Manganese: Human health tier II assessment

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Preface

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

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

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

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

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

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

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

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

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	colloidal manganese manganese, metal, electrolytic manganese, elemental magnacat mangan
Structural Formula	
Molecular Formula	Mn
Molecular Weight (g/mol)	54.94
Appearance and Odour (where available)	Lustrous silver/brown/grey/pink coloured solid metal flakes, with no smell
SMILES	[Mn]

Import, Manufacture and Use

Australian

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

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

The chemical has reported commercial uses as:

- a welding and soldering agent;
- an additive in construction materials; and
- an insulating agent.

The chemical has reported site-limited use in producing ferromanganese or metallic manganese. This is then used to produce steel alloys (carbon steel, stainless steel, high-temperature steel and tool steel); cast iron and superalloys; and non-ferrous alloys (aluminium, magnesium, copper and zinc). The chemical may also be used in commercial surface coatings.

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 the 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).

In drinking water, the National Health and Medical Research Council (NHMRC) Australian Drinking Water Guidelines 6 state that 'Based on aesthetic considerations, the concentration of manganese in drinking water should not exceed 0.1 mg/L, measured at the customer's tap. Manganese would not be a health consideration unless the concentration exceeded 0.5 mg/L.' (NHMRC, 2011).

International

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

The chemical has reported domestic use in articles such as toys, with migration limits of 1200 mg/kg in dry, brittle, powder-like or pliable toy material; 300 mg/kg in liquid or sticky toy material; and 15000 mg/kg in scraped-off toy material (European Directive 2009/48/EC).

The chemical has reported commercial uses, including as:

- an ingredient in liquid cement colourants, nickel metal hydride batteries, magnets, soil fertilisers and kitchen utensils;
- a linseed oil drying agent;
- a welding flux ingredient (chemical cleaning agent);
- a soldering product;
- a blasting material in explosives, including fireworks;
- part of electrical and electronic products, automobile parts and building materials;
- a component in articles for packaging (food and beverages, non-food and pharmaceutical products).

The chemical has reported site-limited uses in:

- manufacturing steel alloy, aluminothermic ferroalloys, cored wire, alloying tablets, pulp paper and paper products, chemicals and pharmaceutical products;
- foundries, for metal casting and treatment/inoculation of molten iron and iron ores;
- metallurgy (smelting, sintering and microfusion);
- thermal spray coating applications; and
- disinfecting and purifying natural gas.

The following non-industrial uses have been identified internationally, including in:

- medicines and dietary substances; and
- infant formulae and follow-on formulae (with a final permitted composition of manganese at 0.25 µg minimum and 25 µg maximum per 100 kJ formula when reconstituted) (EU Commission Directive 2006/141/EC).

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

Restrictions

Australian

No known restrictions have been identified.

International

No known international restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

Manganese, dust and compounds (as Mn) have an exposure standard of 1 mg/m^3 time weighted average (TWA).

Manganese, fume (as Mn) has an exposure standard of 1 mg/m^3 TWA and a 3 mg/m^3 short-term exposure limit (STEL).

International

In 2013, the American Conference of Governmental Industrial Hygienists (ACGIH) adopted a threshold limit value (TLV) for manganese (elemental and inorganic compounds) of 0.02 mg/m^3 TWA for respirable particulate matter and 0.1 mg/m^3 TWA for inhalable particulate matter (ACGIH, 2013).

The following exposure standards are identified (Galleria Chemica):

- a TWA of 0.02–0.1 mg/m^3 in different countries such as Latvia, Norway (respirable), Poland (respirable), Sweden (respirable dust) and the USA (TLV);
- a TWA of 0.15–0.2 mg/m^3 in different countries such as China, Denmark, Japan, Malaysia, Mexico, Poland (inhalable) and Sweden (total dust);
- a TWA of 0.3–0.5 mg/m^3 in different countries such as Bulgaria, Germany, Switzerland and the United Kingdom;
- a TWA of 1–3 mg/m^3 in different countries such as Canada (Alberta - respirable, Saskatchewan - respirable), Egypt, Indonesia (respirable), Norway (inhalable), South Africa (elemental and inorganic compounds), Spain (respirable) and the USA (Minnesota, NIOSH, Vermont);
- a TWA of 4–10 mg/m^3 in different countries such as Canada (Alberta - total, Saskatchewan - inhalable, Yukon), Chile (‘total’), Greece, Hungary, Indonesia (inhalable), Ireland, South Africa (dust and compounds), Spain (inhalable), Taiwan, and the USA (California, Hawaii, Tennessee - respirable, Washington);
- TWA values of 15 and 24 mg/m^3 in the USA (Tennessee - total) and Chile (‘respirable’), respectively;
- an STEL of 3–6 mg/m^3 in different countries such as Bulgaria, Egypt and the USA (Minnesota, Vermont); and
- an STEL of 10–20 mg/m^3 in different countries such as Canada (Saskatchewan), Hungary and the USA (Washington).

