Iron chloride (FeCl2) and its hydrates: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Iron chloride (FeCl2)	7758-94-3
Iron chloride (FeCl2), tetrahydrate	13478-10-9

Preface

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

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

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

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

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

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

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

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

Entries for anhydrous chemicals on the Australian Inventory of Chemical Substances (AICS) are also taken to cover hydrates, although one hydrate of iron (iron(II) chloride, tetrahydrate (CAS No. 13478-10-9)) is independently listed on the AICS. The hydrates are toxicologically different from the anhydrous form of this chemical (iron(II) chloride, CAS No. 7758-94-3) as the corrosive properties of the anhydrous chemical partly relate to its reaction with water. Aqueous formulations containing iron(II) chloride can be considered to contain the hydrates rather than the anhydrous chemical. As the CAS No. for the anhydrous form is considered to also apply to hydrates, these chemicals are grouped despite their toxicological differences.

When in aqueous solution, iron(II) chloride and iron(II) chloride, tetrahydrate are chemically and toxicologically indistinguishable. At high concentrations, the solutions, whether of anhydrous iron(II) chloride or its hydrates, have low pH due to hydrolysis to form hydrochloric acid.

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening Information Data Set International Assessment Report (OECD SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and the US National Library of Medicine's (NLM) Hazardous Substances Data Bank (HSDB).

The anhydrous chemical has reported cosmetic uses, including:

- in hair dyes; and
- as an astringent.

The anhydrous chemical has reported domestic uses, including in:

- adhesives and sealants;
- fillers and putties; and
- modelling clays.

The anhydrous chemical has reported commercial uses, including in:

- metal etching and engraving;
- printing inks;
- textiles;
- stone, wood, glass and ceramic products;
- paint products;
- metal surface treatment products; and
- building and construction products.

The anhydrous chemical has reported site-limited uses, including:

- in antifoaming agents, coagulating agents, dispersion agents, emulsifiers, flotation agents and viscosity adjustors;
- in sewage, sanitation and waste treatment;
- in water treatment;
- in mining;
- in the manufacture of synthetic dyes, pigments, paper, plasters, cements and other chemicals;
- in paint products;
- as a processing aid;
- in solid separation agents; and
- as a complexing agent.

The hydrate has reported site-limited uses in the architectural and engineering industry.

The anhydrous chemical has reported non-industrial uses, including:

- in food colourants;
- in pharmaceuticals and veterinary drugs;
- as an additive in animal feed; and
- in agricultural products including fertilisers and plant protection products.

The anhydrous chemical has reported use in tattoo inks.

Restrictions

Australian

Iron compounds, including the chemicals in this assessment, are listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 2, 4, 5 and 6 (SUSMP, 2019). The only restriction potentially relevant for industrial uses is a listing in schedule 5, relating to garden preparations. The schedule 6 entry relates only to animal treatment, while schedules 2 and 4 relate to human therapeutic use.

Schedule 2:

'IRON COMPOUNDS (excluding iron oxides when present as an excipient, in divided preparations containing 10 mg or less of total iron oxides per dosage unit or in undivided preparations containing 1 per cent or less of total iron oxides) for human internal use **except**:

a) when included in Schedule 4; or

b) when labelled with a recommended daily dose of 24 mg or less of iron:

i) in undivided preparations supplied in packs each containing 750 mg or less of iron; or

ii) in divided preparations:

A) containing more than 5 mg of iron per dosage unit in packs each containing 750 mg or less of iron; or

B) containing 5 mg or less of iron per dosage unit.'

Schedule 4:

'IRON COMPOUNDS in injectable preparations for human use.'

Schedule 5:

'IRON COMPOUNDS:

a) for the treatment of animals (excluding up to 1 per cent of iron oxides when present as an excipient):

i) in preparations for injection containing 20 per cent or less of iron **except** in preparations containing 0.1 per cent or less of iron; or

ii) in other preparations containing 4 per cent or less of iron **except**:

A) in liquid or gel preparations containing 0.1 per cent or less of iron; or

B) in animal feeds or feed premixes; or

b) in garden preparations **except** in preparations containing 4 per cent or less of iron.'

Schedule 6:

'IRON COMPOUNDS (excluding up to 1 per cent of iron oxides when present as an excipient) for the treatment of animals **except**:

a) when included in Schedule 5;

b) in liquid or gel preparations containing 0.1 per cent or less of iron; or

c) in animal feeds or feed premixes.'

