Nickel chloride: Human health tier II assessment

07 February 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Nickel chloride (NiCl2)	7718-54-9
Nickel chloride (NiCl2), hexahydrate	7791-20-0

Preface

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

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

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

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

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

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

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

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of chemicals contains nickel chloride and its hydrated salt; nickel chloride hexahydrate. While anhydrous nickel chloride is listed on the Australian Inventory of Industrial Chemicals (AICS), the listing includes all hydrated forms such as the hexahydrate. Soluble nickel salts produce the $(Ni[H_2O]_6)^{2+}$ ion in aqueous solution regardless of the nominal salt (Cotton et al, 1999; Lascelles et al, 2005) and, therefore, may be grouped together for risk assessment purposes.

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information:

Nickel chloride has reported site-limited use in industrial plating operations.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Chemicals in this group have the following uses:

The chemicals have reported site-limited use including as:

- laboratory reagents;

- electroplating agents;
- chemical mediators (catalysts, accelerators, initiators); and
- chemical intermediates.

Restrictions

Australian

Nickel and its compounds are listed in Schedule 10 (prohibited carcinogens, restricted carcinogens and restricted hazardous chemicals) of the Work Health and Safety Regulations (WHS, 2011) for restricted use in abrasive blasting at a concentration of greater than 0.1 % nickel.

International

REACH Regulations Annex XVII Section 27 on nickel and its compounds states:

"1. Shall not be used:

(a) in all post assemblies which are inserted into pierced ears and other pierced parts of the human body unless the rate of nickel release from such post assemblies is less than 0.2 $\mu g/cm^2$/week (migration limit);

(b) in articles intended to come into direct and prolonged contact with the skin such as:

- earrings,
- necklaces, bracelets and chains, anklets, finger rings,
- wrist-watch cases, watch straps and tighteners,
- rivet buttons, tighteners, rivets, zippers and metal marks, when these are used in garments,
- if the rate of nickel release from the parts of these articles coming into direct and prolonged contact with the skin is greater than 0.5 $\mu g/cm^2$/week;

(c) in articles such as those listed in point (b) where these have a non-nickel coating unless such coating is sufficient to ensure that the rate of nickel released from those parts of such articles coming into direct and prolonged contact with the skin will not exceed 0.5 $\mu g/cm^2$/week for a period of at least two years of normal use of the article.

2. Articles which are the subject of paragraph 1, shall not be placed on the market unless they conform to the requirements set out in those points.

3. The standards adopted by the European Committee for Standardisation (CEN) shall be used as the test methods for demonstrating the conformity of articles to paragraphs 1 and 2" (REACH Annex XVII, 2009).

Existing Worker Health and Safety Controls

Hazard Classification

Nickel dichloride (CAS No. 7718-54-9) is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Carc. Cat. 1; R49 (Carcinogen)

Muta. Cat. 3; R68 (Mutagen)

Repr. Cat. 2; R61 (Reproductive toxicity)

T; R23/25 (Acute toxicity)

T; R48/23 (Repeat dose toxicity)

Xi; R38 (Irritant)

R42/43 (Sensitiser)

Exposure Standards

Australian

The group of chemicals fall under the category of 'Nickel, soluble compounds (as Ni)' in HSIS, and have an exposure standard of 0.1 mg/m³ time weighted average (TWA) (HSIS).

International

The following exposure standards are identified for this group of chemicals (Galleria Chemica):

An exposure limit (TWA) of 0.05 - 1 mg/m^3 in different countries such as USA (in various states), Canada (in various provinces), Norway (0.05 mg/m^3), Greece (1 mg/m^3), Philippines (1 mg/m^3) and Switzerland (0.05 mg/m^3).

Health Hazard Information

Data available for nickel chloride hexahydrate (CAS No. 7791-20-0) have been used in the health hazard assessment for this group of chemicals as it is dissociated in water to the $(Ni[H_2O]_6)^{2+}$ ion, which is the normal species for Ni^{2+} in aqueous solutions (Cotton et al, 1999; Lascelles et al, 2005). Also, when specific data are not available for nickel chloride or nickel chloride hexahydrate, data will be read across from nickel sulfate hexahydrate, as the Ni (II) ion is considered to be the moiety responsible for systemic toxicity and a significant contributor to local toxicity (Henderson et al, 2012). In addition, nickel chloride has similar bioaccessibility and bioavailability to nickel sulfate; this group of nickel chemicals releases the Ni (II) ion into biological fluids at similar rates (Henderson et al, 2012; Goodman et al, 2009). Nickel sulfate can therefore be considered a close analogue and relevant data maybe used according to read-across principles (OECD, 2007) to assess the risk of nickel chloride.

