Manganese oxides: Human health tier II assessment

29 June 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Manganese oxide (MnO)	1344-43-0
Manganese oxide (MnO2)	1313-13-9
Manganese oxide (Mn2O3)	1317-34-6
Manganese oxide (Mn3O4)	1317-35-7

Preface

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

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

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

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

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

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

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

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

These chemicals are assessed together as they all contain manganese ions and are insoluble in water (ATSDR, 2012). The oxidation state of the manganese ions varies for the different oxides. However, the toxicity of the chemicals is expected to be similar, because the ions will become the stable manganese (II) form following systemic absorption, although there could be differences due to variations in water (lung) and acid (stomach) solubility.

Import, Manufacture and Use

Australian

Dimanganese trioxide (Mn_2O_3) was reported under previous mandatory and/or voluntary calls for information, with a volume of <100 tonnes. It has site-limited use as a process regulator.

Trimanganese tetroxide (Mn_3O_4) was listed on the 2002 Australian High Volume Industrial Chemicals List (HVICL) with a total reported volume of 10000–99999 tonnes. (It was not listed in the 2006 Australian HVICL). It has commercial use as a welding and soldering agent.

The following Australian uses have been identified through the National Pollutant Inventory (NPI) and Therapeutic Goods Administration (TGA).

Manganese oxide (MnO) has reported domestic use in paints.

MnO and manganese dioxide (MnO_2) have reported commercial uses including in:

- welding;
- producing porcelain and amethyst glass;
- textile printing; and
- soil fertilisers.

MnO and MnO_2 have reported site-limited uses including in:

- batteries;
- producing matches and fireworks;
- manufacturing glass-bonding materials; and
- manufacturing other chemicals.

MnO and MnO_2 have reported non-industrial uses including:

- as food additives or dietary supplements;
- in animal feeds; and
- in listed medicines.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorization and Restriction 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) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US Department of Health and Human Services Household Products Database; and the US Department of Health and Humans Services Agency for Toxic Substances and Disease Registry (ATSDR).

MnO_2 has reported cosmetic use as an anti-oxidant.

MnO, Mn_2O_3 and Mn_3O_4 have reported domestic uses, including in:

- adhesives and filling agents;
- paints, inks, dyes and varnishes; and
- thinners and paint removers.

All four chemicals have reported commercial uses, including in:

- welding;
- corrosion inhibition;
- water treatment;
- construction materials; and
- soil fertilisers.

All four chemicals have reported site-limited uses including in:

- manufacturing pigments or enamels for colouring clay, glass or rubber;
- producing batteries; and
- manufacturing automotive catatlysts.

MnO and Mn_3O_4 have reported non-industrial use in animal feeds.

Restrictions

Australian

MnO_2 is listed in Appendix B of the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) for agricultural purposes with a specific use pattern. Appendix B chemicals are described as 'Substances not considered to require control by scheduling' (SUSMP, 2015).

No known restrictions have been identified for the other chemicals.

International

No known international restrictions have been identified for the chemicals.

Existing Worker Health and Safety Controls

Hazard Classification

MnO_2 is classified as hazardous, with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R20/22 (acute toxicity)

The other chemicals are not listed in the HSIS (Safe Work Australia).

Exposure Standards

Australian

Manganese, dust and compounds (as Mn) has 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 3 mg/m^3 short-term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica):

- an exposure limit of 0.02–5 mg/m^3 TWA in different countries such as Bulgaria, Canada (Alberta, British Columbia, Quebec, Saskatchewan, Yukon), Chile, China, Denmark, Egypt, Germany, Greece, Hungary, Iceland, Ireland, Japan, Malaysia, Mexico, Norway, Poland, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, the United Kingdom, and the USA (California, Hawaii, Minnesota, Vermont); and
- a STEL of 0.6–20 mg/m^3 in different countries such as Bulgaria, Canada (Saskatchewan), Egypt, Hungary, Iceland and the USA (Hawaii, Minnesota, Vermont).