Schedule 2 chemicals are described as 'Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person.' Schedule 2 chemicals are labelled with '**Pharmacy Medicine**' (SUSMP, 2019).

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.' Schedule 4 chemicals are labelled with '**Prescription Only Medicine**', or '**Prescription Animal Remedy**' (SUSMP, 2019).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with '**Caution**' (SUSMP, 2019).

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.' Schedule 6 chemicals are labelled with '**Poison**' (SUSMP, 2019).

International

Iron compounds, including the chemicals in this assessment, are listed on the following (Galleria Chemica):

- Annex to Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin, in which iron dichloride is a permitted substance with no maximum residue limit.
- Council of Europe Resolution AP (92)2 on control of aids to polymerisation (technological coadjuvants) for plastics materials and articles intended to come into contact with foodstuffs, in which iron compounds should not release to foods in excess of 60 mg/kg.
- US Food and Drug Administration (FDA) Food Additive Status List and in the US Code of Federal Regulations (CFR) Title 21, Section 582.80—Trace minerals added to animal feed (21 CFR 582.80), in which iron chloride is listed as a nutritional dietary supplement in animal feed.
- New Zealand Maximum Residue Levels for Agricultural Compounds, Schedule 2—Exemptions from maximum residue levels for agricultural chemicals, in which elemental iron, iron complexes and iron salts when used in pellet form as a molluscicide have no maximum residue levels.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

- an exposure limit of 1 mg/m^3 time weighted average (TWA) and 2 mg/m^3 short-term exposure limit (STEL) in different countries such as Ireland, Norway, South Africa, the United Kingdom (UK) and Vietnam; and
- an occupational exposure limit of 4 mg/m^3 in Latvia.

Health Hazard Information

Iron(II) chloride, also called iron dichloride or ferrous chloride, has the formula $FeCl_2$, with iron in the +2 oxidation state. This will be referred to as ferrous chloride henceforth.

When ferrous chloride (CAS No. 7758-94-3) is dissolved in water, iron(II) cations and chloride anions are released. At low concentrations, these ions are managed under homeostatic control and are not expected to present a risk of systemic toxicity.

Health hazard information for other iron compounds, such as ferrous sulfate ($FeSO_4$, CAS No. 7720-78-7) and ferrous sulfate, heptahydrate ($FeSO_4.7H_2O$, CAS No. 7782-63-0), have been included in this report and are considered to be suitable read-across compounds for ferrous chloride because these iron compounds also release iron(II) cations and low toxicity anions when dissolved in water.

Various iron formulations were used as read-across for toxicity reports in humans.

Toxicokinetics

Iron is an essential metabolic cofactor in mammals. Iron absorption, metabolism, distribution and excretion are tightly regulated within the body. Most iron in circulating blood is bound to transferrin, a plasma glycoprotein, which transports iron to the bone marrow for incorporation into haemoglobin. Iron is also present in other haem-complexes, such as myoglobin, and several haem-containing and non-haem-containing enzymes in tissues. Iron is stored as ferritin or haemosiderin particularly in the liver, spleen and bone marrow (Harju, 1989).

Iron absorption occurs mostly in the upper part of the small intestine, i.e. in the duodenum and jejunum. For iron to be absorbed from the gastrointestinal tract, it must be in the ferrous state (Fe^{2+}); however, most dietary iron is in the ferric state (Fe^{3+}). Gastric secretions dissolve iron compounds and provide a milieu favourable to its reduction to the ferrous form. Ascorbic acid and other reducing substances in the diet facilitate conversion of ferric iron to the ferrous state. Iron absorption is increased significantly in the presence of ascorbic acid in humans, but only has a small effect in rats (Reddy and Cook, 1991). In iron-deficient rats and humans, iron utilisation from haem and inorganic iron are increased (Mahoney and Hendricks, 1984). Other factors that affect the availability of iron for absorption include phytic acid, phosphates and oxalates, which react with iron to form insoluble compounds in the intestine (Harju, 1989).

Iron is lost mainly from the skin and gastrointestinal tract via desquamation. Iron loss has been calculated to be approximately 1 mg of iron daily in a 70 kg human. In women, menstrual iron losses vary markedly between individuals. Iron menstrual loss is decreased by oral contraceptives and intrauterine contraceptive devices (Harju, 1989).