Toxicokinetics

Nickel compounds can be absorbed via inhalation, ingestion and to a limited extent following dermal exposure. The absorption of nickel compounds and the release of the nickel ion is dependent on the solubility of the compound in the specified physiological solutions (gastric or interstitial). Nickel is metabolised extracellulary through a series of ligand exchange reactions and binds albumin proteins in the blood, which is consistent across humans, rats and bovine species (ATSDR, 2005).

Inhalation exposure:

In Wistar rats, intratracheal administration of nickel chloride (5.9 μg of radio-labelled nickel chloride) resulted in rapid absorption from the lung. Nickel chloride was rapidly distributed (within 0.5 hours) to most tissues examined following administration. No information regarding metabolism was provided. Approximately 70 % of the administered nickel chloride was excreted via urine

and faeces within three days (EU RAR, 2008). In a further study, Sprague Dawley (SD) rats were exposed to respirable nickel chloride (90 or 400 μg Ni/m^3 with a mass median aerodynamic diameter (MMAD) of 0.7 - 0.9 μm) for two hours a day, for 14 days. Nickel chloride was absorbed and excreted efficiently, with 6.9 % of nickel chloride particles being retained in the lung at the end of the study (EU RARa, 2008).

Oral exposure:

In an oral gavage study conducted in Fischer 344 (F344) rats, regardless of the dose of radio-labelled nickel chloride administered (4, 16 or 64 mg Ni/kg bw), 3 - 6 % was absorbed at four hours after dosing. Also, regardless of the dose administered, the entire amount of unabsorbed nickel chloride was eliminated through faeces (EU RARa, 2008). In a further study in Wistar rats, 9.8 % of a single oral dose of nickel (10 mg nickel chloride in 5 % starch solution) was absorbed (EU RARa, 2008). Further studies conducted in mice have identified that 80 % of orally administered nickel chloride was found in the intestines 20 hours post dosing (EU RARa, 2008). No data are available on the metabolism of orally administered nickel chloride.

Based on human data, a biokinetic model to estimate nickel absorption has shown that estimated nickel absorption ranged from 12-27 % of the ingested dose after fasting and an absorption of 1-6 % when nickel was administered either in food, in water, or in a capsule during (or in close proximity to) a meal (EURARa, 2008).

Dermal exposure:

In a study conducted in guinea-pigs, radio-labelled nickel chloride (dose unspecified) applied to the shaven flanks of guinea pigs resulted in 0.005, 0.07 and 0.05 % absorption of nickel chloride into plasma within 4, 12 and 24 hours, respectively. Furthermore, 0.009, 0.21 and 0.51 % of nickel chloride was detected in urine. Further investigation showed that majority of the absorbed nickel stayed close to the skin surface indicating minimal systemic absorption (EU RARa, 2008).

Acute Toxicity

Oral

The chemicals in this group have moderate acute oral toxicity. Nickel chloride is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25). However, considering the weight of evidence including recent well-conducted studies on nickel chloride hexahydrate and nickel sulfate hexahydrate (CAS No. 10101-97-0), an amendment to the classification for nickel chloride is recommended (refer to **Recommendation** section).

A recent oral acute toxicity study, conducted in female SD rats using OECD test guideline (TG) 425, determined a median lethal dose (LD50) value of 500 mg/kg bw nickel chloride hexahydrate. Reported signs of toxicity included hypoactivity and abnormal posture (Henderson et al, 2012; REACH). In another study in SD rats, the LD50 was reported as 200 mg/kg bw for nickel chloride hexahydrate (CAS No. 7791-20-0). Reported signs of toxicity included salivation, ataxia and swollen limbs (REACH). The European Union Risk Assessment Report (EU RAR) on nickel chloride reported a rat study where the LD50 was determined to be 432 and 535 mg/kg bw in males and females respectively (EU RARa, 2008).

Nickel sulfate hexahydrate (CAS No. 10101-97-0) has similar oral bioaccessibility to nickel chloride hexahydrate (Henderson et al, 2012; NICNASa). An oral acute toxicity study conducted in female SD rats using OECD TG 425 reported a LD50 value of 362 mg/kg bw for nickel sulfate hexahydrate (CAS No. 10101-97-0) (Henderson et al, 2012).

Dermal

No data are available.

Reports on nickel compounds (ATSDR, 2005; EU RARa, 2008) indicate that dermal absorption is expected to be very limited (ATSDR, 2005) and therefore acute dermal toxicity has not been evaluated.

Inhalation

Nickel dichloride is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23). No reliable data are available to evaluate this classification. Although, information received during the public comment phase indicate that a study is scheduled for completion in 2014. The existing classification will be reviewed once the results of the study in progress are available.

