Nickel sulfate: Human health tier II assessment

07 February 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Sulfuric acid, nickel(2+) salt (1:1)	7786-81-4
Sulfuric acid, nickel(2+) salt (1:1), heptahydrate	10101-98-1

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**

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of chemicals contains nickel sulfate and its hydrated salt; nickel sulfate heptahydrate (CAS No. 10101-98-1). While anhydrous nickel sulfate is listed on the Australian Inventory of Industrial Chemicals (AICS), the listing includes all hydrated forms such as the hexahydrate and heptahydrate. 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 the chemicals may be grouped together for risk assessment purposes.

Import, Manufacture and Use

Australian

The total volume of sulfuric acid, nickel (2+) salt (1:1) (CAS No. 7786-81-4) introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was over 10000 tonnes.

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

Sulfuric acid, nickel (2+) salt (1:1) (CAS No. 7786-81-4) has reported site-limited use including:

- production of copper chrome arsenate;
- production of nickel metal in nickel refining; and
- electroplating and coating of camshafts in drilling.

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).

The chemicals in this group have the following common uses:

The chemicals have reported domestic use including in:

- paints, lacquers and varnishes; and
- in home maintenance products such as coatings and sealants.

The chemicals have reported commercial use including in:

- colourants, dyes and pigments.

The chemicals have reported site-limited use including as:

- laboratory reagents;
- electroplating agents;
- chemical mediators (catalysts, accelerators, initiators);
- chemical intermediates; and
- in the production of nickel metal in nickel refining.

Restrictions

Australian

Nickel sulfate is listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Schedule 6.

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.

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 sulfate (CAS No. 7786-81-4) 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 (Mutagenic)

Repr. Cat. 2; R61 (Reproductive toxicity)

Xn; R20/22 (Acute toxicity)

T; R48/23 (Repeat dose toxicity)

Xi; R38 (Irritant)

R42/43 (Sensitiser)

Exposure Standards

Australian

The chemicals in this group fall under the category of 'Nickel, soluble compounds (as Ni)' in HSIS, and have an exposure standard of 0.1 mg/m^3 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 sulfate hexahydrate (CAS No. 10101-97-0) 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).

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). Physiologically, 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:

The deposition of inhaled nickel particles is dependent on particle size. Large particles (5 - 30 µm) are generally deposited in the nasopharyngeal area whereas smaller particles (1 - 5 µm) can enter the trachea and bronchiolar region. Even smaller particles (< 1 µm), can enter the alveolar region of the lungs (ATSDR, 2005). In humans, the ATSDR (2005) reported that 20 - 35 % of inhaled nickel that is deposited in the lungs is absorbed in the blood. The remainder of nickel is either swallowed, expectorated or remains in the respiratory tract. However, the EURAR (2008) reported that absorption of soluble nickel compounds is as high as 97 - 99 %.

A repeat dose inhalation study conducted in rats (Fischer 344) and mice (B6C3F1) showed that nickel sulfate hexahydrate (CAS No. 10101-97-0) with a mean mass median aerodynamic diameter (MMAD) ranging from 2.0 - 2.4 µm was extensively cleared from the lung. The average half life for clearance was 2 - 3 days in rats with 99 % clearance, and less than one day in mice with 80 - 90 % clearance (EU RAR, 2008). Repeated administration for two or six months did not affect the rate of clearance, and there was no reported accumulation of nickel in the lungs of rats or mice (EU RAR, 2008).

Oral exposure:

The extent of absorption from the gastrointestinal tract is influenced by the solubility of the nickel compound, whether the nickel compound is administered in drinking water, to fasting subjects, or together with food (EURAR, 2008). A human study using radiolabelled nickel isotopes given in water has indicated that approximately 29 % of the administered dose is absorbed after fasting. One vegetarian female subject had an absorption rate of 40 %, which the authors stated was possibly due to iron deficiency (Patriarca et al., 1997). In humans, absorption of nickel sulfate is 40 times greater when administered under fasting conditions via drinking water (27 %) in contrast to when administered with food (0.7 %) (ATSDR, 2005). 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 (EURAR, 2008). Studies in rats and dogs indicate that 1 - 10 % of nickel sulfate is absorbed through the gastrointestinal tract. In animal studies, nickel was primarily distributed in the kidneys, with significant amounts also in the liver, heart, lungs and fat. Unabsorbed nickel sulfate was excreted in faeces (ATSDR, 2005).