Acute Toxicity

Oral

The anhydrous form has moderate acute toxicity based on results from a rat study following oral exposure. The median lethal dose (LD50) for ferrous chloride in rats is 500 mg/kg body weight (bw). Observed clinical signs included hypoactivity, piloerection, prone position, dyspnoea, hypothermia, nasal discharge, reddish change and oedema in the ears and legs. There is sufficient evidence to warrant hazard classification (see **Recommendation** section).

In an acute oral toxicity study conducted according to OECD Test Guideline (TG) 423, female Sprague Dawley (SD) rats were administered ferrous chloride by oral gavage (in corn oil) at a single dose at concentrations of 300 mg/kg bw (6 rats) or 2000 mg/kg bw (3 rats). Rats were observed for 14 days after administration. All animals from the 2000 mg/kg bw dose group died on day 1 and 1 animal at 300 mg/kg bw died on day 2. Clinical signs included hypoactivity, piloerection, prone position, dyspnoea, hypothermia, nasal discharge, soft stools, reddish change and oedema in the ears and legs. Gross pathology findings included haemorrhage in the lymph nodes, stomach, intestine and thymus, as well as hypertrophy of the pancreas and spleen. The reported LD50 for ferrous chloride was 500 mg/kg bw, equivalent to 220 mg/kg bw as Fe^{2+} (REACH).

In an acute oral toxicity study conducted according to OECD TG 401, SD rats of both sexes (5/sex/dose) were administered ferrous sulfate, heptahydrate ($FeSO_4.7H_2O$, CAS No. 7782-63-0) by oral gavage at a single dose at concentrations of 0, 250, 500, 1000 or 2000 mg/kg bw. Significantly reduced body weight in females was observed at 1000 mg/kg bw. No body weight changes were observed in both sexes at 2000 mg/kg bw. Clinical signs observed at 2000 mg/kg bw included salivation and reduced activity. No abnormalities were observed at 250, 500 and 1000 mg/kg bw. No mortality occurred at any of the doses. The reported LD50 for both sexes combined was >2000 mg/kg bw for $FeSO_4.7H_2O$, equivalent to >402 mg/kg bw as Fe^{2+} (REACH).

The following acute oral LD50 in rats and mice were reported for similar iron compounds (REACH):

- 2625 mg/kg bw for $FeSO_4$ (965 mg/kg bw as Fe^{2+}), both sexes of Wistar rats;
- 3200 mg/kg bw for $FeSO_4.7H_2O$ (643 mg/kg bw as Fe^{2+}), both sexes of Wistar rats;
- 3200 mg/kg bw for $FeSO_4$ (1177 mg/kg bw as Fe^{2+}), rats (strain unspecified);
- 1025 mg/kg bw for $FeSO_4$ (305 mg/kg bw as Fe^{2+}), male Swiss Webster mice; and
- 670 mg/kg bw (male) and 680 mg/kg bw (female) for $FeSO_4$ (246 and 250 mg/kg bw as Fe^{2+}, respectively), Swiss mice.

Dermal

The anhydrous form has low acute toxicity based on the results from rats following dermal exposure.

In an acute dermal toxicity study according to OECD TG 402, SD rats of both sexes (5/sex/dose) were dermally treated with ferrous chloride (in corn oil) at 2000 mg/kg bw for 24 hours under semi-occlusive conditions and observed for 14 days. No mortalities occurred during the study. A yellowish-brown change on the skin was observed at the site of application in all animals on day 2, but this was fully reversible by day 15, except in 3 females. Two males and 4 females had reddish nasal discharge on day 2; this was considered a distress sign caused by pressure of taping on the thorax area. The acute dermal LD50 for both sexes combined was >2000 mg/kg bw for ferrous chloride, equivalent to 881 mg/kg bw as Fe^{2+} (REACH; OECD SIAR, 2004).

Inhalation

No data are available for the chemicals.

Observation in humans

Information on acute toxicity in humans relate to ionic iron, and is considered to be a suitable read-across.