EU RAR (2008) for nickel chloride indicates that the data available are sourced from studies not conducted according to current guidelines. In addition, the available studies did not establish a clear median lethal concentration (LC50) (EU RARa, 2008). The above classification is based on a recommendation from the Classification and Labelling Health Effects Group (EU) that, based on the existing classification for oral acute toxicity and considering toxicokinetic information, the same level of classification can be applied to acute inhalation toxicity of nickel chloride (EU RARa, 2008).

While the recent well conducted oral acute toxicity studies on nickel chloride hexahydrate and nickel sulfate hexahydrate (CAS No. 10101-97-0) result in a recommendation for a lower oral acute toxicity classification (refer **Acute Toxicity - Oral**), an amendment to the inhalation acute toxicity classification may be considered in line with the justification provided in the EU RAR for nickel chloride (EU RARa, 2008). An acute inhalation toxicity study is scheduled for completion in June 2014 (information received during the public comment phase). The existing classification will be reviewed once the results of the study become available.

Observation in humans

A case report describes acute nickel toxicity in 32 nickel plating workers who accidentally ingested a solution containing nickel sulfate and nickel chloride (estimated to be between 0.5 - 2.5 g of nickel). Signs of toxicity reported included nausea, vomiting, abdominal discomfort, headache and shortness of breath. The case report indicated that the symptoms persisted for two days (EU RARa, 2008). No further information is available.

Corrosion / Irritation

Skin Irritation

Nickel chloride (CAS No. 7718-54-9) is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). The available data from observations in humans (refer to **Observation in Humans**) support this hazard classification.

Eye Irritation

The chemicals in this group are eye irritants. No data are available on nickel chloride. Another soluble nickel chemical, nickel sulfate hexahydrate (CAS No. 10101-97-0), was reported to be a slight eye irritant in animal studies (NICNASa).

Observation in humans

Skin irritation data are available from studies conducted to evaluate skin sensitisation. In such studies, a 10 % solution of nickel chloride was reported to induce skin irritation on unoccluded skin, while a 5 % solution produced skin irritation under occlusion (EU RARa, 2008). Further studies have also reported skin irritation as a result of application of nickel chloride at concentrations ranging from 0.5 - 5 % (EU RARa, 2008).

Another soluble nickel chemical, nickel sulfate, produced skin irritation on intact skin at 20 % when tested on human volunteers (NICNASa).

Sensitisation

Respiratory Sensitisation

The chemicals in this group are respiratory sensitisers. Nickel chloride is classified as hazardous with the risk phrase 'May cause sensitisation by inhalation' (R42) in HSIS (Safe Work Australia).

No data are available to evaluate the existing classification for nickel chloride. However, data available for nickel sulfate and other soluble nickel salts indicate that inhalation of soluble nickel compounds may result in respiratory sensitisation. Therefore, based on read-across data (OECD, 2007) for other soluble nickel compounds, no changes to the existing classification for respiratory sensitisation are recommended.

Skin Sensitisation

The chemicals in this group are skin sensitisers. Nickel chloride is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in HSIS (Safe Work Australia). The positive results reported in several guinea pig maximisation tests as well as observations in humans support this classification.

Nickel chloride induced skin sensitisation in two guinea pig maximisation tests (GPMTs). Refer to **Observation in Humans** for further data.

Observation in humans

Skin

In a study conducted in human volunteers, skin patch tests carried out in human volunteers showed a positive reaction in 62/101 and 23/50 human volunteers exposed to 47 and 12 µg of nickel chloride, respectively (EU RARa, 2008). In a second study, 35 human volunteers with pre-existing eczema were sensitised to nickel chloride by dipping one finger in a 10 ppm solution for 10 minutes a day for one week. When tested for sensitisation one week later in a 100 ppm solution of nickel chloride, all volunteers showed a significant increase in eczema symptoms (EU RARa, 2008).

Respiratory

For nickel sulfate, five individual cases of occupational exposure to nickel sulfate through electro- or metal plating were considered to be clinical asthma based on evaluation with specific tests such as, the bronchial inhalation provocation test or testing for specific IgE antibodies (EU RARa, 2008).

Repeated Dose Toxicity

Oral

Four animal studies of varying duration (28 days, 77 days, 90 days and 25 weeks) have been conducted using three different methods of oral administration; in drinking water, by gavage and via food. A lowest observed adverse effect level (LOAEL) of 5 mg Ni/kg bw/day in the form of nickel chloride hexahydrate (23 mg/kg bw/day) was reported in the 90 day study (EU RARa, 2008). However, due to excessive mortality as a result of gavage errors, this study cannot be considered for classification purposes.