Health Hazard Information

When data for systemic toxicity are lacking for any of the chemicals in this group, available data for MnO_2 are considered appropriate to use (read-across), due to similar bioavailabilities based on insolubility in water.

Manganese solubility increases at low pH (OECD, 2007). Following oral exposure, manganese metal is solubilised at stomach pH. Therefore, IMAP reports on manganese (NICNASa) and soluble manganese compounds (NICNASb) complement this report.

Toxicokinetics

In human volunteers exposed by inhalation to radio-labelled Mn_2O_3 (dose and duration not specified), more than 60 % of the particulates deposited in the lungs was transferred to the gastrointestinal tract (Clayton & Clayton, 1994), most likely by mucociliary clearance, and excreted in the faeces within four days (ATSDR, 2012). Similar to manganese (NICNASa) and soluble manganese compounds (NICNASb), particulate matter of Mn_2O_3 that remained in the lungs was slowly absorbed into the blood stream (Clayton & Clayton, 1994).

In rats that were exposed by intratracheal instillation to Mn_3O_4 (dose and duration not specified), approximately 50 % of the dose was excreted in the faeces within 3–7 days (ATSDR, 2015).

Acute Toxicity

Oral

MnO_2 is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The chemical also has a harmonised classification in the EU for acute oral toxicity. However, the available data for MnO, MnO_2 and Mn_3O_4 indicate these chemicals have low acute oral toxicity.

The following oral median lethal dose (LD50) values were available:

- >2000 mg/kg bw in female Wistar rats for MnO (Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 420) (REACHa);
- >2197 mg/kg bw in male Sprague Dawley (SD) rats for MnO_2 (TG not indicated) (OECD, 2007); and
- >2000 mg/kg bw in female Wistar rats for Mn_3O_4 (OECD TG 420) (REACHb).

The available data are not sufficient to recommend changes in classification for any of the chemicals in this group.

Dermal

Based on the data available for manganese dioxide, all the chemicals in this group are considered to have low acute dermal toxicity.

The dermal LD50 for MnO_2 was reported to be >2000 mg/kg bw in SD rats (OECD, 2007).

Inhalation

MnO_2 is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS (Safe Work Australia). The available data for the chemical are not conclusive. The existing classification is not recommended to be amended, as the highest dose tested in the rat study falls within the hazard classification range for inhalation toxicity. However, there were no mortalities observed at this highest dose tested (1.5 mg/L). Based on the available data for MnO and Mn_3O_4, the other chemicals in this group are considered to have low acute inhalation toxicity.

The following median lethal concentration (LC50) values were available:

- >5.35 mg/L in Wistar rats exposed (nose only) to manganese oxide dust for four hours (OECD TG 403) (REACHa);
- >1.5 mg/L in SD rats exposed (whole body) to MnO_2 dust for four hours in a study conducted according to OECD TG 403. No mortalities were observed at this highest concentration tested (OECD, 2007); and

- >5.17 mg/L in Wistar rats exposed (nose only) to Mn_3O_4 dust for four hours (OECD TG 403). There were no mortalities, but significant observations such as increased respiratory rate and hunched posture were noted in all animals, with occasional instances of noisy respiration on the days after exposure. All animals appeared normal after 10–12 days (REACHb).

The ATSDR (2012) report stated that acute inhalation exposure to high concentrations of manganese dusts from MnO_2 and Mn_3O_4 can cause an inflammatory response in the lungs, leading to impaired lung function, which is common for many inhalable particulate substances.

The available data are not sufficient to recommend changes in classification for any of the chemicals in this group.

Corrosion / Irritation

Skin Irritation

The chemicals in this group are not considered to be skin irritants.

In a skin irritation study (OECD TG 404), New Zealand White rabbits (n = 3 males) were exposed to 0.5 g MnO (mixed with 0.5 mL distilled water to create a paste) on shaved skin with semi-occlusive coverage for four hours. There were no signs of erythema or oedema during the observation period of 72 hours post-exposure (REACHa).

