Nickel oxide: Human health tier II assessment

07 February 2014

- Chemicals in this assessment
- Preface
- Grouping Rationale
- Import, Manufacture and Use
- Restrictions
- Existing Worker Health and Safety Controls
- Health Hazard Information
- Risk Characterisation
- NICNAS Recommendation
- References

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Nickel oxide, (NiO)	1313-99-1
Nickel oxide	11099-02-8

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

NICNAS has made every effort to assure the quality of information available in this report. However, before relying on it for a specific purpose, users should obtain advice relevant to their particular circumstances. This report has been prepared by NICNAS using a range of sources, including information from databases maintained by third parties, which include data supplied by industry. NICNAS has not verified and cannot guarantee the correctness of all information obtained from those databases. Reproduction or further distribution of this information may be subject to copyright protection. Use of this information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. NICNAS does not take any responsibility whatsoever for any copyright or other infringements that may be caused by using this information.

ACRONYMS & ABBREVIATIONS

Grouping Rationale

This group of chemicals contains nickel oxide (CAS No. 1313-99-1) and an unknown or variable composition, reaction product or biological (UVCB) form of nickel oxide (CAS No. 11099-02-8). Nickel oxide (CAS No. 1313-99-1) is available as green and black nickel oxide. Green nickel oxide is a finely divided pure form of nickel monoxide which is produced by firing a mixture of nickel powder and water in air at 1000 °C. In comparison, black nickel oxide is produced by calcining nickel hydroxycarbonate or nickel nitrate at 600 °C (EU RAR, 2008). These compounds are grouped together as they are expected to have similar toxicity given that the health effects of exposure to these chemicals are driven by the Ni^{2+} cation.

Import, Manufacture and Use

Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was over 10000 tonnes for both chemicals in this group

The following Australian industrial uses were reported by the National Pollutant Inventory (NPI), and under previous mandatory and/or voluntary calls for information:

Nickel oxide (CAS No. 1313-99-1) has reported site-limited use including:

- as a catalyst and in the production of nickel catalysts;
- in fuel cell electrodes;
- in electroplating;
- in decolourising glass; and

- in the manufacture of other nickel salts.

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 reported commercial use including:

- as corrosion inhibitors;
- as colouring agents;
- as adhesives and binding agents;
- in printing and publishing; and
- in fuel cell electrodes.

The chemicals in this group have reported site-limited use including:

- as catalysts;
- in the manufacture of catalysts;
- as process regulators;
- in refining of nickel;
- in electroplating;
- for decolourising glass;
- in the pulp and paper industry; and
- as formulation components.

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 for restricted use in abrasive blasting at a concentration of greater than 0.1 % of nickel (WHS, 2011).

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 oxide (CAS No. 1313-99-1) 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); and

Xi; R43 (Skin sensitiser).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for nickel oxide (CAS No. 1313-99-1) (Galleria Chemica):

An exposure limit of 0.005 - 1 mg/m^3 time weighted average (TWA) in different countries such as USA (Vermont, Washington - 1 mg/m^3), Canada (Quebec - 1 mg/m^3), United Kingdom (0.5 mg/m^3) and Russia (0.005 mg/m^3).

Health Hazard Information

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 compounds' solubility in the specified physiological solutions (gastric or interstitial). Nickel is metabolised extracellularly through a series of ligand exchange reactions and binds albumin proteins in the blood, consistently across humans, rats and bovine species (ATSDR, 2005).

Inhalation

Experimental data indicate that nickel oxide is retained in the lungs for an extended period of time when compared with soluble nickel compounds such as nickel sulfate. In a 13 week study in Fischer 344 (F344) rats and $B6C3F_1$ mice comparing the toxicity of nickel sulfate, nickel subsulfide and nickel oxide; the amount of nickel sulfate and nickel subsulfide in the lungs stabilised at weeks 9-13, while nickel oxide continued to increase as a function of time (rats only) (ATSDR, 2005; REACHa). This is in line with other studies which show soluble nickel salts are cleared from the lungs, whereas insoluble nickel compounds accumulate in the rat lung (REACHa). The half-life of nickel in the lungs of rats exposed to nickel oxide (activity median aerodynamic diameter (AMAD) of 1.3 μm) was 120 days. In another study, elimination half-lives of nickel oxide were 7.7, 11.5 and 21 days for particles with a mass median aerodynamic diameter (MMAD) of 0.6, 1.2 and 4.0 μm, respectively. Following intratracheal administration of nickel oxide, the majority was excreted in faeces (ATSDR, 2005).