Dermal exposure:

Human studies using radioactive isotopes of nickel applied through occluded skin patches showed that 55 - 77 % can be absorbed; however, it could not be established what percentage of nickel penetrated the deep layers of the skin or blood (ATSDR, 2005). However, further studies reported in the European Union Risk Assessment Report (EU RAR) indicate that dermal absorption of nickel sulfate and other soluble nickel compounds is extremely low (2 %). In an in vitro study using human skin, 97 % of the administered dose was present in the application solution 96 hours after application, 1 % in the receptor fluid and 0.6 % in the upper layers of the skin (stratum corneum), indicating that absorption was minimal (EU RAR, 2008).

Acute Toxicity

Oral

The chemicals in this group have moderate acute oral toxicity. Nickel sulfate is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). The available data support this classification.

Available oral median lethal dose (LD50) values for the hexahydrate salt range from 275 - 500 mg/kg bw (REACH; EU RAR, 2008). Reported signs of toxicity included lethargy, piloerection and weakness. Histopathological analysis showed discolouration of the small intestines at 200 - 500 mg/kg and red intestines at higher doses (1000 - 2000 mg/kg bw) (REACH). In a recent study carried out according to OECD Test Guideline (TG) 425, the LD50 of nickel sulfate hexahydrate (CAS No. 10101-97-0) was determined to be 362 mg/kg bw (Henderson et al, 2012).

Dermal

No data are available.

Reports on nickel sulfate hexahydrate (EU RAR, 2008; ATSDR, 2005) indicate that dermal absorption is expected to be very limited (ATSDR, 2005) and therefore acute dermal toxicity has not been evaluated using OECD TGs.

Inhalation

The chemicals in this group have moderate acute inhalation toxicity. Nickel sulfate is classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in HSIS (Safe Work Australia). The available data support this classification.

In a study carried out according to OECD TG 403, nickel sulfate hexahydrate (CAS No. 10101-97-0) was administered as an aerosolised dust (0.063 - 5.08 mg/L of nickel sulfate hexahydrate) to male and female Sprague Dawley (SD) rats. The median lethal concentration (LC50) value was calculated to be 2.48 mg/L in male and female rats exposed to nickel sulfate hexahydrate (REACH). At the highest dose (5.08 mg/L) 100 % mortality was observed within three days of administration. Gross pathological necropsy conducted 14 days after administration showed discolouration of the lungs and liver, and rigor mortis at 2.12 mg/L. At the highest dose (5.08 mg/L), discolouration of the lungs, liver and/or intestines, distension of the stomach and/or intestines, and/or rigor mortis were observed (REACH).

Observation in humans

Oral:

Accidental ingestion of nickel sulfate crystals (approximately 570 mg Ni/Kg) by a two year child resulted in cardiac arrest and death within eight hours of ingestion (ATSDR, 2005).

Inhalation:

Without using any personal protective equipment for 90 minutes, a man conducting metal arc spraying (which produces nanosize particles (50 nm)), was reported to have urinary nickel concentrations of 700 μg/L compared with < 0.1 - 13.3 μg/L in persons not occupationally exposed to nickel. The man died 13 days after exposure due to adult respiratory distress syndrome (ARDS). Histological examination after death showed alveolar damage and oedema in the lungs, and tubular necrosis in the kidneys (ATSDR, 2005). The worker is reported to have been exposed to high levels (≥ 380 mg Ni/m^3) of nickel.

Corrosion / Irritation

Skin Irritation

Nickel sulfate is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). The available data from human observations support this classification.

Nickel sulfate hexahydrate (CAS No. 10101-97-0) was mildly irritating when tested according to OECD TG 404 in New Zealand White rabbits. Dermal exposure to the chemical for four hours produced mild erythema which was completely reversible within 48 hours (REACH).

Further evaluation for irritation has been conducted in human volunteers, refer **Observation in Humans**.

Eye Irritation

The chemicals of this group are mild eye irritants. Nickel sulfate is reported to be a slight eye irritant in animal studies. Effects were not sufficient to warrant a hazard classification.

Data available for nickel sulfate hexahydrate (CAS No. 10101-97-0) indicate that 0.1 g of the chemical instilled into the eyes of New Zealand White rabbits produced iritis and conjunctivitis which resolved within 48 hours and seven days, respectively (REACH).

Observation in humans

Human volunteers with no previous history of eczema were exposed to nickel sulfate at various concentrations in a patch test on intact and scarified skin. Nickel sulfate was reported to be a "marginal irritant at 0.13 %" and a "ferocious one at 1 %" on scarified skin. In comparison, the threshold to produce a skin reaction on intact skin was 20 % (EU RAR, 2008).