There are 5 clinical stages of iron poisoning, in which progression to each stage may occur rapidly and not every stage occurs in patients. In stage 1, acute gastrointestinal symptoms are observed up to 6 hours after ingestion, including abdominal pain, vomiting and diarrhoea, that can progress to shock, coma, seizures and death. Stage 2 occurs from 6–24 hours after ingestion, where patients may be asymptomatic and gastrointestinal symptoms may resolve; however, evaluation and treatment for iron poisoning should be provided immediately due to toxic amounts of iron absorbed. Stage 3 occurs from 6–72 hours after ingestion, characterised by recurrence of gastrointestinal symptoms, metabolic acidosis, shock, hepatic and renal failure, as well

as cardiovascular collapse. Stage 4 (12–96 hours after ingestion) signs may include elevation of aminotransferase levels, gastrointestinal obstruction, hepatic cirrhosis, and possibly hepatic failure. In stage 5 (2–8 weeks), the injured gastrointestinal mucosa undergoes repair including scarification and obstruction (Centers for Disease Control and Prevention (CDC), 1993; Yuen and Becker, 2019).

The majority of reports of acute iron poisoning occur in children, mainly due to accidental ingestion of iron supplements. A single dose of approximately 20 mg/kg bw of iron can lead to acute toxicity in infants. In children, the fatal dose is approximately 200–300 mg/kg bw; however, ingestion of approximately 60 mg/kg bw has resulted in death (CDC, 1993; Expert Group on Vitamins and Minerals (EVM), 2003).

The incidence of acute iron poisoning in adults is relatively uncommon, but can occur when receiving high doses of iron therapy. An adult anaemic patient was diagnosed with acute iron poisoning after receiving a high dose of oral and parenteral iron therapy (total of 4.7 g Fe^{2+}). The patient recovered after receiving treatment for iron poisoning (Skoczynska et al., 2007).

Corrosion / Irritation

Respiratory Irritation

No data are available for the chemicals.

Skin Irritation

Based on the available data, the anhydrous form is a slight skin irritant producing slight oedema on the skin. Hazard classification is not warranted.

In a skin irritation/corrosion study conducted according to OECD TG 404, 3 male New Zealand White (NZW) rabbits were treated with anhydrous ferrous chloride (0.5 g powder, moistened with distilled water) by dermal application onto shaved skin under semi-occlusive conditions. No mortalities occurred and no abnormalities were observed in the animals during the study. At 1 hour and 4 hours after application, very slight oedema was observed in all the animals, which fully resolved in 14 days. At histopathological examination, several lesions were found in the dermis. Haemorrhage and haemosiderosis were observed at the application sites, along with increased neutrophils, eosinophils and lymphocytes. Based on the test results, the chemical was not determined to be a skin irritant (REACH; OECD SIAR, 2004).

Eye Irritation

The anhydrous form is corrosive to the eyes, producing irreversible damage to the cornea, and inflammation of the conjunctivae, nictitating membranes and eyelids. There is sufficient evidence to warrant hazard classification for the anhydrous form (see **Recommendation** section). This cannot be read across to the tetrahydrate.

In an eye irritation study conducted according to OECD TG 405, 0.1 g of anhydrous ferrous chloride powder was applied to the conjunctival sac of 1 eye of 3 female NZW rabbits. During the study, all the animals had reduced mobility. Severe redness, discharge, yellow pigmentation, purulent keratitis and granulomatous inflammation were observed in the conjunctiva, as well as severe redness and oedema in the conjunctiva and nictitating membrane. Redness and oedema were reversible at 7–14 days after application. Oedema, inflammation and haemosiderosis were observed in the eyelids. The lesions in the eyelids recovered partially during the observation period. The iris showed hyperaemia and was not responsive to light. No histopathological abnormalities were found in the iris. Diffuse opacity was observed in the corneas of all animals, which was not reversible in 2 animals. On the basis of severe and irreversible effects observed in the eyes of some animals, the chemical was considered to be corrosive under these test conditions (REACH; OECD SIAR, 2004).

Sensitisation

Skin Sensitisation

Skin sensitisation data are not available for the chemicals. A similar iron compound, ferrous sulfate ($FeSO_4$) gave negative results in a local lymph node assay (LLNA).

In an LLNA conducted according to OECD TG 429, 50 % ferrous sulfate ($FeSO_4$) in acetone/olive oil (4:1 v/v) was applied to the dorsal surface of both ears (25 µL/ear) of CBA/J female mice (5/dose) for 3 days. Slight erythema was observed on the ears treated at 50 %. Ferrous sulfate at 50 % did not elicit a stimulation index (SI) =3, and was determined not to be a skin sensitiser (REACH).

