severely irritating or corrosive in this model (REACHe; REACHf).

Sensitisation

Skin Sensitisation

Based on the data available for manganese chloride and manganese oxalate, the chemicals in this group are not considered likely to be skin sensitisers.

In a mouse local lymph node assay (LLNA) (similar to OECD TG 429), female Balb/c mice (n = 3/dose) were exposed on the back of each ear to 25 µL of vehicle (20 % ethanol) or 10 % manganese chloride, once a day for three days. On the fourth day, mice were euthanised, and auricular (ear) and axillary (arm pit) lymph nodes were excised. The stimulation index (SI) was 0.82, indicating that the chemical is not a skin sensitiser at this concentration (REACHb).

In another mouse LLNA (similar to OECD TG 429), female CBA/Ca mice (n = 4/dose) were exposed on the back of each ear to 25 µL of manganese chloride at 0, 5, 10 or 25 % concentrations in petrolatum daily for three days. Auricular lymph nodes were excised from the animals five days after the first dose. The SI was below three for all doses (1.1, 0.6 and 1.0 for 5, 10 and 25 %, respectively), indicating that the chemical is not a skin sensitiser (REACHb).

In an LLNA (OECD TG 429) using female CBA mice (n = 4/dose), animals were exposed on the back of the ear to 25 µL of manganese oxalate at 0, 2.5, 5 or 10 % concentrations in propylene glycol, daily for three consecutive days. Draining lymph nodes were excised from the animals five days after the first dose. The SI was below three for all doses (1.00, 1.18 and 1.14 for 2.5, 5 and 10 %, respectively), indicating that the chemical is not a skin sensitiser (REACHe).

Observation in humans

In a patch-test (non-guideline), healthy human volunteers (number not specified) were exposed to 10 µL of various solutions containing a mixture of the chemicals manganese sulfate (75–83 % of the mixture) and nickel sulfate (17–25 % of the mixture). No skin reactions were reported (REACHc).

Repeated Dose Toxicity

Oral

Manganese sulfate is classified as hazardous with hazard category ‘Specific target organ toxicity (repeated exposure) Category 2’ and hazard statement ‘May cause damage to organs through prolonged or repeated exposure’ (H373) in the HCIS (Safe Work Australia). Although the available animal data for manganese sulfate monohydrate and manganese oxalate indicate no significant systemic toxicity (except at high doses), based on neurological effects reported in humans with manganese exposure (see **Observation in humans** section below; NICNAS), a higher hazard classification is supported for all chemicals in this group.

A reference dose (RfD) of 0.14 mg/kg bw/day for manganese was reported based on chronic oral exposure data in humans (IRIS).

In a two-year study, Fischer 344/N (F344/N) rats (n = 70/sex/dose) were exposed to manganese sulfate monohydrate at 0, 1500, 5000 or 15000 ppm in the diet (based on food consumption, the doses were calculated as 0, 60, 200 and 615 mg/kg bw/day in males and 0, 70, 230 or 715 mg/kg bw/day in females). Survival was significantly decreased in males exposed to 15000 ppm (615 mg/kg bw/day) from week 93 of the study. Decreased survival was due to increased severity of kidney disease and failure. This was characterised by the progressive appearance of regenerating tubules, dilated tubules, interstitial fibrosis and mineralisation, as well as tubule degeneration and loss. Other lesions that were significantly increased included blood vessel and glandular stomach mineralisation, abnormal growth in the femur bones and hyperplasia of the parathyroid gland (NTP, 1993).

In a two-year study, B6C3F1 mice (n = 70/sex/dose) were exposed to manganese sulfate monohydrate at 0, 1500, 5000 or 15000 ppm in the diet (based on food consumption, the doses were calculated as 0, 160, 540 and 1800 mg/kg bw/day in males and 0, 200, 700 and 2250 mg/kg bw/day in females). Non-neoplastic lesions were reported in the forestomach of high dose mice, with significantly increased incidence of focal squamous cell hyperplasia in combination with ulceration and inflammation (NTP, 1993).