In a skin irritation study (OECD TG 404), New Zealand White rabbits (n = 3 males) were exposed to 0.5 g MnO_2 (mixed with 0.5 mL distilled water to create a paste) on shaved skin with semi-occlusive coverage for four hours. There were no signs of erythema or oedema during the observation period of 72 hours post-exposure (REACHc).

In another skin irritation study (OECD TG 404), New Zealand White rabbits (n = 3 males) were exposed to 0.5 g Mn_3O_4 (mixed with 0.5 mL distilled water to create a paste) on shaved skin with semi-occlusive coverage for four hours. There were no signs of erythema or oedema during the observation period of 72 hours post-exposure (REACHb).

Using the in vitro EPISKIN^{TM} reconstituted human epidermis model (EU method B.46) and the in vitro SkinEthic reconstituted human epidermal model (OECD TG 431), negative results were reported for skin irritation or corrosion with exposure to MnO, MnO_2 and Mn_3O_4 (REACHa; REACHb; REACHc).

Eye Irritation

The chemicals in this group are considered to be slight eye irritants.

In an eye irritation study (OECD TG 405), New Zealand White rabbits (n = 3 males) were exposed to 100 mg of MnO for up to 72 hours. The maximum mean total score for irritation was 10.7/110 at one hour post-exposure. There was no corneal opacity or iritis. Conjunctival lesions (redness, chemosis and discharge) were maximal at one hour post exposure (score = 2), but decreased at 24 hours (score = 1) and were completely reversed by 48 hours post exposure. The chemical was reported as slightly irritating to the eyes (REACHa).

In an eye irritation study (OECD TG 405), New Zealand White rabbits (n = 3 males) were exposed to 32 mg of MnO_2 for up to 72 hours. There was no corneal opacity or iritis. Conjunctival lesions (redness, chemosis and discharge) were maximal at one hour post exposure (average score = 1.33) and completely reversed by 48 hours post exposure. The chemical was reported as non-irritating (REACHc).

In another eye irritation study (OECD TG 405), New Zealand White rabbits (n = 3 males) were exposed to 54 mg of Mn_3O_4 for up to 72 hours. There was no corneal opacity or iritis. Conjunctival lesions (redness, chemosis and discharge) were maximal at one hour post exposure (score = 2), reduced at 24 hours (score = 1) and completely reversed by 48 hours post exposure. The chemical was reported as non-irritating (REACHb).

In vitro eye irritation tests were conducted using MnO, MnO_2 and Mn_3O_4 with reconstituted human corneal epithelium (SkinEthic model). The chemicals were reported as non-irritating (REACHa; REACHb; REACHc).

Observation in humans

The limited information in human studies indicate no or slight skin and eye irritation following MnO_2 exposure (OECD, 2007).

Sensitisation

Skin Sensitisation

The chemicals in this group are not considered to be skin sensitisers.

In a mouse local lymph node assay (LLNA) (OECD TG 429), female CBA/Ca mice (n = 4/dose) were exposed to 25 µL of 0, 2.5, 5 or 10 % concentrations of MnO in propylene glycol on the back of each ear for three days. Auricular (ear) lymph nodes were excised on day six. The stimulation index (SI) was below three for all

doses (1.21, 1.31 and 1.03 for 2.5, 5 and 10 %, respectively), indicating that the chemical was not a skin sensitiser (REACHa).

In a mouse LLNA (OECD TG 429), female CBA/Ca mice (n = 4/dose) were exposed to 25 µL of 0, 10, 25 or 50 % concentrations of MnO_2 in acetone/olive oil on the back of each ear for three days. Auricular lymph nodes were excised on day six. The SI was below three for all doses (2.26, 2.26 and 1.86 for 10, 25 and 50 %, respectively), indicating that the chemical was not a skin sensitiser (REACHc).

In another mouse LLNA (OECD TG 429), female CBA/Ca mice (n = 4/dose) were exposed to 25 µL of 0, 10, 25 or 50 % concentrations of Mn_3O_4 in acetone/olive oil on the back of each ear for three days. Auricular lymph nodes were excised on day six. The SI was below three for all doses (2.34, 1.88 and 1.41 for 10, 25 and 50 %, respectively), indicating that the chemical was not a skin sensitiser (REACHb).