Although a few case studies in humans considered hypersensitive allergic reactions following repeated exposures to oral or parenteral iron formulations, these are not relevant for skin sensitisation.

Repeated Dose Toxicity

Oral

Based on the available human data, the anhydrous form does not cause serious damage to health from repeated oral exposure, except in populations with certain genetic defects or diseases (e.g. haemochromatosis). Therefore, the chemicals are not recommended for classification.

In a combined repeated oral dose and reproductive/developmental toxicity study conducted according to OECD TG 422, SD rats (15/sex/dose) were administered ferrous chloride (in water) by oral gavage at doses of 0, 125, 250, or 500 mg/kg bw/day for 42 days (males) or 42–54 days, depending on mating and delivery of offspring (females). No mortality occurred in males, while 3 mortalities occurred in the 500 mg/kg bw/day female group. Mortalities were thought to be due to gastrointestinal damage caused by treatment. Gastric haemorrhage and blackened liver were observed at necropsy and were presumed to be caused by treatment; however, these partly resolved in the 2-week recovery period. At 250 and 500 mg/kg bw/day in males and at 500 mg/kg bw/day in females, absolute and relative liver and adrenal organ weight changes were observed. Histopathological examination showed parenchymal haemosiderosis and hyperplasia of the adrenocortical zona fasciculate. The reported no observed adverse effect level (NOAEL) was 125 mg/kg bw/day (equivalent to 55 mg/kg bw/day as Fe^{2+}) for males, and 250 mg/kg bw/day (equivalent to 110 mg/kg bw/day as Fe^{2+}) for females (REACH).

Dermal

No data are available for the chemicals.

Inhalation

In 2 non-guideline subchronic inhalation toxicity studies, male rats (strain and number of animals unspecified) were exposed via whole body inhalation to iron chloride (iron oxidation state unspecified) aerosol at concentrations of 0, 0.2, 1, 4, 5, 20, 25, 80 or 150 mg/m^3 2–3 times daily (duration unspecified) for up to 65 days. At 20, 25, 80 and 150 mg/m^3, clinical signs observed included diarrhoea, thirst, loss of appetite, anxious behaviour and agitation. At necropsy of animals exposed to 0.2 mg/m^3, congestion of blood circulation in the brain, lungs, liver, adrenals and spleen was observed, as well as dystrophic alteration of the liver, kidneys and heart muscle (REACH). In both studies, the lowest observed adverse effect concentration (LOAEC) was 0.2 mg/m^3 for inhalation toxicity based on multi-organ congestion.

Observation in humans

Chronic iron overload may result from parenteral administration (as therapeutic iron or blood transfusions). Increased oral iron intake does not generally result in significant iron overload. Factors that may lead to iron overload include bioavailability of iron, certain genetic defects (e.g. haemochromatosis), or increased demand (e.g. anaemia). 'Generalised iron overload' has been arbitrarily defined as an excess total body iron of more than 5 g in adults, and 'severe iron overload' as an excess of 10 g or more, associated with iron-induced tissue damage, including hepatic cirrhosis, impaired heart and endocrine function (EVM, 2003).

In a long-term (1991–2001) prospective study of women (n=3976 participants) with a history of gestational diabetes, total iron intake, dietary haem iron and supplemental iron were reported to be positively associated with type 2 diabetes risk, whereas dietary non-haem iron intake was inversely associated with type 2 diabetes risk. The link between iron-overload and increased risk of type 2 diabetes were thought to be due to a number of mechanisms including: (1) excess iron attacking pancreatic β cells through elevated oxidative stress, leading to β cell apoptosis and a decrease in glucose-induced insulin secretion; and (2) excess iron interfering with glucose use in muscle tissues leading to a shift from glucose to fatty acid oxidation and diminished insulin-induced glucose transport in adipocytes, which may impair insulin action and result in increased insulin resistance (Bao et al., 2016).

Genotoxicity

Based on the available data, the anhydrous form is not considered to be genotoxic.

In an in vitro study conducted according to OECD TG 471, ferrous chloride was not mutagenic in any of the strains of *Salmonella typhimurium* tested (TA98, TA100, TA1535 and TA1537) and in an *Escherichia coli* strain (WP2 uvrA) in the presence or absence of metabolic activation (REACH).