In a 13-week repeated dose toxicity study, F344/N rats (n = 10/sex/dose) were exposed to manganese sulfate monohydrate at 0, 1600, 3130, 6250, 12500 or 25000 ppm in the diet (based on food consumption, actual doses ranged from 110–1700 mg/kg bw/day in males and 115–2000 mg/kg bw/day in females). The lowest observed effect level (LOEL) was 1600 ppm (110 or 115 mg/kg bw/day for males and females, respectively), based on significantly reduced absolute (10.6–16.1 %) and relative (by 10.5–14.8 %) liver weights in all exposed male rats, and significantly reduced absolute (12.7–29.2 %) and relative (8.5–25.9 %) lung weights in all exposed female rats, compared with control rats. Absolute and relative liver weights were also significantly reduced in the female rats exposed to 25000 ppm (2000 mg/kg bw/day), compared with control rats (NTP, 1993).

In a 13-week repeated dose toxicity study, B6C3F1 mice (n = 10/sex/dose) were exposed to manganese sulfate monohydrate at 0, 3130, 6250, 12500, 25000 or 50000 ppm in food. (Based on food consumption, actual doses ranged from 330–7400 mg/kg bw/day in males and 390–6900 mg/kg bw/day in females). The no observed adverse effect level (NOAEL) was 25000 ppm, based on significantly reduced haematocrit concentration, haemoglobin concentration and mean erythrocyte volume observed at 50000 ppm (7400 or 6900 mg/kg bw/day). These haematological effects indicated microcytic anaemia and may be a consequence of iron deficiency due to increased manganese ingestion (NTP, 1993), most likely due to competition for gastrointestinal absorption between manganese and iron since they share similar uptake mechanisms in the gut (ATSDR, 2012).

In a 28-day repeated dose toxicity study (OECD TG 407), Wistar rats (n = 5/sex/dose) were exposed to manganese oxalate at 0, 100, 300 or 1000 mg/kg bw/day by oral gavage. Compared with control rats, decreased activity was noted in males exposed at 300 mg/kg bw/day during behavioural observations in the third week of study; and mean body weight was significantly reduced in

males exposed at the highest dose on days 15, 22 and 28. The NOAEL was reported to be 1000 mg/kg bw/day, as the study authors considered the findings not to be toxicologically relevant (REACHe).

Dermal

No data are available.

Inhalation

Manganese sulfate is classified as hazardous with hazard category 'Specific target organ toxicity (repeated exposure) Category 2' and hazard statement 'May cause damage to organs through prolonged or repeated exposure' (H373) in the HCIS (Safe Work Australia). Only limited animal data are available, indicating no significant systemic toxicity from repeated inhalation exposure to manganese chloride and manganese sulfate. However, based on neurological effects reported in humans following manganese exposure (see **Observation in humans** section below; NICNAS), a higher hazard classification is supported for all chemicals in this group.

A lowest observed adverse effect concentration (LOAEC) of 0.15 mg Mn/m³ (0.00015 mg/L) was reported for chronic inhalation of manganese dust in humans (IRIS).

In a non-guideline study, male rabbits (strain not specified, n = 8/dose) were exposed (whole body) to manganese chloride as an aerosol at 0, 1.1 or 3.9 mg/m³ for six hours per day, five days per week, for four to six weeks. There were no treatment-related effects reported. Minor inflammatory changes in the lungs (eosinophil and macrophage infiltration) were observed in all groups, including controls (REACHb).

In a repeated dose inhalation toxicity study, male rhesus monkeys (number not specified) were exposed to manganese sulfate at 0, 0.06, 0.3 or 1.5 mg/m³ for six hours per day, five days per week, for 90 days. The no observed adverse effect concentration (NOAEC) was 0.3 mg/m³, based on mild bronchiolitis, alveolar duct inflammation and proliferation of bronchus-associated lymphoid tissue in the lower respiratory tract observed at 1.5 mg/m³. These effects were reversible, since they were not observed in monkeys assessed 45 days after the final exposure (ATSDR, 2012).