In a further study, 25 volunteers with no history of eczema underwent five patch tests with nickel sulfate at concentrations ranging from 5 - 20 %. No skin irritation was seen in this study (EU RAR, 2008).

Sensitisation

Respiratory Sensitisation

The chemicals of this group are respiratory sensitisers. Nickel sulfate is classified as hazardous with the risk phrase ‘May cause sensitisation by inhalation’ (R42) in HSIS (Safe Work Australia). This classification is based on observations in humans exposed to nickel (refer to **Observation in Humans**).

Skin Sensitisation

Nickel sulfate 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 and observations in humans support this classification.

All six studies reported by the European Union Risk Assessment Report (EU RAR) for skin sensitisation in guinea pigs found a positive response to nickel sulfate hexahydrate (CAS No. 10101-97-0). Methods included the guinea pig maximisation test (GPMT), open epicutaneous testing and skin painting studies (EU RAR, 2008).

Observation in humans

Skin

Allergic contact dermatitis was found to occur in 15.5 % of approximately 75 000 people undergoing patch-testing with nickel sulfate (ATSDR, 2005). Further skin-patch studies have shown a similar incidence of allergic contact dermatitis to nickel patch

tests (11 - 21%) (ATSDR, 2005; EU RAR, 2008). The prevalence of nickel sensitivity is reported to be higher in younger females than in males or older individuals (ATSDR, 2005). This is related to nickel exposure through jewellery rather than biochemical susceptibility (ATSDR, 2005).

Furthermore, contact dermatitis resulting from nickel exposure is reported to occur through an immunologic response. A relationship between the human lymphocyte antigen (HLA) and patients with nickel sensitisation has been reported (ATSDR, 2005).

Respiratory

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

Repeated Dose Toxicity

Oral

The chemicals of this group do not cause serious damage to health by prolonged exposure if swallowed. While the lowest observed adverse effect levels (LOAELs) available from two year rat studies were 6.7 - 11 mg Ni/kg bw/day, the severity of effects seen in these studies do not meet the criteria for hazard classification.

In a two year oral gavage study, male and female Fischer 344 (F344) rats were administered 10 - 50 mg/kg bw/day nickel sulfate hexahydrate (CAS No. 10101-97-0). Adverse effects included a biologically significant dose dependent decrease (> 10 %) in body weight which was significant at the two highest doses (30 and 50 mg/kg bw/day) (REACH). No further differences were noted between control or treated animals with respect to haematology, biochemistry or urinalysis parameters. The LOAEL for weight loss was found to be 30 mg/kg bw/day (6.7 mg Ni/kg bw/day (REACH).

In a 13 week repeated dose study, SD rats were exposed to nickel sulfate hexahydrate via drinking water at doses of 0.02, 0.05 or 0.1 % (44.7, 111.75 or 223.5 mg Ni/L). A 4 % decrease in body weight was noted in animals exposed to the highest dose (0.1 % equivalent to 223.5 mg Ni/L). There were no histopathological changes noted, although a 10 % decrease in liver weight (0.02 and 0.1 %), a 10 % decrease in lung weight (0.1 %), a 5 % decrease in heart and testes weight (all dose groups) and a 5 % decrease in spleen weight (all doses) were observed. No other specific signs of toxicity were observed (EU RAR, 2008). Based on a daily water intake assumption of 0.1 L/kg bw/day, the LOAEL was defined for organ weight changes as 11 mg Ni/kg bw/day (EU RAR, 2008).

Dermal

There are no reliable studies to assess repeated dose toxicity via the dermal route. However, considering the ionic nature of nickel salts, dermal absorption is expected to be poor. Therefore, hazard classification is not warranted for the chemicals in this group.

In a study where male rats (species unspecified) were dermally exposed to nickel sulfate (40, 60 or 100 mg Ni/kg bw/day) for 15 or 30 days, no mortality or clinical symptoms were observed. Adverse effects reported were more pronounced in animals treated for 30 days and included dermal effects such as hyperkeratinisation, degeneration and atrophy of the basal layer of the epidermis. The testes were not affected at 15 days, but showed signs of degeneration and oedema of the seminiferous tubules after 30 days of exposure. Liver effects included swollen hepatocytes and degeneration in animals exposed to 15 days at 60 and 100 mg Ni/kg bw/day. After 30 days of exposure, severe liver effects including areas of necrosis, congestion and dilatation of sinusoids were noted in animals exposed to 60 and 100 mg Ni/kg bw/day. The NOAEL for this study was defined as 40 mg Ni/kg bw/day (EU RAR, 2008). Critical analysis of this study suggested that animals may have been orally exposed to the chemical through grooming or licking of the chemical paste applied onto the back of animals (REACH).