Observation in humans

In 1993, dermatological allergy testing was conducted using an occupational test series (details not available) in 190 workers, including 126 enamellers and 64 decorators (71 males and 119 females) from five ceramic factories. On exposure to 10 % MnO_2 in petrolatum, two workers (one enameller and one decorator) were reported to show skin sensitisation reactions (OECD, 2007).

Repeated Dose Toxicity

Oral

The available data for mice indicate effects on neurotransmitters and decreased white blood cells when they were exposed to MnO_2 in the diet at ~275 mg/kg bw/day. Rats showed impaired weight gain due to interference with their metabolism when exposed to Mn_3O_4 at 4–13 mg/kg bw/day. However, these animal studies were of limited value due to a lack of details. Based on neurological effects reported in humans with manganese exposure (see ***Observations in humans*** below and NICNASa), hazard classification is supported for all chemicals in this group (see **Other health effects** section).

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 an 84-day study, Florida native wether sheep (n = 3/dose) were exposed to 0, 500, 1000, 2000 or 4000 ppm of MnO in the diet. Food intake was decreased at a high dietary MnO intake (dose not reported), and manganese levels were elevated in the liver, spleen and kidneys in the 4000 ppm group. Manganese content in bones increased with increasing exposure, and manganese content in the heart was increased in all treated animals, except the 500 ppm group. There were no reported signs of systemic toxicity and no mortalities (REACHa).

In a 100-day study, male ddY mice (n = 8/dose) were exposed to 17 or 276 mg Mn/kg bw/day as MnO_2 in their diet. The manganese content in the liver, kidneys, bones, muscles, hair and spleen was increased, but spontaneous motor activity was not changed in the high-dose group compared with the low-dose group. A statistically significant decrease in the white blood cell count was reported in the high dose group (OECD, 2007), but any impact on immune function was not reported (ATSDR, 2012). The lowest observed adverse effect level (LOAEL) was reported as 276 mg/kg bw/day (OECD, 2007). It should be noted that the units used in the above studies have, on occasion, been interchangeably applied in those reports, such that mg/kg bw/day was used for ppm and vice versa, leading to a lack of clarity in the results.

In a 12-month study, male ddY mice (n = 6/dose) were exposed to 17 or 275 mg manganese/kg bw/day as MnO_2 in the diet. Manganese content was significantly increased in the cerebral cortex, spleen and urine in the high-dose group. In the corpus striatum of the brain (a region responsible for controlling body movement), the neurotransmitters dopamine, noradrenaline and adrenaline were significantly reduced, and homovanillic acid was significantly increased, in high-dose animals. In the hypothalamus, a brain region that has a role in hormone production, dopamine, noradrenaline and homovanillic acid were reduced in high-dose animals. In the cerebral cortex, a brain region that has a role in language and emotion, dopamine was significantly inceased in high-dose animals. Significant reductions in body weight gain and decreased locomotor activity were also reported in the high-dose group. An LOAEL of 275 mg/kg/day in male mice was reported, based on changes in the concentrations of biogenic amines and decreased locomotor activity (OECD, 2007). It should be noted that the units used in the above studies have, on occasion, been interchangeably applied in those reports, such that mg/kg bw/day was used for ppm and vice versa, leading to a lack of clarity in the results.

In a 28-day study, male Wistar rats (n = 4/dose) were exposed to 0, 200, 2000, 20000 or 200000 ppm of Mn_3O_4 in the diet. This was equivalent to approximately 4–13, 70–110, 630–1220 or 7500–8900 mg/kg bw/day for the 200, 2000, 20000 and 200000 ppm doses, respectively. Rats in the highest dose group consumed <50 % of the food intake of other treatment groups, lost weight as the study progressed, and were lethargic and emaciated at the end of the study (REACHb). In the lowest-dose group, weight gain was only 44 % compared with the control group, despite similar food consumption. The study authors hypothesised that the impaired weight gains were related to excess manganese interfering with calcium, phosphorus and iron metabolism (ATSDR, 2012).