In a repeated dose inhalation toxicity study, male Crl:CD(SD)BR rats (number not specified) were exposed to 0, 0.1 or 0.5 mg/m³ manganese sulfate for six hours per day, five days per week, for 13 weeks. The NOAEC was 0.1 mg/m³, based on inflammatory infiltrates and debris in the nasal respiratory epithelium (but not olfactory epithelium) at 0.5 mg/m³. These effects were reversible, since they were not observed in rats assessed 45 days after the final exposure (ATSDR, 2012).

The transient inflammatory responses described in monkeys and rats are consistent with the lesions being due to inhalation of particulate matter, and not specific to manganese exposure (ATSDR, 2012).

In a reproductive toxicity study (similar to OECD TG 415), CD rats (n = 10/sex/dose for F0 generation and n = 5/sex/litter for F1 generation) were exposed (whole body) to manganese sulfate monohydrate as an aerosol at 0, 0.15, 1.53 or 3.10 mg/m³ (equivalent to 0, 0.05, 0.5 or 1 mg Mn/m³) for six hours per day, seven days a week for up to 79 days (during the pre-mating, mating, gestation and lactation periods). The F1 generation was exposed for up to 19 days in the post-natal period and pups were euthanised on post-natal day (PND) 1, 14, 19, 45 and 63. The parental NOAEC was reported to be 1 mg Mn/m³ as systemic toxicity was not seen. Maternal body weight gain was not significantly affected by exposure for the duration of the study. Terminal (PND 18) brain and lung weights were similar in dams from the different treatment groups, but liver and pancreas weights were reduced (not significant) by approximately 13.8 % and 21.4 %, respectively, in the dams exposed at the highest concentration. Terminal (PND 18) body weight was approximately 10 % reduced in the dams exposed at the highest concentration, but this was reported as not statistically significant. Maternal manganese tissue concentrations were increased dose-dependently in the olfactory bulb; increased in the striatum, cerebellum and lung at concentrations ≥0.5 mg Mn/m³; and increased in the liver, femur and milk at the highest concentration only. Absolute pup body weight was significantly reduced on PND 1, 14 and 19 in the pups exposed at the highest concentration only; a similar (non-significant) effect was observed on PND 45, while no body weight data were available for PND 63. Pup manganese tissue concentrations were increased in a dose-dependent manner in: blood, liver and bone (skull cap) on PND 1; brain (striatum), lung and bone (femur) on PND 14; and olfactory bulb, cerebellum and striatum on PND 19. At exposure concentrations ≥0.5 mg Mn/m³, pup manganese tissue concentrations were increased in the blood on PND 14; in the liver on PND 14 and 19; and in the pancreas and bone (femur) on PND 19. Manganese tissue concentrations in the pups were similar to control values from PND 45. Urinary calculi and urinary tract lesions (secondary hydronephrosis and hydroureter) were observed in the dams and pups, but were deemed not to be treatment-related as they were also observed in control animals and did not occur in a dose-dependent manner. Alopecia (hair loss) was the only other reported clinical sign in both dams and pups (Dorman et al., 2005; REACHa).

Observation in humans

The ATSDR (2012) report stated that 'there is conclusive evidence from studies in humans that inhalation exposure to high levels of manganese compounds (usually manganese dioxide, but also compounds with Mn(II) and Mn(III)) can lead to a disabling syndrome of neurological effects referred to as manganism'. Although oral exposure to excess manganese is less studied, excess consumption via food or drinking water results in neurological impairment, and oral ingestion following inhalation exposure to manganese can occur via mucociliary clearance (ATSDR, 2012).

Genotoxicity

Based on the data available for manganese chloride, manganese gluconate, manganese hypophosphite, manganese oxalate and manganese sulfate (including hydrated forms), the chemicals are not considered to be genotoxic.