Health Hazard Information

As data for the chemical are not always available, data on soluble manganese compounds (NICNASa) were used where appropriate. Since manganese metal releases manganese (II) ions when absorbed systemically, soluble manganese compounds are considered appropriate analogues for the chemical.

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 inhalation exposure, the chemical is deposited in the nasal mucosa, upper airways and lungs. The particle size of the chemical is a major determinant of inhalation absorption. Smaller particles entering the lower airways (respirable fraction, ≤5 µM in size) can, upon dissolution, be absorbed into blood and lymph fluids directly, whereas larger particles accumulating in the nasal mucosa (inhalable fraction) can be transported into the brain via neural tracts. The chemical can also be absorbed via the gastrointestinal tract following particle deposition in the lungs, by mucociliary transport back to the throat where it can be swallowed (SCOEL, 2011; ATSDR, 2012). A Trojan-horse type mechanism, similar to that observed for cobalt ions (NICNASb), can increase local lung cell availability and systemic toxicity of manganese (II) ions following inhalation exposure, as the insoluble particles become

ingested by macrophages and enter the cellular recycling pathway (Ortega et al., 2014). This might also contribute to direct cell toxicity, via generating reactive oxygen species for example, with the intracellular release of manganese (II) ions (Ortega et al., 2014).

Following oral exposure, manganese metal is solubilised at stomach pH. Gastrointestinal absorption of the chemical is rapid and in the range of 3–8 %. Dietary iron and calcium intake are major determinants of oral absorption of manganese; low levels of iron or calcium can lead to increased manganese absorption, whereas high levels of iron or calcium can lead to decreased manganese absorption. Manganese and iron share similar uptake mechanisms in the gut, which may account for the inverse relationship in their absorption. Gastrointestinal absorption of the chemical may also be age-dependent, whereby absorption decreases with age; however, this may be due to changes in dietary iron and calcium intake, or the capacity of the hepatobiliary excretion process (which is not fully developed in human infants, or can be affected by liver disease) (SCOEL, 2011; ATSDR, 2012).

Manganese is found in all mammalian tissues. The liver, pancreas, kidney and adrenals generally contain the highest concentrations; the brain, heart, lungs, testes and ovaries contain intermediate concentrations; and spleen, muscle, bone and fat contain the lowest concentrations. Manganese can exist in different oxidation states (e.g. Mn(II) or Mn(III)), or complexed with organic and inorganic ligands (e.g. bicarbonate, albumin, transferrin, metalloproteinases). The chemical is primarily excreted in the faeces; with a very small portion (<2 %) excreted via the urine; and even less through sweating, the hair or breast milk (EPA, 2004; ATSDR, 2012).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure.

The median lethal dose (LD50) was reported to be 9 g/kg bw in rats (RTECS). In female Wistar rats, the LD50 was reported to be >2000 mg/kg bw (REACH).

Dermal

No data are available.

Dermal exposure to the chemical was not considered to be an important route of potential systemic toxicity (ATSDR, 2012).

Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation exposure.

The median lethal concentration (LC50) in Han Wistar rats was reported to be >5.14 mg/L after four hours of exposure to dust (REACH).

Observation in humans

The lowest published toxic concentration (TCLo) was reported to be 2300 $\mu g/m^3$ for inhalation exposure (RTECS).

Corrosion / Irritation

Skin Irritation

The chemical produced mild or no skin irritation in animals.

In an acute dermal irritation/corrosion study (conducted according to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 404), New Zealand White rabbits (n = 3 males) were exposed to 0.5 g of the chemical (mixed with 0.5 mL of distilled water to create a dry 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 (REACH).