In an in vivo mammalian erythrocyte micronucleus test conducted according to OECD TG 474, ferrous chloride at doses of 0, 12.5, 25 or 50 mg/kg bw/day did not induce micronuclei in bone marrow cells of male ICR mice (6/dose) (REACH).

Carcinogenicity

Based on the available data, the chemicals are not expected to be carcinogenic. Studies in humans have not provided evidence to support that iron supplementation or dietary iron intake causes cancer, but rather may play a protective role by reducing the risk of gastrointestinal cancer (REACH).

Iron overload is believed to be a risk factor for hepatocellular carcinoma. Liver cancer is a frequent complication in hereditary haemochromatosis (HHC), with most hepatocellular carcinomas developing on a background of cirrhosis. The reported pooled incidence of hepatocellular carcinoma in HHC is about 5–10 %, and this incidence can increase to 18 % in the presence of cirrhosis. However, some cases of hepatocellular carcinoma have been reported in HHC patients without cirrhosis (Deugnier and Turlin, 2007; Finianos et al., 2018).

A meta-analysis has found evidence of an association between high serum ferritin and primary liver cancer risk (6 studies, hazard ratio (HR) 1.49, 95 % CI 1.13, 1.96), as well as high serum iron and primary liver cancer risk (3 studies, HR 2.47, 95 % CI 1.31, 4.63), but these associations were subject to heterogeneity (Tran et al., 2019).

Reproductive and Developmental Toxicity

Based on the available information, the anhydrous form does not show specific reproductive or developmental toxicity. Reports in humans indicate that the effects on pregnancy may have been secondary to maternal toxicity.

In a combined oral repeated dose and reproductive/developmental toxicity study conducted according to OECD TG 422, SD rats were orally exposed to ferrous chloride at up to 500 mg/kg bw/day (see **Repeat Dose Toxicity** section). No treatment-related effects were observed on mean live neonates, birth rates, survival rates and sex ratios. An acaudate (lack of a tail) was observed in one neonate at 500 mg/kg bw/day. A significant decrease in crown rump length (CRL) of female neonates was observed at 125 mg/kg bw/day on day 4 post-partum. The reported maternal NOAEL was 250 mg/kg bw/day (equivalent to 110

mg/kg bw/day as Fe^{2+}) for females. The reported NOAEL for reproductive/developmental toxicity was 500 mg/kg bw/day (equivalent to 220 mg/kg bw/day as Fe^{2+}) (REACH).

In a combined oral repeated dose and reproductive/developmental toxicity study conducted according to OECD TG 422, SD rats (12/sex/dose) were administered ferrous sulfate, heptahydrate ($FeSO_4.7H_2O$) by oral gavage at doses of 0, 30, 100, 300 or 1000 mg/kg bw/day for 42–47 days (females) or 49 days (males). At 1000 mg/kg bw/day, mortality occurred for both female and male rats. In the 1000 mg/kg bw/day parental group, food consumption and body weights were reduced, while weights of the liver, adrenals, brain and uterus were increased. In the 300 and 1000 mg/kg bw/day parental group, salivation was observed in animals. Testes weights were increased at 300 mg/kg bw/day, but not at 1000 mg/kg bw/day, and this was considered not to be treatment-related. No significant changes or adverse effects were observed in pups including the number of stillbirths, live pups, sex ratio, birth index, viability index and body weights. The reported NOAELs were 100 mg/kg bw/day (equivalent to 20 mg/kg bw/day as Fe^{2+}) for parental toxicity, and 1000 mg/kg bw/day (equivalent to 200 mg/kg bw/day as Fe^{2+}) for reproductive toxicity (REACH).

Observation in humans

Studies on iron poisoning during pregnancy have not provided strong evidence of causing adverse effects on pregnancy and babies; however, the incidence is low, limited information is available on co-morbidities or other medications taken, and other factors have not been taken into account.