Most in vitro tests were negative for gene mutation and clastogenicity (REACH; Prival et al., 1991); in vitro tests that gave positive results only occurred in the presence of severe cytotoxicity (NTP, 1993). These included:

- several negative bacterial reverse mutation assays (Ames tests) in *Salmonella typhimurium* strains TA 97, TA 98, TA 100, TA 102, TA 1535, TA 1537 or TA 1538, with or without metabolic activation, using manganese chloride, manganese gluconate, manganese hypophosphite, manganese oxalate or manganese sulfate (including hydrated forms);
- three positive cytogenetic tests (induction of sister chromatid exchanges (SCEs)) in Chinese hamster ovary (CHO) cells, with or without metabolic activation, using manganese sulfate monohydrate (2/3 positive responses without metabolic activation were associated with cytotoxicity);
- negative in vitro mammalian cell gene mutation assays in mouse lymphoma L5178Y cells and Chinese hamster lung fibroblasts (V79) exposed to manganese chloride or manganese oxalate, respectively, with or without metabolic activation;
- a positive in vitro mammalian chromosome aberration test in CHO cells without metabolic activation (but negative with metabolic activation), using manganese sulfate monohydrate (the positive response without metabolic activation was associated with cytotoxicity);
- a negative in vitro mammalian chromosome aberration test in Chinese hamster lung fibroblasts (V79), with or without metabolic activation, using manganese oxalate; and
- a negative in vitro mammalian chromosome aberration test in human peripheral lymphocytes, with or without metabolic activation, using manganese chloride.

Most in vivo genotoxicity tests gave negative results for manganese chloride and manganese sulfate monohydrate, including a:

- mammalian chromosomal aberration test in bone marrow and spermatogonial cells of albino rats orally exposed to manganese chloride at 0.014 mg/kg bw/day for 180 days (ATSDR, 2012);
- somatic mutation test in *Drosophila melanogaster* where larvae were exposed to manganese chloride by soaking (ATSDR, 2012); and
- sex-linked recessive lethal (SLRL) tests in *D. melanogaster* exposed to manganese sulfate monohydrate at 12500 ppm in the feed or 1000 ppm by injection (NTP, 1993).

However, a mammalian chromosomal aberration test in albino mice gave positive results when animals were exposed orally to manganese sulphate at doses ≥10.25 mg/100 g bw for up to three weeks (ATSDR, 2012).

Carcinogenicity

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

In a two-year study, F344/N rats (n = 70/sex/dose) were exposed to manganese sulfate monohydrate at 0, 1500, 5000 or 15000 ppm in the diet (based on food consumption, the doses were calculated as 0, 60, 200 and 615 mg/kg bw/day in males and 0, 70, 230 or 715 mg/kg bw/day in females). No chemical-specific non-neoplastic or neoplastic changes were reported (NTP, 1993).

In a two-year study, B6C3F1 mice (n = 70/sex/dose) were exposed to manganese sulfate monohydrate at 0, 1500, 5000 or 15000 ppm in the diet (based on food consumption, the doses were calculated as 0, 160, 540 and 1800 mg/kg bw/day in males and 0, 200, 700 and 2250 mg/kg bw/day in females). A significantly increased incidence of thyroid follicle dilation was reported in mice at the highest dose; focal hyperplasia of the follicular epithelium of the thyroid was also reported in high dose males and in all exposed females; and the presence of follicular cell adenomas was reported in the high dose male and female mice, but the incidence was not significantly increased compared with control mice. These lesions represent part of a 'morphological continuum' (gradual transition) in the progression to thyroid gland adenoma (NTP, 1993).

Reproductive and Developmental Toxicity

Based on the limited available data for manganese chloride using an oral route of exposure, and the limited available data for manganese sulfate using an inhalation route of exposure (which is also relevant to human health being the primary route of occupational exposure to manganese compounds and since mucociliary clearance can lead to secondary oral exposure—see **Toxicokinetics** section), the chemicals in this group are not considered likely to have reproductive and developmental toxicity. While there were some effects consistent with reproductive toxicity, these were not seen across all studies. This is supported by other, more limited, data available on manganese acetate, manganese chloride, manganese oxalate and manganese sulfate, where there was a lack of consistent observations following oral exposure.