In a Draize test, 500 mg of the chemical was administered to rabbit skin for 24 hours and mild irritation was observed (RTECS).

In an in vitro skin irritation test (conducted according to EU method B.46), reconstituted human epidermis (EPISKIIN ™ model) was uniformly exposed to flakes of the chemical 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 treatment (REACH).

In an in vitro corrosion study (conducted according to OECD TG 431), reconstituted human epidermis (SkinEthic) was exposed to 20 mg of the chemical (sufficient for uniform coverage of the skin) for three or 60 minutes. The mean viability of the reconstituted human epidermis was not significantly changed by exposure, compared with the control, indicating that the chemical was not corrosive (REACH).

Dermal exposure to the chemical was not considered to be an important route of potential systemic toxicity (ATSDR, 2012).

Eye Irritation

The chemical produced mild or no eye irritation in animals.

In an acute eye irritation/corrosion study (OECD TG 405), New Zealand White rabbits (n = 3 males) were exposed to approximately 38 mg of the chemical for up to 72 hours. Both the mean corneal and iridial irritation scores were zero at 24, 48 and 72 hours post exposure. The mean chemosis and redness scores were both two and one at 24 and 48 hours post exposure, respectively, and both effects were fully reversed by 72 hours (REACH).

In a Draize test, the eye of a rabbit was exposed to 500 mg of the chemical for 24 hours and mild irritation was observed (RTECS).

In an in vitro eye irritation test, reconstituted corneal epithelium (SkinEthic model) was uniformly exposed to flakes of the chemical for 10 minutes. No irritation was observed at three hours post exposure, measured by the mean viability of the reconstituted corneal epithelium, which was not significantly changed by chemical exposure compared with the control treatment (REACH).

Observation in humans

The chemical dust and fumes are reported to be eye and respiratory tract (mucous membrane) irritants. However, this response is typical of all inhalable particulate matter, and so the direct contribution of the chemical is unclear (ATSDR, 2012; HSDB).

Exposure to the chemical in particulate or dust form is associated with lung irritation and inflammation, characterised by macrophage and leukocyte (white blood cell) infiltration, phagocytosis (engulfing) of particles and areas of local oedema in the lung. This has been reported in occupational settings as well as in residential areas near to industrial or mining sites. Signs and symptoms can include cough, bronchitis, pneumonitis and reduced lung function (ATSDR, 2012).

Sensitisation

Skin Sensitisation

The chemical does not produce skin sensitisation.

In a mouse local lymph node assay (LLNA) (OECD TG 429), female CBA/Ca mice (n = 4/dose) were exposed to 25 µL of the chemical at a concentration of 0, 2.5, 5.0 or 10.0 % weight/weight (w/w) in dimethyl formamide to the back of each ear daily for three days. Auricular (ear) lymph nodes were excised from the animals five days after the first dose, and the stimulation index (SI) measured. The SI was 0.79, 1.16 and 0.73 for the 2.5, 5.0 and 10.0 % w/w dose groups, respectively, indicating that the chemical was not sensitising (REACH).

Repeated Dose Toxicity

Oral

No data are available for the chemical. Soluble manganese compounds (NICNASa) do not show significant systemic toxicity to animals following repeated oral exposure. However, based on human cross-sectional and epidemiological data (see **Other health effects** section), the chemical warrants hazard classification for repeated dose oral toxicity (see **Recommendation** section).

Dermal

No data are available.

Inhalation

Only limited data are available for the chemical. Soluble manganese compounds (NICNASa) do not show significant systemic toxicity following repeated inhalation exposure in animals. However, based on human cross-sectional and epidemiological data (see **Other health effects** section), the chemical warrants hazard classification for repeated dose inhalation toxicity (see **Recommendation** section).