In a 90 day oral gavage study, male and female SD rats were exposed to 5, 35 or 100 mg of nickel/kg bw/day in the form of nickel chloride hexahydrate. High mortality was reported in the high dose group (100 mg of nickel/kg bw/day) from day 2 - 72 of the study. Necropsy of these animals showed a high incidence of gastrointestinal abnormalities (green content in various parts of the gastrointestinal tract). Further adverse effects included lung abnormalities (pneumonitis) which occurred in males (7/25) and females (10/25) administered 35 mg Ni/kg bw/day. Also at this dose (35 mg Ni/kg bw/day), final body weight was significantly decreased which was associated with an increase in relative organ weights (adrenal gland, brain, testes in males and, adrenals and the heart in females). Blood glucose was significantly decreased in females gavaged with 35 mg of nickel/kg bw/day at the end of the study. The LOAEL of this study was reported to be 5 mg of nickel/kg bw/day. However, it is reported that the high mortality in this study could have been a result of gavage errors (EU RARa, 2008).

In a further study, male Wistar rats were exposed to 2.5, 5 or 10 μg/mL nickel chloride in drinking water for 28 days (EU RARa, 2008. The study assumed a water intake of 100 mL/kg bw/day which equates to 0.025, 0.5 or 0.1 mg/kg bw/day of nickel chloride. Adverse effects included a 20 % decrease in body weight gain (all doses) and a dose related significant increase (14 - 27 %) in serum glucose. The EU RARa (2008) reported that this study had limitations in design and reporting.

Also available is a two year rat study (LOAEL, 6.7 - 11 mg Ni/kg bw/day) conducted with nickel sulfate hexahydrate (CAS No. 10101-97-0). However, the severity of effects reported in these studies on nickel chloride and nickel sulfate do not meet criteria for hazard classification (EU RARb, 2008).

Dermal

There are no reliable studies to assess repeated dose toxicity through the dermal route. Considering the toxicokinetic data on nickel chemicals, dermal absorption is expected to be poor (EU RARa, 2008). Therefore, hazard classification is not warranted for chemicals in this group.

Inhalation

Nickel chloride is classified as hazardous with the risk phrase 'Toxic: danger of serious damage to health by prolonged exposure through inhalation' (T; R48/23) in HSIS (Safe Work Australia). While limited data are available for nickel chloride, the existing classification is supported based on read-across data available for nickel sulfate (EU RARb, 2008; NICNASa). Lung fibrosis was reported in a two year rat study at a concentration of 0.25 mg/m^3 nickel sulfate hexahydrate (CAS No. 10101-97-0) (equivalent to 0.06 mg Ni/m^3).

In a study conducted in rabbits, exposure to nickel chloride (0.2 - 0.6 mg Ni/m^3) for up to eight months resulted in adverse effects described as inactive nodular accumulation of macrophages and decreased lysozyme content in macrophages of the lungs at the lowest dose administered (0.2 mg Ni/m^3 equates to 0.8 mg/m^3 nickel chloride hexahydrate) (EU RARa, 2008). No further studies are available for nickel chloride.

For nickel sulfate, the National Toxicology Program (NTP) has conducted 13 week and two year studies in male and female Fischer 344 (F344) rats. These are described below.

In the 13 week study, male and female rats were exposed to 0, 0.12, 0.25, 0.5, 1 or 2 mg/m^3 nickel sulfate hexahydrate (equivalent to 0, 0.03, 0.06, 0.11, 0.22 or 0.44 mg Ni/m^3). Chronic active inflammation was significantly increased in female rats at a concentration ≥ 0.5 mg/m^3 nickel sulfate hexahydrate and in males at a concentration ≥ 1 mg/m^3 nickel sulfate hexahydrate (NTP, 1996). Atrophy of the olfactory epithelium occurred at exposure levels equal to and greater than 0.5 mg/m^3 and 0.25 mg/m^3 in males and females, respectively. Dose dependent increases in neutrophil and lymphocyte numbers were reported in female rats (EU RARb, 2008).

In the two year NTP study (conducted similarly to OECD TG 453), animals were exposed to 0, 0.12, 0.25 or 0.5 mg/m^3 of nickel sulfate hexahydrate (equivalent to 0, 0.03, 0.06, 0.11 mg Ni/m^3) for six hours a day, five days a week for two years. Survival rates were not affected at any exposure level. Adverse effects including: chronic active inflammation, macrophage hyperplasia, alveolar proteinosis and fibrosis were noted in both sexes exposed to 0.25 and 0.5 mg/m^3 of nickel sulfate hexahydrate. Atrophy of the olfactory epithelium was noted in both sexes at the highest dose only (0.5 mg/m^3). While chronic lung inflammation was observed at the lowest dose of 0.12 mg/m^3 nickel sulfate hexahydrate (equivalent to 0.03 mg Ni/m^3) in males at the 7 month interim evaluation phase, no significant effects were seen in male or female rats after 15 and 24 months of exposure (NTP, 1996). Based on chronic active lung inflammation, fibrosis, and macrophage hyperplasia observed in males and females at 0.25 mg/m^3 nickel sulfate hexahydrate (CAS No. 10101-97- 0) at the end of the two year evaluation, a no observed adverse effect concentration (NOAEC) of 0.12 mg/m^3 has been determined (NTP, 1996; EU RARb, 2008).