In a one-generation reproductive toxicity study (non-guideline), rats (n = 37 male and 27 female; strain not specified) were exposed to manganese chloride tetrahydrate in the drinking water at 0 or 3 mg/mL for 90 days. Water was provided *ad libitum* and the calculated manganese intake was 301–410 mg/kg bw/day for study day 0–30, 240–495 mg/kg bw/day for study day 30–60, and 260–585 mg/kg bw/day for study day 60–90. It was reported that parental body weight and food intake were not affected, but water intake was reduced, in manganese-exposed rats compared with control rats. Brain manganese content was significantly increased 2.2-fold in the exposed rats compared with controls. Litter sizes, pup viability and lactation were not significantly

affected by manganese exposure. Pup body and brain weights were similar between control and treated rats; brain manganese content was significantly increased 2.8-fold in exposed rats compared with controls. The developmental indices of eye opening and auditory startle reflex were similar between control and manganese-treated rats, but the air righting reflex was delayed in manganese-treated rats (REACHb).

In a one-generation reproductive toxicity study (similar to OECD TG 415), CD rats (n = 10/sex/dose for F0 generation and n = 5/sex/litter for F1 generation) were exposed (whole body) to manganese sulfate monohydrate as an aerosol at 0, 0.15, 1.53 or 3.10 mg/m³ (equivalent to 0, 0.05, 0.5 or 1 mg Mn/ m³) for six hours per day, seven days a week. The F0 generation was exposed for 28 days pre-mating, for 14 days during mating, and for females only, during pregnancy (gestation day (GD) 0–19) and lactation (PND 0–18). The F1 generation was exposed for up to 19 days, and pups were euthanised on PND 1, 14, 19, 45 and 63. Effects on reproduction were not specifically assessed. The parental NOAEC was reported to be 1 mg Mn/m³ based on lack of systemic toxicity (see **Repeated dose toxicity: Inhalation** section). Maternal body weight gain was not significantly affected by exposure for the duration of the study. Terminal (PND 18) body weight was approximately 10 % reduced in the dams exposed at the highest concentration, but this was not reported as statistically significant. Effects on developmental toxicity were not specifically assessed. Pup body weight gain overall was not significantly affected by exposure in the post-natal period. Absolute pup body weight was significantly reduced on PND 1, 14 and 19 in the pups exposed at the highest concentration only; a similar (non-significant) effect was observed on PND 45 and no body weight data were available for PND 63. The F1 NOAEC was reported to be 0.5 mg Mn/ m³ based on significantly decreased absolute brain weight in pups exposed at the highest concentration on PND 14, 19 and 45; in female pups on PND 19, brain weight relative to body weight was significantly increased. (It is noted that on PND 1, the brain weight of two control animals was excluded due to being deemed 'outliers'). Absolute liver weight was also significantly decreased in pups exposed at the highest concentration on PND 19. Effects on pup tissue manganese concentrations were also reported (see **Repeated dose toxicity: Inhalation** section) (Dorman et al., 2005; REACHa).