In an inhalation toxicity study (non-guideline), male Sprague Dawley (SD) rats (n = 4–5/group) were exposed to manual metal arc-stainless steel (MMA-SS) welding fumes in an inhalation chamber at a concentration of 57–67 (low dose) or 105–118 (high dose) mg/m^3 total suspended particulate (TSP), for two hours per day once, or for 15, 30, 60 or 90 days. A control group of rats was also used (treatment details not available). The proportion of manganese in the welding fumes was approximately 24 % (concentration = 1.4–1.8 mg/m^3) in the low dose group and 22 % (concentration = 2.7–3.3 mg/m^3) in the

high dose group. Compared with the control animals, rats exposed to the high dose of welding fumes had significantly increased lung weights, and lymphocyte and macrophage mobilisation and accumulation (indicators of inflammation) from day 15 onwards. Fibrosis was 'early and delicate' on day 15, and crossed through the lung tissue over time from perivascular and bronchiolar (day 30), to interstitial (day 60) and then pleural regions (day 90). In exposed rats, there were no histopathological changes detected in the nasal epithelium, the trachea and the large bronchi; and no behavioural changes were observed (Yu et al., 2001).

In a follow-up study examining recovery from fibrosis, SD rats were exposed to MMA-SS welding fumes in an inhalation chamber at a concentration of 64 (low dose) or 107 (high dose) mg/m^3 TSP, for two hours per day once, or for 15, 30, 60 or 90 days. Animals were then allowed to recover for 90 days before they were euthanised and markers for lung fibrosis examined. Lung weights were significantly increased in both the low and high dose groups from day 15 onwards compared with controls. Fibrosis was not evident in the low dose group, but was evident in the high dose group from day 15. In rats exposed to welding fumes at either dose for up to 30 days, lung weights were reduced after the 90-day recovery period. Lung weights in rats exposed to low dose welding fumes for 60–90 days were also reduced after the recovery period. Lung weights were not reduced, nor was fibrosis reversed, in the high-dose group exposed to welding fumes for 60–90 days (HSDB).

Given the mixed chemical composition of welding fumes, the contribution of manganese specifically to lung fibrosis was not clear.

Observation in humans

The main route of manganese toxicity in humans is from chronic inhalation exposure in occupational settings, targeting the central nervous system (CNS). Neurotoxicity can also occur following repeated oral exposure to excess managanese (ATSDR, 2012) (see **Other health effects**).

Effects on male fertility have also been reported following repeated inhalation exposure to the chemical (ATSDR, 2012) (see **Reproductive and developmental toxicity** section).

In workers of a ferromanganese/silicomanganese plant (number and sex not specified), an increased incidence of sudden death was reported for the duration of their employment (sudden death mortality ratio = 2.47), due to cardiac arrest and other natural causes. Furnace workers exposed to manganese dusts and fumes had significantly increased mortality compared with non-furnace workers. However, other work conditions in the ferromanganese/silicomanganese plant that could have contributed to this effect (e.g. heat, noise, carbon monoxide) cannot be excluded (ATSDR, 2012).

Genotoxicity

Only limited data are available for the chemical. Based on the data available for soluble manganese compounds (NICNASa), manganese is not considered to be genotoxic.

Rats were exposed to MMA-SS welding fumes in an inhalation chamber at a concentration of 66 or 117 mg/m^3 TSP, for two hours per day once, or for 15 or 30 days (non-guideline study). Lung injury caused by welding fume inhalation was confirmed by DNA markers using a comet assay (for DNA strand breaks) and immunohistochemistry for 8-hydroxydeoxyguanine (for oxidative DNA damage) in bronchoalveolar lavage fluid (HSDB).

In a gene-expression profiling study (non-guideline), SD rats were exposed to a stainless steel arc welding fume in an inhalation chamber at a concentration of 1108 mg/m^3 TSP, for two hours per day for 30 days. Ribonucleic acid (RNA) extracted from peripheral blood mononuclear cells was analysed using two different microarrays. The first microarray found five genes with ≥1.9-fold increased expression, 36 genes with unchanged expression and 30 genes with ≥59 % decreased expression; the second microarray found that of 5200 genes analysed, 5.1 % of genes had increased expression and 15 % had decreased expression. Down-regulated genes included those involved in the immune response, and enzymes that control cellular function (HSDB).

In humans, significantly increased DNA single strand breaks and increased frequency of micronuclei (in peripheral blood lymphocytes and buccal (cheek) epithelial cells) have been reported in welders. However, there were inconsistencies in studies on other cytogenetic effects (chromosomal aberrations, sister chromatid exchanges) (IARC, 2009). Given the mixed chemical composition of welding fumes, the specific contribution of manganese to genotoxicity was not clear.

Carcinogenicity

Only limited data are available for the chemical. Based on the data available for soluble manganese compounds (NICNASa), manganese is not considered to be carcinogenic.