Simultaneous 13 week and two year NTP studies conducted in $B6C3F_1$ mice showed similar adverse effects in the lung and olfactory epithelium (EU RARb, 2008). In the 13 week study, mice were exposed to 0, 0.12, 0.25, 0.5, 1 or 2 mg/m^3 of nickel sulfate hexahydrate (equivalent to 0, 0.03, 0.06, 0.11, 0.22 or 0.44 mg Ni/m^3) for six hours a day, five days a week, for 13 weeks. Mortality was reported in three mice from the control group and one male mouse from the 0.12 mg/m^3 exposure group. Similar to the 13 week rat study, haematology parameters (neutrophils and lymphocytes) were elevated in female mice, although to a lesser extent than in rats. Mice exposed to the highest doses (1 and 2 mg/m^3 of nickel sulfate hexahydrate) had significantly increased lung weights when compared with the control group. There was a significant increase in chronic active inflammation and interstitial infiltration at the highest dose (2 mg/m^3 of nickel sulfate hexahydrate) in male and female mice. In addition, at the highest dose, atrophy of the olfactory epithelium was observed in the nasal passages of male and female mice (EU RARb, 2008).

In the two year study conducted in mice, survival was not affected across any exposure group (0, 0.25, 0.5, or 1 mg/m^3 of nickel sulfate hexahydrate, equivalent to 0, 0.06, 0.11 or 0.22 mg Ni/m^3). Chronic active inflammation, macrophage hyperplasia, bronchiolisation, alveolar proteinosis and infiltrating cells of the interstitium were significantly increased in male ($\geq$ 0.5 mg/m^3 of nickel sulfate hexahydrate) and female mice ($\geq$ 0.25 mg/m^3 of nickel sulfate hexahydrate). Atrophy of the olfactory epithelium was observed in males (0.5 and 1 mg/m^3 of nickel sulfate hexahydrate) and females (1 mg/m^3 of nickel sulphate hexahydrate) at the end of the study. As all levels of exposure were reported to induce chronic lung inflammation in female mice, a LOAEC of 0.25 mg/m^3 nickel sulfate hexahydrate was assigned for females and a LOAEC of 0.5 mg/m^3 nickel sulfate hexahydrate was assigned for males (EU RARb, 2008).

Observation in humans

A study investigated biochemical markers of kidney damage in 14 male and 12 female workers exposed to soluble nickel compounds (nickel sulphate and nickel chloride) in a chemical plant for 25 and 15 years, respectively. It is reported that the workers were exposed to nickel concentrations exceeding (4-26 times) the designated threshold values (TLV) of 0.05 mg/m^3. After analysis of biochemical kidney markers (lysozyme and N-acetyl-beta-D-glucosaminidase) it was concluded that exposure to high levels of soluble nickel compounds can have adverse effects on kidney function: specifically, renal tubular function (EU RARa, 2008).

Genotoxicity

Nickel chloride is classified as hazardous—Category 3 mutagenic substance—with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in HSIS (Safe Work Australia). The positive results reported in several in vitro and in vivo tests support this classification for all members in this group.

In vitro

Genotoxicity data available for nickel chloride indicate that chemicals of this group are not mutagenic in bacterial assays with *Salmonella typhimurium* and *Escherichia coli*. However, studies conducted with human and mammalian cells show that nickel chloride (12 studies) is clastogenic and can induce chromosomal effects (sister chromatid exchanges and chromosomal aberrations) in a dose dependent manner (EU RARa, 2008). Nickel chloride (0 - 1000 μM) induced a dose dependent increase in chromosomal aberrations (gaps, breaks and exchanges) in Chinese hamster ovary cells (CHO) (REACH).

In vivo

Nickel chloride is reported to induce DNA damage (single and double stranded DNA breaks) in leucocytes in Swiss albino male mice. Animals in this study exposed to nickel chloride (3.4, 6.8, 13.6, 27.2, 54.4 or 108.8 mg/kg bw/day, orally administered) showed a significant time and dose dependent increase in DNA damage as assessed using the comet assay (EU RARa, 2008). Nickel chloride is also reported to induce chromosomal aberrations in the bone marrow of mammals (positive in three out of four

studies (three intraperitoneal and one oral administration)) and tested positive in two out of four micronucleus tests (three intraperitoneal and one oral administration) conducted in mice of varying strains (EU RARa, 2008).