In three reproduction / developmental toxicity screening tests (similar to OECD TG 421), Swiss mice (n = 14 males and 15 females/dose, mated with untreated mice—n = 28 females and n = 5 males/dose, respectively) were exposed to manganese chloride tetrahydrate in drinking water at up to approximately 700 mg/kg bw/day for 12 weeks prior to mating; SD rats (n = 17 females/dose) were exposed to manganese sulfate heptahydrate in the diet at up to 60 mg Mn/kg bw/day for eight weeks prior to mating and during pregnancy up to GD 21; Wistar rats (n = 11/sex/dose) were exposed to manganese oxalate by oral gavage at up to 1000 mg/kg bw/day for approximately 28 days total, from prior to pairing, during mating, gestation and up to PND 4. In Swiss mice, the NOAEL was approximately 350 mg/kg bw/day, based on significantly impaired fertility in males (reduced pregnancy rate in untreated females) and impaired reproduction in females (reduced number of implantations and viable foetuses when mated with untreated males) exposed at the highest dose. In SD rats, no adverse effects were observed in the dams or pups. In Wistar rats, post-natal loss of pups up to four days post-partum was significantly increased in females exposed at 300 mg/kg bw/day; a similar trend was observed in females exposed at 1000 mg/kg bw/day, but this did not reach statistical significance (ATSDR, 2012; REACHa; REACHb; REACHe).

In CD-1 mice, oral exposure to manganese acetate at 7.5–30 mg/kg bw/day for 43 days resulted in a dose-dependent reduction in testicular sperm count, reduced sperm motility at doses ≥15 mg/kg bw/day and increased epididymis weight at 30 mg/kg bw/day; fertility was not affected in the highest dose males when mated with untreated females. In SD rats, oral exposure to manganese acetate at doses ≥137 mg/kg bw/day for 63 days resulted in an increased incidence of testicular degeneration; exposure to manganese chloride at 33 mg/kg bw/day by oral gavage throughout gestation resulted in significantly increased post-implantation loss; exposure to manganese sulfate at 23–198 mg/kg bw/day by oral gavage for 21 days resulted in significantly increased percentages of abnormal sperm compared with controls; and exposure to manganese sulfate at 1000 ppm in drinking water, *ad libitum* for 12 weeks, resulted in significantly reduced body, testes and seminal vesicle weights, no effect on male fertility, but significantly increased total resorptions in females impregnated by exposed males (ATSDR, 2012; REACHc; REACHd).

In two-year studies in F344/N rats and B6C3F1 mice exposed to manganese sulfate monohydrate at up to 715 and 2250 mg/kg bw/day, respectively, there were no significant treatment-related effects on reproductive organs. In teratology studies (non-guideline), mice, rats, hamsters and rabbits (sex, number of animals and time of exposure not specified) were exposed to manganese sulfate monohydrate by oral gavage at doses of 0.783–78.3 mg/kg bw/day, 1.25–125 mg/kg bw /day, 1.36–136 mg/kg bw/day and 1.12–112 mg/kg bw/day respectively, for 10 days. There were no effects on embryo implantation, maternal or foetal survival, or soft or skeletal tissue abnormalities in animals exposed to the chemical compared with control animals (NTP, 1993).

Human data on reproductive outcomes following occupational manganese exposure were not conclusive (NICNAS).

Other Health Effects

Neurotoxicity

Chronic exposure to manganese via inhalation and oral routes impaired the central nervous system (CNS) function in humans (see the IMAP report on manganese (NICNAS) for details). The chemicals in this group are recommended for classification as hazardous, for repeated dose oral and inhalation toxicity (see **Recommendation** section).

Although studies in rodents have shown neurological effects due to manganese exposure, it is difficult to draw a conclusion based on the available information. Studies in monkeys better represent the human condition, although these are limited. Classification is therefore based on information on human exposure with neurotoxic outcomes (NICNAS).

Inhalation exposure studies using manganese sulfate in animals have focused on brain biochemistry. SD rats were exposed by inhalation to 0 or 0.71 mg/m³ of manganese sulfate for two hours per day on gestation day (GD) 9–10 or post-natal day (PND) 37–47 (equivalent to early adulthood) or both GD 9–10 and PND 37–47. Activation of brain biochemical markers of neurotoxicity

(measured as changes in mRNA levels and gene transcription), affecting oxidative stress or inflammatory pathways, were reported in all exposed rats (ATSDR, 2012).