Inhalation

Nickel sulfate (CAS No. 7786-81-4) 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). Based on lung fibrosis seen 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), this hazard classification is supported for both members of the group.

The National Toxicology Program (NTP) conducted 13 week and two year studies in male and female Fischer 344 (F344) rats. 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 RAR, 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 RAR 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 RAR, 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 RAR, 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 (≥ 0.5 mg/m^3 of nickel sulfate hexahydrate) and female mice (≥ 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 RAR, 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 sulfate 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 RAR, 2008).

Genotoxicity

Nickel sulfate 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 of this group.

In vitro

Mutagenicity data available for nickel sulfate hexahydrate (CAS No. 10101-97-0) indicate that the chemical is not mutagenic in bacterial assays with *Salmonella typhimurium* and *Escherichia coli*. However, studies conducted with human and mammalian cells show that nickel sulfate (10 studies) is clastogenic and induces chromosomal effects (sister chromatid exchanges and chromosomal aberrations) in a dose dependent manner (EU RAR, 2008).

Nickel sulfate hexahydrate (CAS No. 10101-97-0) (1, 2.5 or 5 μg/ml) increased the frequency of sister chromatid exchanges (SCEs) and chromosomal aberrations (gaps, breaks and exchanges) in both human lymphocytes and hamster embryo cells in a dose dependent manner (REACH).

In vivo

Genotoxicity studies conducted using nickel sulfate have reported both positive and negative results after various routes of exposure (oral, inhalational and intraperitoneal) and testing paradigms investigating deoxyribonucleic acid (DNA) damage, gene mutations and chromosomal effects. Nickel sulfate hexahydrate (CAS No. 10101-97-0) administered via inhalation was reported to induce strand breaks (assessed through the Comet assay) at the highest exposure level (0.22 mg Ni/m^3). Furthermore, it was reported that DNA strand breaks persisted after 13 weeks of recovery (EU RAR, 2008). A study carried out in accordance with OECD TG 474 (mammalian erythrocyte micronucleus test) in SD rats orally exposed to nickel sulfate hexahydrate (CAS No. 10101-97-0) (125, 250 or 500 mg/kg bw/day) did not report any micronucleation in the bone marrow of exposed rats (REACH). In a further study, nickel sulfate was reported to induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. In the same study, nickel sulfate was also reported to weakly induce sex chromosome loss (EU RAR, 2008).

Carcinogenicity

Nickel sulfate 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 soluble nickel compounds as 'Carcinogenic to humans' (Group 1) (IARC, 2012). The available epidemiological data support this classification.

Epidemiological studies

Epidemiological study data from nickel refineries demonstrate a positive dose-dependent association between exposure to nickel sulfate and an increased risk of respiratory cancers (EU RAR, 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 nickel sulfate was a significant contributing risk factor in the development of lung and nasal cancers (EU RAR, 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/m³ 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 RAR, 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 RAR, 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 RAR, 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 RAR, 2008).

Promoter studies

Available data on nickel sulfate indicate that the chemical may have a promoting effect in combination with other initiators of carcinogenicity. 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 RAR, 2008).

Reproductive and Developmental Toxicity

Nickel sulfate is classified as hazardous—Category 2 substance 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 three-generation study, weanling male and female Wistar rats were exposed to nickel sulfate hexahydrate (CAS No. 10101-97-0) in feed (0, 250, 500 or 1000 ppm) for 11 weeks. After 11 weeks of exposure, 20 male and female rats were mated to produce the first generation (F1a) which were euthanised for evaluation and the parental animals (Po) were re-mated to produce a second litter (F1b). Further generations (F1b and F2b) of rats were mated to produce a F3 generation. Based on animal average daily food intake, a daily oral intake of 0, 13-20, 36-40 and 52-80 mg Ni/kg bw/day was calculated. Adverse effects reported included an average 8 and 13 % decrease in body weight in female and male Po animals, respectively. While the fertility index was lower in animals exposed to 250 and 1000 ppm in the F1a generation and at 1000 ppm in the F2b generation, this was not statistically significant; therefore, the NOAEL for fertility was 1000 ppm (52-80 mg Ni/kg bw/day) in this study (EU RAR, 2008). With respect to developmental toxicity, an increase in pup mortality at birth was reported across all concentrations in the F1a generation and at 500 and 1000 ppm in the F1b generation. Also, an overall 27 % decrease in bodyweight was reported across all generations. No further data are available for the F2 or F3 generation animals (EU RAR, 2008).