While a mixture of positive and negative results were reported in a variety of mammalian species and strains, overall, there is evidence for an in vivo clastogenic effect to nickel chloride (EU RARa, 2008).

Carcinogenicity

Nickel chloride is classified as hazardous—Category 1 carcinogenic substances—with the risk phrase 'May cause cancer by inhalation' (T; R49) in HSIS (Safe Work Australia). The International Agency for Research on Cancer (IARC) has classified the chemical as 'Carcinogenic to humans' (Group 1) (IARC, 2012). There are no specific data on nickel chloride. However, data from nickel sulfate can be read-across to chemicals of this group given that nickel chloride has similar bioaccessibility and bioavailability to nickel sulfate (Goodman et al, 2009; Oller et al., 2009; Henderson et al, 2012). The available epidemiological data on nickel sulfate and nickel chloride support this classification.

Epidemiological studies

Epidemiological study data from nickel refineries demonstrate a positive dose-dependent association between exposure to soluble nickel compounds (nickel sulfate and nickel chloride) and an increased risk of respiratory cancers (EU RARb, 2008). Data from key epidemiological studies are summarised below.

The risk of lung and nasal cancer was investigated in 2521 men who had previously worked in a refinery in Clydach, South Wales. From this cohort, 216 developed lung cancers and 75 developed nasal cancers. While the men were exposed to various types of nickel, men who worked in the hydrometallurgy department were exposed to mainly nickel sulfate. A further multivariate regression analysis confirmed that the results of this study could be interpreted as water-soluble nickel compounds to be a significant contributing risk factor in the development of lung and nasal cancers (EU RARb, 2008).

The second epidemiological study was carried out in 3250 men working in a Norwegian refinery in Kristiansand. Men employed for at least one year between 1946 - 1969 were followed up until 1984. During the follow-up period, 77 cases of deaths from lung cancer, three deaths from nasal cancer and four cases of nasal cancer were reported. Furthermore, 19 deaths from lung cancer and two from nasal cancer were reported in an analysis of workers with five or more years of work in the electroplating department (where exposure to nickel sulfate was highest (0.3 - 5.0 mg/m^3 Ni) in the refinery). A larger cohort study from the same refinery analysed using multivariate regression (taking into account factors such as smoking, exposure to other nickel compounds and age) demonstrated a three-fold increased risk for lung cancer in workers exposed to water-soluble nickel compounds. In addition, this study identified that the process was changed in the electrolysis department leading to the replacement of 80 % of the nickel sulfate with nickel chloride. This did not affect the level of lung cancer risk, which still remained elevated. After conducting a regression analysis (taking into account smoking, exposure to nickel oxide and age), a dose-dependent relationship was demonstrated between lung cancer and exposure to soluble nickel compounds (nickel sulfate and/or nickel chloride) (EU RARb, 2008).

Two further cohorts have been assessed: nickel refinery workers in Harjavalta (Finland) and Port Colborne (Ontario, Canada). There were no reported significant increases in lung or nasal cancers in electrolysis workers exposed to an inhalable aerosol fraction of approximately 0.4 mg Ni/m^3 in the Port Colborne cohort (EU RARb, 2008). In the Harjavalta cohort, up to 90 % of exposure to soluble nickel compounds between 1960 - 1985 was nickel sulfate (approximate inhalable aerosol fraction of 0.1 - 0.4 mg Ni/m^3). This cohort had an increased risk of lung and nasal cancers (EU RARb, 2008).

Animal studies

Two-year studies with oral and inhalation routes of exposure undertaken in male and female rats and mice have shown no carcinogenic activity attributable to nickel sulfate exposure. These studies are described in detail in the **Repeated Dose Toxicity** section of this report.

Further studies using other methods of exposure such as intraperitoneal (i.p.) injections, intramuscular (i.m.) injections or intramuscular implants have been conducted with nickel sulfate. While some of these studies have reported development of tumours at the site of the injection, the route of administration is not considered relevant as humans are likely to be exposed via inhalation, oral intake or dermal contact (EU RARb, 2008).

Promoter studies

Available data on nickel sulfate and nickel chloride indicate that the chemicals may have a promoting effect in combination with other initiators of carcinogenicity. Nickel chloride orally administered enhanced the renal carcinogenicity (but not hepatocarcinogenicity) of N-ethyl-N-hydroxyethylnitrosamine in rats (EU RARa, 2008). Based on three carcinogenic promoter studies conducted, nickel sulfate may be a weak promoter in experimental studies in rats. However based on the limited information, a conclusion cannot be drawn (EU RARb, 2008).