A meta-analysis of relevant English language publications between 1966 and 1998 was conducted to: 1) determine if peak maternal serum iron level or iron toxicity stage after intentional overdose was associated with adverse maternal-foetal outcomes; and 2) describe the use of deferoxamine antidote therapy in obstetric patients. For this analysis, 5 stages of iron toxicity used were asymptomatic (0), gastrointestinal symptoms (1), metabolic disturbance (2), organ failure (3), and gastrointestinal scarring (4). Symptoms of iron toxicity were more frequently observed in women with peak serum iron levels =400 µg/dL compared with women who had lower peak levels (12/13 vs. 5/10, respectively, $p = 0.05$). Peak iron level =400 µg/dL was not associated with increased risk of spontaneous abortion, preterm delivery, congenital anomalies, perinatal or maternal death. The proportions of spontaneous abortion (1/3 vs. 1/56, respectively), preterm delivery (2/3 vs. 6/56, respectively) and maternal death (3/3 vs. 0/56, respectively) were higher in women with stage 3 toxicity compared with women with less advanced toxicity. The authors concluded that stage 3 toxicity was associated with spontaneous abortion, preterm delivery and maternal death (Tran et al., 2000). These effects may have been secondary to maternal toxicity.

A study assessed the effect of iron overdose patients on the outcome of pregnancy that have been reported to the UK National Poisons Information Centre and the Teratology Information Service. There were 49 records of pregnant patients who took iron overdoses and where the outcomes of the pregnancy and desferrioxamine treatment were known. Twenty-five of these patients were treated with desferrioxamine, and another 12 patients underwent other types of treatment for iron overdose. In 48/49 (98 %) patients, the dose of iron taken was reported. In 28/49 patients (57 %), over 20 mg/kg bw (60 kg woman) was taken, sufficient to put them at risk of toxicity. In the 35 patients, both the dose and serum iron levels were known, with 13 patients having serum iron levels from 60–89 µmol/L, indicating a risk of moderate toxicity, and another 6 had serum iron levels >90 µmol/L (severe toxicity). Of the 49 pregnancies, 43 resulted in live babies, 2 were spontaneous abortions, and 4 were elective terminations. One of the elective terminations was of an anencephalic foetus, where the mother had an iron overdose at 24 weeks of gestation. Of the live babies, 3 were premature, and 6 babies had abnormalities including webbed fingers, unstable hips, congenital dislocated hips, bilateral accessory nipples, positional talipes (the foot rests down and inwards) and pansystolic murmur. All babies with abnormalities were associated with overdoses after the first trimester, and therefore, the abnormalities were not considered to be directly related to iron overdose or desferrioxamine treatment. Based on these results, there is no evidence to suggest that iron overdose caused toxicity to the baby (McElhatton et al., 1991).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include acute toxicity from oral and dermal exposure, and eye irritation (for the anhydrous form). The chemicals can also cause harmful systemic effects following repeated exposure to high doses through

oral exposure. Harmful systemic effects following repeated inhalation exposure cannot be ruled out. Adverse effects are more common in individuals with certain genetic defects or diseases (see **Repeat Dose Toxicity: Oral**).

Public Risk Characterisation

Although no Australian use information is available for the chemicals, evidence indicates that the chemicals are present in a range of domestic and cosmetic products internationally. The main route of public exposure is expected to be via dermal and ocular routes, through the use of products such as adhesives and hair dyes. Inclusion in formulations is expected to greatly reduce the risk from ocular exposure. Therefore, the public risk from the chemicals are not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, ocular, oral and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise ocular and inhalation exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available warrant hazard classification in the HCIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

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

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2019).

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. The eye irritation classification only applies to the anhydrous form (CAS No. 7758-94-3). This assessment does not consider classification of physical and environmental hazards.

As of 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]

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)