In two other studies, CD rats were exposed by inhalation to 0, 0.05 or 1 mg/m³ manganese sulfate for six hours per day on GD 0–19 and PND 1–18. Five brain regions were examined for biochemical markers of oxidative stress on PND 19 and three weeks after the last exposure. The striatum was reported to be the most consistently affected brain region. Increased manganese concentration in this area was associated with decreased mRNA and levels of protein markers of oxidative stress. Significantly decreased levels of relevant proteins persisted even three weeks after the last exposure (ATSDR, 2012).

Young male rhesus monkeys were exposed by inhalation to 0, 0.06, 0.3 or 1.5 mg/m³ of manganese sulfate for six hours per day for 15, 33 or 65 days, with or without a recovery period of 45 or 90 days after the last exposure. Six brain regions were examined (including the caudate, globus pallidus, frontal cortex) for biochemical markers of oxidative stress and significant changes were reported, which persisted even after chemical exposure had ended (ATSDR, 2012).

Various neurological alterations have been reported in animals after oral exposure to manganese chloride. These effects included altered neurochemical levels and altered neurobehavioural test outcomes. In general, noradrenaline levels were decreased in rats, and dopamine levels were decreased in rats and mice following exposure. In neurobehavioural tests (e.g. open field test, radial arm test, passive-avoidance task), rats displayed increased activity (including repetitive actions and rearing), as well as fear and aggression following exposure. Studies in mice were mixed, with one study reporting increased locomotor activity in female C57BL/6N mice and two studies reporting decreased locomotor activity in male ddY mice (ATSDR, 2012).

In male rhesus monkeys exposed to manganese chloride at doses ≥7 mg/kg bw/day for 18 months, muscle weakness and rigidity, as well as neuronal alterations in the substantia nigra, were reported. The monkey model is considered useful for predicting neurotoxicity in humans due to the similar neurological responses to toxic substances, although the studies were limited (ATSDR, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are the systemic long-term toxic effects following repeated inhalation and oral exposure. Manganese nitrate is also corrosive. The chemicals can also cause severe eye irritation and systemic effects from acute oral exposure.

Public Risk Characterisation

The international uses indicate that some of these chemicals can be included in skin conditioning agents (cosmetics). The concentrations used in cosmetic products are not available. Currently, there are no restrictions in Australia on using these chemicals in cosmetics. However, limited dermal absorption is expected, and so the risk from exposure is not considered unreasonable.

The chemicals are also used in paints and varnishes. The main route of public exposure is expected to be through the skin and inhalation from products applied as aerosols. However, high concentrations are not expected to be present in paints as these chemicals are used as drying agents. Hence, the risk from exposure is not considered unreasonable

Soil fertilisers used in home gardens may also contain trace amounts of some of these chemicals. However, the risk from exposure is not considered unreasonable due to limited and infrequent use.

Occupational Risk Characterisation

Given the critical health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification of manganese sulfate in the HCIS (Safe Work Australia), considering the hazard classification recommended for all chemicals in the group. The corrosivity classification (H314) applies to manganese nitrate compounds only (see **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended 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.

Further risk management is required if these chemicals are used in cosmetic products at high concentrations. The chemicals may be recommended for Tier III assessment to evaluate the concentrations and uses in cosmetic products manufactured or imported into Australia, to identify if an unacceptable risk of exposure exists from these chemicals.

Regulatory Control

Public Health

The need for regulatory control for public health will be determined as part of a Tier III assessment, if required.

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. For the irritation / corrosivity end-point, the corrosivity classification (H314) applies to manganese nitrate compounds only and the eye irritation classification (H318) applies to all other chemicals apart from manganese oxalate. 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	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318) Causes severe skin burns and eye damage - Cat. 1 (H314)
Repeat Dose Toxicity	Not Applicable	Causes damage to organs through prolonged or repeated exposure through inhalation and oral routes - Cat. 1 (H372)

[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 inhalation, oral and ocular 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 which 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;
- 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 chemicals.

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

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

Obligations under workplace health and safety legislation

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

- ensuring that hazardous chemicals are correctly classified and labelled;

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

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

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

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

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