Reproductive and Developmental Toxicity

Nickel chloride is classified as hazardous—Category 2 substances toxic to reproduction—with the risk phrase 'May cause harm to the unborn child' (T; R61) in HSIS (Safe Work Australia). The available data from animal studies support this classification.

Animal Studies

In a one generation/two breeding period study, Long-Evans female rats were exposed to nickel chloride hexahydrate (10, 50 or 250 ppm equivalent to 1.33, 6.80 or 31.63 mg Ni/kg bw/day) via drinking water for 11 weeks prior to mating, through gestation and lactation. Maternal effects included reduced water intake in all treatment groups across all stages of the experiment (pre-mating, gestation and lactation), although the overall average daily nickel doses were maintained. Reproductive performance was not affected in both breeding periods but prolactin levels were increased in the 250 ppm dams. The number of litters with dead pups was increased in the 250 ppm group in the first breeding period. In the second breeding period, the number of litters with dead pups at birth was significantly increased in the 10 and 250 ppm dose groups. Also, survival of male pups during the second lactation period was significantly reduced in the 50 and 250 ppm groups. The LOAEL in this study was 10 ppm (1.33 mg/kg bw/day) (REACH; EU RARa, 2008).

In a two generation study conducted in female CD rats, nickel chloride hexahydrate was administered (0, 20, 250, 500 or 1000 ppm) via drinking water 11 weeks before mating and continued for a total of 24 and 30 weeks in males and females respectively. The 1000 ppm dose was discontinued due to excessive mortality after two weeks. The intake of nickel was estimated to be 0, 6, 25 and 42 mg Ni/kg bw/day. At 500 ppm, a significant decrease in liver weight (females only) and body weight was observed (both sexes). The first litter from the first generation (F1a) had a significantly decreased litter size, significantly increased pup mortality and significantly decreased average pup weight at the highest dose (500 ppm). The second litter from the first generation (F1b) also had a significant decrease in litter size at the highest dose (500 ppm), but effects at 50 and 250 ppm of increased pup mortality and decreased live litter size respectively. However, the study reported that during the second gestation phase the room temperature varied by 3-5 degrees Celsius which may have impacted on the results of the F1b generation. Surviving F1b generation animals were mated to produce a two further litters (F2a and F2b). Similarly to previous generations, at the highest dose (500 ppm), significant decrease in body weight of dams and pups was reported. Also at this dose, there was a reported increase in neonatal mortality during the postnatal development period. Due to the incident with room temperature change, a reliable NOAEL cannot be established from this study. However, the clear developmental effects observed in the first generation pups at 500 ppm (equivalent to 42 mg Ni/kg bw/day warrant the existing classification (EU RARa, 2008).

Epidemiological Data

The spontaneous abortion rate was increased (15.9 %) in a cohort of 356 women who worked in a nickel hydrometallurgy plant compared with a cohort of 342 local female construction workers (8.5 %) in the arctic region of Russia. The nickel hydrometallurgy workers were exposed to primarily nickel sulfate (0.08 - 0.196 Ni/m³). However, the authors of the study note that the nickel hydrometallurgy workers may also have been exposed to high concentrations of chlorine. In addition, there was no assessment of alcohol or smoking habits and the confounding from these factors does not allow a conclusion to be made (ATSDR, 2005).

Further data published after the finalisation of the EU RAR include an analysis of the Kola birth register in Russia (Vaktskjold et al, 2004). This register was set up in 1997 in response to a report indicating possible increased spontaneous abortions and structural malformations in infants from mothers occupationally exposed to nickel up to 0.33 mg Ni/m^3 (Vaktskjold et al, 2004) at the Severonikel nickel refinery in the town of Moncegorsk. Analysis of the Kola birth register by Vaktskjold and colleagues have concluded that mothers occupationally exposed to soluble nickel compounds were not at an increased risk of the following reproductive outcomes: genital malformation, spontaneous abortions, small for gestational age newborns and skeletal malformations (Vaktskjold et al,. 2006, 2007, 2008a, 2008b).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (genotoxicity and developmental toxicity), local long-term effects (carcinogenicity), local and systemic acute effects (acute toxicity by the oral and inhalation routes of exposure) and local acute effects (skin and respiratory sensitisation). The chemical may also cause harmful effects on the respiratory tract following repeated exposure through inhalation and skin irritation.

Public Risk Characterisation

Given the site-limited uses identified for the chemical, it is unlikely that the public will be exposed to chemicals of this group. Although, the public may come into contact with articles/coated surfaces containing the chemical, it is expected that the chemical will be bound within the article/coated surface and hence will not be bioavailable. Therefore the risk to the public is not considered to be unreasonable.