Dermal

No data are available.

Inhalation

Based on neurological effects reported in humans with manganese exposure (see ***Observations in humans*** below and NICNASa), hazard classification is supported for all the chemicals in this group (see **Other health effects** section).

A lowest observed adverse effect concentration (LOAEC) of 0.15 mg Mn/m^3 (0.00015 mg/L) was reported for chronic inhalation of manganese dust in humans (IRIS).

Animal data are available only for MnO_2 and Mn_3O_4. Severe effects in the lungs of monkeys (at 3 mg Mn/m^3) and neorological impairment in mice (at 72 Mn/m^3) were reported with MnO_2 exposure, but not with Mn_3O_4 exposure.

In a 10-month study, rhesus monkeys (n = 2–3/dose) were exposed (whole body) to MnO_2 dust at 0, 0.7 or 3.0 mg Mn/m^3 for 22 hours per day. Lungs were examined radiographically once a month, and the lung tissue was removed for histopathological examination at the end of the study. In the high-dose group, granular shadows (indicative of inflammation) appeared within one month of dust exposure, and increased in prevalence with ongoing exposure. Shadows indicative of inflammatory infiltration, thickening of lung tissue and emphysema progressively developed with ongoing expsoure. Similar shadows were observed in the low-dose group, but did not occur until 3–4 months after the initial exposure. Histopathological examination at the end of the study revealed dust accumulation, necrotic cells, fluid accumulation and thickening in the alveoli and interstitium of the lower airways indicating mucous membrane inflammation and emphysema (OECD, 2007).

Male ICR mice (numbers not reported) were exposed to MnO_2 dust at 0 or 72 mg Mn/m^3 for seven hours per day, five days per week for up to 32 weeks, and Swiss mice (n = 8–10/dose) were exposed (whole body) to MnO_2 dust at 0 or 70 mg/m^3 for 35 hours per week for up to nine months. Increased manganese content was reported in the blood, liver, kidneys, brain (cerebrum or cerebellum plus brainstem), testes and gastrointestinal tract of mice exposed to manganese. These mice also had significantly increased body weight and signs of neurological impairment (OECD, 2007).

In a non-guideline study, squirrel monkeys (n = 4/sex/dose) were exposed (whole body) to an aerosol of Mn_3O_4 at 0, 11.6, 112.5 or 1152 µg Mn/m^3 for 21–22 hours per day, seven days per week for nine months. No mortalities were reported and there was no effect on lung function in manganese-exposed monkeys. Manganese was significantly increased in blood in the highest-dose group. Brain histopathology was unchanged; there were no limb tremors; and arm muscle and nerve health was not affected in manganese-exposed monkeys compared with controls, indicating no signs of neurotoxicity (ATSDR, 2012; REACHb).

In a non-guideline study, SD rats (n = 30/sex/dose) were exposed (whole body) to Mn_3O_4 aerosol at 0, 11.6, 112.5 or 1152 µg Mn/m^3 for 21–22 hours per day, seven days per week for nine months. No mortalities were reported and there was no significant lung inflammation in manganese-exposed rats. Rats exposed to the highest dose had increased body weight, as well as increased haemoglobin, an increased red blood cell count, increased mean corpuscular haemoglobin concentration and decreased mean corpuscular volume, compared with all other animals. Increased manganese content was reported in the kidneys and lungs. There were no histopathological changes in the brain (REACHb).

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 also occur, via mucociliary clearance (ATSDR, 2012) (see **Other health effects** section).

Effects reported from multiple studies examining chronic occupational (e.g. in alloy plants or manganese mines) inhalation exposure to MnO_2 for up to 19 years at 0.97–90 mg/m^3 included respiratory effects such as cough, reduced lung function and pneumonia. This was considered a result of inflammation due to particulate matter, rather than specific to manganese toxicity (ATSDR, 2012).