[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, ocular 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- 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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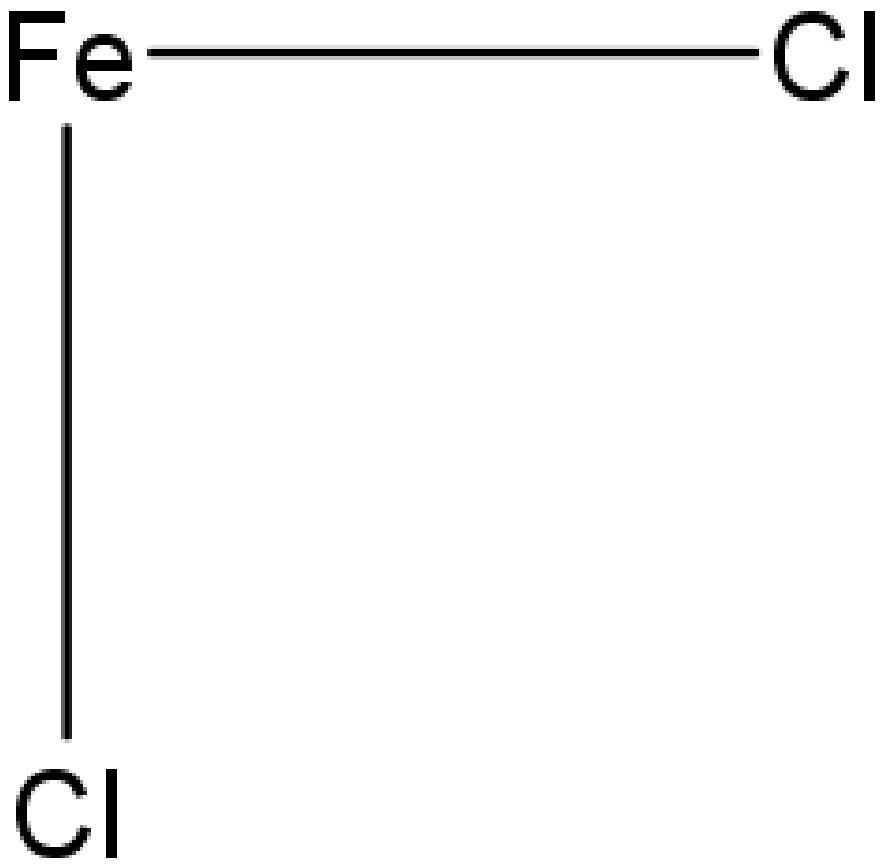
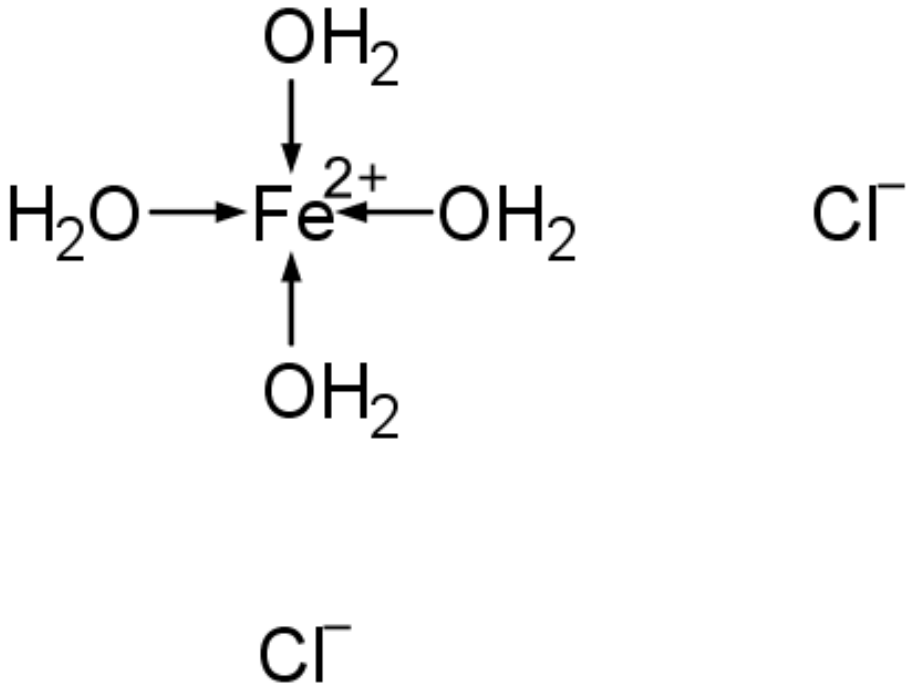
Last Update 12 December 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Iron chloride (FeCl2)** ferrous chloride iron dichloride
CAS Number	7758-94-3
Structural Formula	

	
Molecular Formula	Cl2Fe
Molecular Weight	126.75 g/mol

Chemical Name in the Inventory and Synonyms	**Iron chloride (FeCl2), tetrahydrate** ferrous chloride, tetrahydrate
CAS Number	13478-10-9
Structural Formula	

	
Molecular Formula	Cl2Fe.4H2O
Molecular Weight	198.81 g/mol

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