Occupational Risk Characterisation

During use of chemicals in this group in electroplating, as chemical mediators and as chemical intermediates, dermal, ocular and inhalation exposure of workers to these chemicals may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemicals at lower concentrations may 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 long-term effects, local long-term effects and systemic acute/local health effects, these chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemicals 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 appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

Based on available data on nickel sulfate hexahydrate from animal studies, there is a concern that the current occupational exposure standard (0.1 mg Ni/m^3 - inhalable fraction) for 'Nickel, soluble compounds (as Ni)' in HSIS may not be sufficiently protective of the health of workers. A concentration of 0.25 mg/m^3 nickel sulfate hexahydrate (CAS No. 10101-97-0) (equivalent to 0.06 mg Ni/m^3) was identified in the inhalation repeated dose toxicity studies as a level at which severe effects are observed. The Scientific Committee on Occupational Exposure Limits (SCOEL) in the EU proposed a lowering of the exposure standard to 0.01 mg Ni/m^3 (TWA - inhalable fraction) for water soluble and poorly water soluble nickel compounds, excluding metallic nickel (SCOEL, 2011). The differences between rats and humans with respect to particle deposition in the alveolar region should be considered and quantified in considering an exposure standard (SCOEL, 2011).

NICNAS Recommendation

A Tier III assessment may be necessary to provide further information as to whether the current exposure controls are appropriate to offer adequate protection to workers.

All other risks are considered to have been sufficiently assessed at the Tier II level, subject to implementing any risk management recommendations, and provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

It is recommended that the existing SUSMP classification for nickel sulfate be altered to "Nickel, soluble salts" as it is likely that for any publicly available product containing nickel sulfate, other soluble nickel compounds including chemicals in this group could be substituted.

Work Health and Safety

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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Toxic by inhalation (T; R23)*	Harmful if swallowed - Cat. 4 (H302) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Irritating to skin (Xi; R38)*	Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by inhalation (Xn, R42)* May cause sensitisation by skin contact (Xi; R43)*	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)*	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 1 - May cause cancer by inhalation (T; R49)*	May cause cancer - Cat. 1A (H350i)
Reproductive and Developmental Toxicity	Repro. Cat 2 - May cause harm to the unborn child (T; R61)*	May damage the unborn child - Cat. 1B (H360D)

[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 exposure to nickel chloride 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 may 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 assist with meeting 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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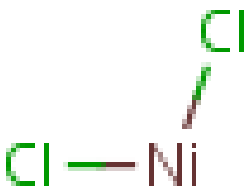
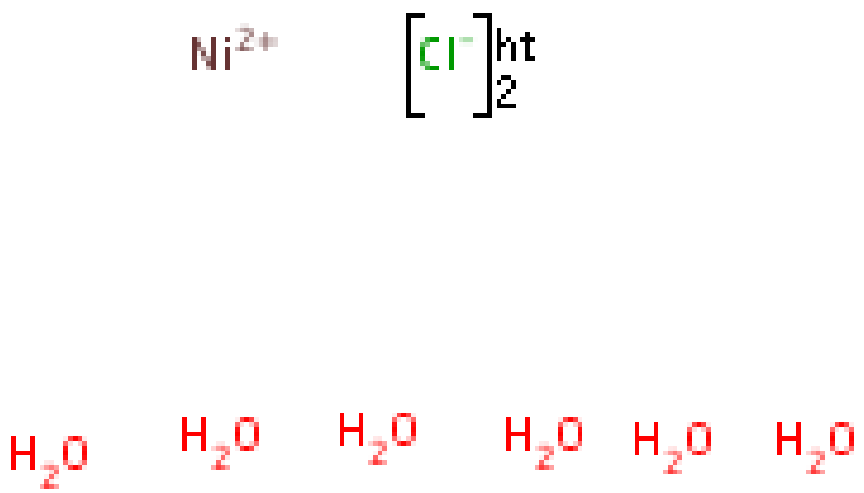
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Nickel chloride (NiCl2)** Nickel dichloride Nickel (II) chloride Nickelous chloride
CAS Number	7718-54-9
Structural Formula	
Molecular Formula	Cl2Ni
Molecular Weight	129.6

Chemical Name in the Inventory and Synonyms	**Nickel chloride (NiCl2), hexahydrate** Nickel dichloride, hexahydrate Nickel chloride hexahydrate Nickel (II) chloride hexahydrate Nickel chloride hexahydrate (NiCl2.6H2O) Nickel chloride (NiCl2) hydrate (1:6)
CAS Number	7791-20-0
Structural Formula	
Molecular Formula	Cl2Ni.6H2O
Molecular Weight	237.69

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