Genotoxicity

Limited data are available for manganese dioxide. Although the available in vivo genotoxicity study for MnO_2 showed positive results, the available data are not sufficient to make a conclusion on genotoxicity of these chemicals.

Three in vitro genotoxicity tests have been conducted for MnO_2 (OECD, 2007):

1. bacterial reverse mutation assays (OECD TG 471) in *Escherichia coli* strain WP2*uvrA* gave negative results, with or without metabolic activation;
2. bacterial reverse mutation assays (OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA 1535 and TA1537 gave negative results, with or without metabolic activation; and
3. in a chromosomal aberration test (OECD TG 473) using Chinese hamster lung (CHL/IU) cells, no increase in the number of cells with chromosomal aberrations was observed following six hours of treatment with concentrations up to 869.4 µg/mL, with or without metabolic activation. However, continuous treatment for 24 hours increased the frequency of aberrations from concentrations of 217.4 µg/mL, with or without metabolic activation.

An in vivo micronucleus assay (OECD TG 474) in male ICR mice (n = 5/dose) gave positive results for significantly induced micronuclei in bone marrow cells, following a single oral administration of MnO_2 at doses of 500, 1000 or 2000 mg/kg bw (OECD, 2007).

The ATSDR (2012) report stated that 'There is some evidence from a study on occupationally exposed welders that manganese may cause chromosomal aberrations; the welders were exposed to other potentially toxic compounds including nickel (known to cause chromosomal aberrations) and iron; therefore, the observed increase in chromosomal aberrations cannot be attributed solely to manganese'. It further stated, 'Mutagenicity studies in both bacteria and mammalian strains are equivocal'; and 'no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds'.

Soluble manganese compounds were not considered to be genotoxic (NICNASb).

Carcinogenicity

Limited data are available for MnO_2, indicating that it is not carcinogenic. No data are available for other chemicals.

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 oxides are only one component of welding fumes, which are complex mixtures (IARC, 1990).

In non-guideline studies, Fischer 344 (F344) rats (n = 25/sex/dose) were exposed to MnO_2 at 0 or 10 mg by intramuscular injection once per month for nine months, and Swiss mice (n = 25 females/dose) were exposed to MnO_2 at 0, 3 or 5 mg by intramuscular injection, once per month for six months. There were no increases in tumour incidence in rats or mice exposed to MnO_2 (OECD, 2007). It should be noted that the intramuscular route of exposure is not relevant in humans.

Soluble manganese compounds were not considered to be carcinogenic (NICNASb).

Reproductive and Developmental Toxicity

Limited data are available from both human and animal studies on MnO_2 or Mn_3O_4. In general, although the chemicals have been shown to affect reproductive organs in both animals and humans, fertility has not been shown to be affected in humans. Further, manganese exposure is not expected to be teratogenic, although neurotoxicity is observed in litters of mice exposed in utero or via suckling in the post natal period. No conclusion can be derived from the available information on specific reproductive or developmental toxicity of these chemicals.

Male rabbits (n = 24 manganese-exposed and 12 in the control group) were exposed to MnO_2 at 0 or 250 mg/kg bw once by the intratracheal route and assessed at two, four, six and eight months post-exposure. Testes size was reduced at six and eight months in the manganese-exposed rabbits. Progressive degeneration of the seminiferous tubules was reported from two months, with 50 % damage reported at six months and severe damage at eights months (collapsed tubules and some calcification). The reported changes were associated with sterility, as there were no pregnancies in female rabbits mated with exposed males, compared with females mated with control males (ATSDR, 2012; REACHc).

Long–Evans rats (numbers not reported) were exposed to manganese in the diet as Mn_3O_4 at 0, 350, 1050 or 3500 ppm (equivalent to 0, 20, 55 and 177 mg/kg bw/day, respectively). Exposure was from the in utero stage where dams were fed the diet, followed by feeding the pups from day 14 post partum. At day 100 post partum, offspring rats were mated and continued on the diet for 224 days in total. In 100-day-old male offspring exposed to Mn_3O_4 at 1050 ppm, reproductive organ maturity was delayed (based on serum gonadotrophin and testosterone levels, as well as epididymal sperm counts). Pregnancy rate was significantly decreased (by 25 %) in mated male and female offspring exposed to Mn_3O_4 at 3500 ppm, but there were no effects in female offspring on ovulation, resorption, foetal weights or litter size (ATSDR, 2012).