The International Agency for Research on Cancer (IARC) has classified welding fumes and gases as ‘Possibly carcinogenic to humans’ (Group 2B), based on limited evidence for carcinogenicity in humans and inadequate evidence for carcinogenicity in animal testing. Manganese is one component of welding fumes, which are complex mixtures (IARC, 1990).

In a non-guideline study, Fischer 344 (F344) rats and Swiss albino mice were exposed to the chemical dust (n = 25/sex/dose) in a suspension of trioctanoin, by oral gavage (10 mg, twice per month, for two years) and/or intramuscular injection (dose not reported, once per month for nine months). There were no increases in tumour incidence in rats and mice exposed to the chemical by any route (REACH).

In a non-guideline study, male F344 rats (n = 15/dose) were injected (intramuscluar) with 0.5, 1.0, 2.0 or 4.0 mg of the chemical once and observed for at least two years. No tumours were reported (Sunderman et al., 1976).

In a non-guideline study, male WAG (inbred) rats (n = 10/dose) were injected (intramuscular) concurrently with 20 mg of the chemical and 20 mg of nickel (a known carcinogen) once and the animals were observed for at least one year. Other groups of animals were exposed to paraffin oil (vehicle control) or 20 mg nickel alone. The addition of manganese reduced the incidence of tumours (2/10) compared with animals treated with nickel alone (7/10). No tumours were observed in rats in the vehicle control group (REACH).

Reproductive and Developmental Toxicity

Only limited data are available for the chemical and also for soluble manganese compounds (NICNASa). Therefore, no conclusion can be derived on the reproductive and developmental toxicity of the chemical.

In men exposed to manganese in an occupational setting, and in particular in those with clinical signs of a neurological syndrome known as manganism (see **Other health effects** section), decreased libido, impotence, sexual dysfunction and reduced sperm quality have been reported, which could decrease reproductive success. However, there was conflicting evidence. Reduced fertility (assessed as fewer children per married couple) was reported in male workers exposed to manganese dust at 0.97 mg/m^3 for 1–19 years. In another study, 314 men exposed to 0.145 mg/m^3 (mean value) manganese dust for up to 35 years reported impotence and lack of sexual desire, although there were no significant differences in reproductive outcomes compared with the control group (ATSDR, 2012).

Other Health Effects

Neurotoxicity

Long-term exposure to the chemical (as dust or manganese ions in drinking water) caused neurological symptoms in humans. Considering the lowest observed adverse effect concentration (LOAEC) established for inhalation of chemical dust and the reference dose (RfD) established for chronic oral exposure, both based on neurological effects, the chemical is considered to cause severe effects following repeated inhalation and oral exposure warranting hazard classification (see **Recommendation** section).

Long-term occupational inhalation exposure to low levels of chemical dust (0.07–0.97 mg manganese/m^3) resulted in impaired motor and cognitive function (e.g. poorer hand-eye coordination, hand steadiness and postural stability; reduced reaction time), as well as altered mood in workers. The proportion of manganese in the chemical dusts ranged from <20–80 % of total dust levels (ATSDR, 2012).

Long-term occupational exposure to high levels of inorganic manganese dust at concentrations of 2–22 mg manganese/m^3 resulted in a neurological syndrome known as manganism. Early symptoms included weakness and lethargy, irritability, aggressiveness, hallucinations, concentration difficulties and memory problems. Clinical signs included tremors, walking difficulties, facial muscle spasms and speech disturbances. With disease progression, severe muscle tension and rigidity can develop, leading to complete and irreversible physical disability. Frank manganism, as reported in workers in manganese mines or foundries, also includes psychomotor excitement known as 'manganese madness'—nervousness, irritability, aggression, destructivenenss and uncontrollable acts of laughter or crying or singing or aimless running. Cases of frank manganism increased with increasing duration of exposure to high levels of the chemical, and neurological impairments persisted even after exposure had ceased (ATSDR, 2012).