In a dose finding one generation study conducted in male and female SD rats, eight rats per sex were exposed to nickel sulfate hexahydrate (CAS No. 10101-97-0) via oral gavage (0, 10, 20, 30, 50 or 75 mg/kg bw/day). Dosing was initiated two weeks prior

to mating in the parental animals (F0) and on postnatal day 21 in the F1 offspring. Dosing did not effect survival, growth, gestation or pathological findings on necropsy in the F0 animals, although postimplantation losses were significantly increased in F0 animals exposed to 50 and 75 mg/kg bw/day and the average litter size was significantly reduced at the highest dose (75 mg/kg bw/day). Also, the number of pup mortalities on lactation day zero was significantly increased across all exposure groups except 50 mg/kg bw/day. The LOAEL for neonatal death was, therefore, the lowest dose used in the study (10 mg/kg bw/day, equivalent to 2.2 mg Ni/kg bw/day) (EU RAR, 2008).

A two generation study was carried out similarly to OECD TG 416 in male and female SD rats. Males and females were exposed to nickel sulfate hexahydrate (CAS No. 10101-97-0) (1, 2.5, 5.0 or 10 mg/kg bw/day) by oral gavage daily for 10 weeks prior to mating, during mating and through weaning of first generation (F1) offspring. F1 parental animals were exposed from postpartum day 22 until the end of the study. Parents in the F1 generation did not show any signs of reproductive toxicity but were reported to have significant reduction in liver weight (male rats at 10 mg/kg bw/day), brain weight (females at 2.5 mg/kg bw/day) and body weight (females at 1, 2.5 and 10 mg/kg bw/day) (REACH). In F1 animals, mean body weight gain was significantly lower in the 1 and 5 mg/kg bw/day groups. There were no treatment related signs of reproductive toxicity noted in the second generation (F2) (REACH; EU RAR, 2008). The EU RAR reports further supplementary statistics, using the litter as the statistical unit show that postimplantation/perinatal mortality in the F1 generation is statistically significant. As these effects were not reported in the F2 generation, the NOAEL for developmental toxicity is reported as 5 mg/kg bw/day (1.1 mg Ni/kg bw/day) (EU RAR, 2008).

In the NTP 13 week inhalation study, exposure to nickel sulfate hexahydrate (CAS No. 10101-97-0) (0.5 - 2 mg/m^3) in rats (F344) and mice ($B6C3F_1$) did not result in any reproductive toxicity as assessed through necropsy and evaluation of sperm number, sperm motility or vaginal cytology in male or female animals (NTP, 1996).

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/m^3). 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 drawn (ATSDR, 2005; EU RAR, 2008).

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. Furthermore, these chemicals are currently risk managed through listing in Schedule 6 of the SUSMP for preparations containing the chemical.

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, local long-term 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.

Based on the available data for nickel sulfate hexahydrate, the hazard classification in HSIS for nickel sulfate is considered appropriate.

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

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]

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
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 sulfate 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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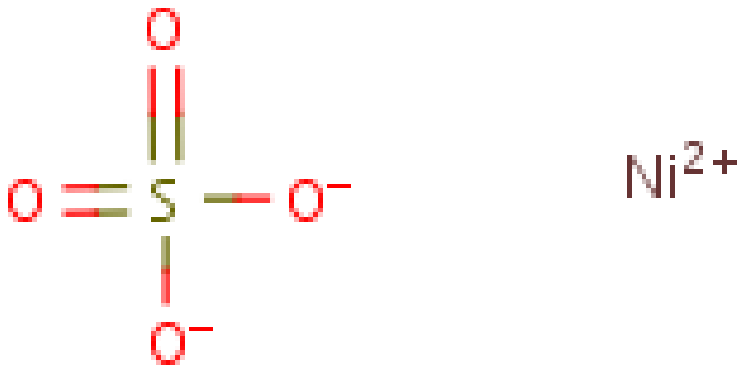
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Sulfuric acid, nickel(2+) salt (1:1)** Nickel sulfate Nickel monosulfate Nickel (II) sulfate
CAS Number	7786-81-4
Structural Formula	
Molecular Formula	H2O4S.Ni
Molecular Weight	154.76

Chemical Name in the Inventory and Synonyms	**Sulfuric acid, nickel(2+) salt (1:1), heptahydrate** Nickel sulfate, heptahydrate Nickel (II) sulfate, heptahydrate Nickelous sulfate heptahydrate Nickel (2+) sulfate heptahydrate
CAS Number	10101-98-1
Structural Formula	

	
Molecular Formula	H2O4S.7H2O.Ni
Molecular Weight	280.91

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