CD-1 mice (n = 26 pups/group) were exposed to manganese in the diet as Mn_3O_4 at 0 or 205 mg/kg bw/day from post partum day 15–90. Male offspring had decreased growth of reproductive organs (preputial gland, seminal vesicle and testes), but no changes in body, liver or kidney weights were reported (OECD, 2007; ATSDR, 2012).

Female Swiss ICR mice (n = 5/dose) were exposed to manganese dioxide dust by inhalation at 0 or 49 mg/m^3 for seven hours per day, five days per week for four months before mating. Exposure was stopped for mating and, once pregnant, dams were randomly assigned to receive either 0 or 85 mg/m^3 until gestation day (GD) 17. After birth, pups were fostered in a crossed-design pattern, to allow for effects of prenatal and postnatal exposure to be separately examined. Toxicity was not reported in offspring, but pups that were exposed to manganese during gestation were retrieved preferentially by the mothers from the nest, had reduced body weight at birth that persisted into adulthood, and showed reduced neonatal activity scores, with progression to neurological impairment in adulthood (reduced rearing and exploratory behaviour) (OECD, 2007; REACHc).

In male workers (miners or ore processors, n = 68), exposed to manganese dust as MnO_2 at a mean concentration of 2.82 mg Mn/m^3 for at least one year, decreased viable sperm count and semen quality (in terms of increased semen liquefaction time) were reported, compared with control workers from the same workplace that were not exposed to manganese or other reproductive toxins. The presence of other metals in the workplace is a confounding factor and so the reported effects can not be specifically attributed to manganese (ATSDR, 2012).

Partners of male workers (n = 70) from a dry alkaline battery plant exposed to manganese dust as MnO_2 at a median concentration of 0.71 mg Mn/m^3 for an average of 6.2 years, were reported to have birth rates similar to the partners of control workers (ATSDR, 2012).

Other Health Effects

Neurotoxicity

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

The studies supporting the hazard classification are provided in the IMAP report for manganese (NICNASa). Several additional studies have reported neurological deficits in male workers specifically exposed to different manganese oxides.

An epidemiological study was conducted in 58 male workers from a ferroalloy plant who were exposed to MnO_2 dust at 0.149 mg Mn/m^3 for 1–28 years (mean = 13 years). Blood and urine manganese levels were significantly, positively correlated with cumulative exposure to the chemical and neuromotor test scores in the exposed workers (ATSDR, 2012).

Male workers (number not reported) in a manganese ore milling plant, exposed to MnO_2 dust at 1.59 mg Mn/m^3 for 1–16.7 years, had decreased neurobehavioural function and 'an increased tendency for postural sway when walking with their eyes closed' (ATSDR, 2012).

In a study examining male workers in a ferroalloy plant over time, where exposure to manganese dust (MnO_2 and Mn_3O_4, at a mean concentration of 0.0967 mg/m^3) decreased over a period of 14 years, impaired neurobehavioural function compared with controls (workers from a nearby hospital that had not been exposed to neurotoxins) did not improve. Cumulative exposure was positively correlated with impaired test performance (ATSDR, 2012).

In a cross-sectional study, male workers (n = 35) from a ferroalloy production plant who were exposed to manganese oxides (MnO_2, Mn_2O_3 and Mn_3O_4) were randomly selected to undergo a neurological assessment. They were compared with 37 male workers who were not exposed to manganese. Manganese levels were elevated in the blood and urine of exposed workers, and they had significantly increased white blood cell counts. Lower psychomotor function scores were also reported in exposed workers (REACHb).