An LOAEC of 0.15 mg manganese/m^3 and a reference concentration (RfC) of 0.05 µg manganese/m^3 were reported for chronic inhalation exposure to the chemical. An RfC is defined as 'an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime' (IRIS). A minimal risk level (MRL) of 0.3 µg manganese/m^3 was also reported for chronic (>365 days) inhalation exposure. The MRL is defined 'as as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure' (ATSDR, 2012). Both the RfC and MRL values were derived from the same cross-sectional study on occupational exposure to manganese dioxide (CAS No. 1313-13-9), an inorganic manganese compound, and are based on neurobehavioural impairments; varied assumptions and correction factors account for the differences in reported values (IRIS; ATSDR, 2012). In the study reported by Roels et al. (1992), 92 male workers from a dry alkaline battery plant, exposed to a respirable dust concentration of 215 µg manganese/m^3 (total dust concentration = 948 µg manganese/m^3) for an average of 5.3 years (geometric mean; range 0.2–17.7 years), performed significantly worse in neurobehavioural tests compared with 101, age- and area-matched controls with no history of industrial manganese exposure (cited in ATSDR, 2012). Significant impairments in reaction time, hand-eye coordination and hand steadiness were reported in the manganese-exposed men, compared with the control group (Roels et al., 1992; cited in ATSDR, 2012). Self-reported respiratory function and direct lung spirometry measurements were not significantly different between the groups, and fertility was also unaffected in a subgroup (n = 70) of manganese exposed men (IRIS). Other reports (Iregren et al., 1990; Mergler et al., 1993) from different cohorts of men exposed to manganese in an industrial setting support the detailed analyses undertaken by Roels et al. (1992) (cited in ATSDR, 2012).

An RfD of 0.14 mg/kg bw/day was reported for chronic human oral exposure to manganese (equivalent to a recommended dietary intake of not more than 10 mg manganese/day for a 70 kg body weight) (IRIS). Collectively, studies reporting on oral exposure to manganese indicate that excess consumption in food or drinking water results in neurological impairments, with subtle effects observed following acute or intermediate duration exposure (15–364 days) and more pronounced effects following chronic exposure (ATSDR, 2012).

In an epidemiological study, three populations were examined from different areas within a 200 km^2 region based on their exposure to different manganese concentrations in their drinking water, which was sourced from natural wells. The areas were designated area A for 3.6–14.6 µg/L manganese, area B for 81.6–252.6 µg/L manganese and area C for 1600–2300 µg/L manganese. Individuals over the age of 50 were randomly chosen from each area (n = 62, 49 and 77 for areas A, B and C, respectively) and subjected to neurological assessment for 33 symptoms of manganism. There

were significantly higher neurologic scores in area C, compared with area A, indicating increased presence and/or severity of symptoms with increased manganese exposure. The total intake of manganese for each individual was not determined (IRIS).

In another epidemiological study, manganese poisoning in 25 people was reported following buried batteries leaching into a drinking water well. There were three deaths reported—one from suicide, and two with no determined cause; as well as symptoms of lethargy, stiff muscles, muscle tremors and mental disturbances in the rest of the population tested. Analysis of the well water indicated that the manganese concentration was at least 14 mg/L at the time of poisoning (IRIS).

In three separate cross-sectional studies in children (age range = 8–11 or 6–15 years), decreasing intelligence (e.g. poor functioning at school, impaired cognition) or increased hostility and hyperactivity were reported with increasing manganese levels in drinking water. In three separate case studies in children aged five (female), six (female) and 10 (male), manganism-like neurotoxicity symptoms were reported and linked to elevated manganese in drinking water (ATSDR, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects following repeated inhalation and oral exposure.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Although the public could come into contact with articles containing the chemical, such as stainless steel, it is expected that the chemical will be bound within the article and hence the chemical will not be bioavailable. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

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

Based on the lowered TLV by the ACGIH in 2013, the current Australian exposure standard might not be adequate to mitigate the risk of adverse effects.

NICNAS Recommendation

Assessment of the chemical 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.

It is recommended that Safe Work Australia consider whether current controls adequately minimise the risk to workers. A Tier III assessment may be necessary to provide further information about whether the current exposure controls offer adequate protection to workers.

Regulatory Control

Work Health and Safety

A PCBU 'that carries out welding activities must eliminate risks arising from welding, or if that is not reasonably practicable, minimise the risks so far as is reasonably practicable' by complying with the code of practice for welding processes (Safe Work Australia, 2012).

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed (T; R48/23/25)	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 industry

Control measures

Control measures to minimise the risk from inhalation and oral exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

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