The outcomes reported in the above studies indicate the early stages of neurological impairment following low levels of exposure. Frank manganism has also been reported following exposure to higher levels of manganese. For example, in miners exposed to manganese dust as MnO_2 at 6 mg/m^3 for 1–9 years, psychomotor disturbances and muscle pain/weakness were sometimes reported as early as nine months following exposure, but occurred on average after eight years and two months of exposure (ATSDR, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects identified for risk characterisation are systemic long-term effects following repeated oral and inhalation exposure. Data available are not sufficient to derive conclusions on genotoxicity, carcinogenicity, reproductive or developmental toxicity of these chemicals.

Public Risk Characterisation

The international uses of MnO_2 indicate that it can be used as an anti-oxidant in cosmetics. The concentrations used in cosmetic products are not available. Currently, there are no restrictions in Australia on using these chemicals in cosmetics. However, dermal absorption is expected to be minimal and, therefore, the risk from dermal 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 these products and inhalation of free manganese oxides will not occur. Hence, the risk from exposure is not considered unreasonable.

Soil fertilisers used in home gardens could 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 MnO_2 in the HSIS (Safe Work Australia). Hazard classification is recommended for all chemicals in this group (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.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2015).

Work Health and Safety

The chemicals are 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.

Apart from the risk phrases indicated in the table below, MnO_2 should continue to have the existing risk phrases, 'Harmful by inhalation' (Xn; R20) and 'Harmful if swallowed' (Xn; R22).

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 consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from oral and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures 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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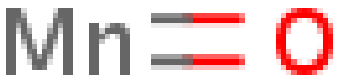
Last Update 29 June 2018

Chemical Identities

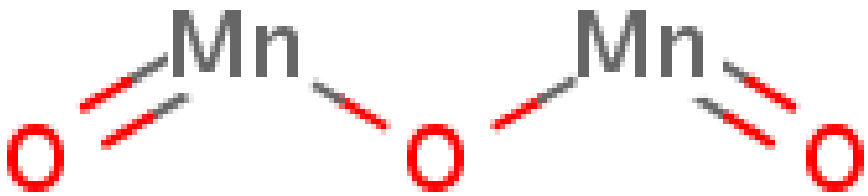
Chemical Name in the Inventory and Synonyms	**Manganese oxide (MnO)** manganous oxide manganese (II) oxide manganese monoxide

	manganese protoxide manganese green
CAS Number	1344-43-0
Structural Formula	
Molecular Formula	MnO
Molecular Weight	70.94

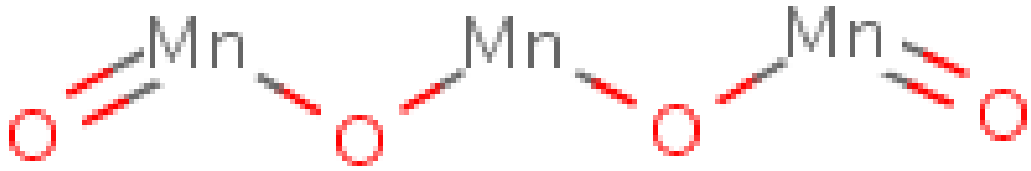
Chemical Name in the Inventory and Synonyms	**Manganese oxide (MnO2)** manganese dioxide manganese (IV) oxide manganese peroxide manganese superoxide manganese black
CAS Number	1313-13-9
Structural Formula	

	
Molecular Formula	MnO2
Molecular Weight	86.94

Chemical Name in the Inventory and Synonyms	**Manganese oxide (Mn2O3)** dimanganese trioxide manganese (III) oxide manganese sesquioxide manganese manganate Van Dyke Brown
CAS Number	1317-34-6
Structural Formula	

	
Molecular Formula	Mn2O3
Molecular Weight	157.87

Chemical Name in the Inventory and Synonyms	**Manganese oxide (Mn3O4)** trimanganese tetroxide manganese (II,III) oxide manganese tetroxide manganomanganic oxide
CAS Number	1317-35-7
Structural Formula	

	
Molecular Formula	Mn3O4
Molecular Weight	228.81

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