Oral

A suspension of 10 mg of nickel oxide (CAS No. 1313-99-1) (green or black) in 5 % saline was administered to eight Wistar rats via oral gavage. Based on nickel levels in blood and organs, 0.01 % and 0.04 % of green and black nickel oxide were absorbed within 24 hours, respectively (ATSDR, 2005). Orally administered nickel oxide is expected to be excreted largely unchanged in the faeces (ATSDR, 2005).

Dermal

No data are available on dermal exposure to oxidic nickel compounds and resultant toxicokinetics. Low dermal absorption is expected given the low water solubility and the ionic nature of nickel oxide.

Acute Toxicity

Oral

Nickel oxide (CAS No. 1313-99-1) had low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats is greater than 5000 mg/kg bw (Henderson et al, 2012). No deaths or treatment related effects were reported.

Dermal

No data are available.

Inhalation

Nickel oxide (CAS No. 1313-99-1) had low acute toxicity in animal tests following inhalation exposure with no mortalities or toxic effects observed.

In a study conducted according to OECD Test Guideline (TG) 403, five male and female Sprague Dawley (SD) rats were exposed to 0.183 or 5.08 mg/L of green nickel oxide (CAS No. 1313-99-1) for 4 hours. No adverse effects, gross toxicity, behavioural abnormalities or mortalities were noted within the 14 day observation period (REACHa). In a further study, a single exposure of black nickel oxide (5.15 mg/L) to five male and female SD rats did not induce any adverse effects or mortalities within 14 days (REACHa).

In a study using acute intratracheal administration, 0.01, 0.1 or 1 μmol of nickel as black nickel oxide was administered once to SD rats and evaluated at one or seven days post exposure. Compared with other nickel compounds in the study (nickel sulfide, nickel sulfate and nickel chloride), nickel oxide did not induce any changes in lung biochemistry or pathology (REACHa).

Corrosion / Irritation

Skin Irritation

Nickel oxide (CAS No. 1313-99-1) was reported to slightly irritate skin in animal studies performed in accordance with OECD TG 404. The effects were not sufficient to warrant a hazard classification.

A study conducted in New Zealand (NZ) White rabbits assessed the irritation potential of 0.56 g of a 90 % w/w mixture of green nickel oxide under semiocclusive conditions. Exposure to green nickel oxide for four hours resulted in mild erythema within an hour of patch removal. No oedema was observed and all animals were reported to be free of irritation within 24 hours (REACHa).

Eye Irritation

Nickel oxide (CAS No. 1313-99-1) is reported to slightly irritate eyes when tested according to OECD TG 405. Adverse effects were reversible within four days and were not sufficient to warrant a hazard classification.

Nickel oxide (grey) (0.1 g) was instilled into the right eye of NZ White rabbits and the left eye acted as a control. Animals were monitored for up to four days after exposure to the chemical. Nickel oxide induced conjunctivitis in all animals one hour after exposure. There were no signs of corneal opacity or iritis, and conjunctivitis resolved within the four day observation period (REACHa).

Sensitisation

Skin Sensitisation

Nickel oxide (CAS No. 1313-99-1) is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). While the available data do not support this classification, in the absence of more comprehensive information on the materials tested in animals and bioaccessibility studies on range of nickel oxide materials, there is insufficient evidence to support a recommendation to amend this classification.

In a guinea pig maximisation study conducted according to OECD TG 406, female Hartley guinea pigs were assessed for sensitisation using nickel oxide (0.2 g). The guinea pigs were initially sensitised using intradermal nickel sulfate (0.1 mL of 1 % w/v) on day one, and topical nickel sulfate (0.3 mL of 5 % w/v; 48 hours occluded) on day eight. On day 22 after initial induction, nickel oxide was tested using occlusive dermal application of the chemical for 24 hours. In this study, nickel oxide did not induce erythema and was negative for skin sensitisation (REACHa).

In a further study, a Buehler test was conducted according to OECD TG 406 in male and female Hartley guinea pigs. Sensitisation was induced through topical application of a 90 % w/w paste of nickel oxide (green) in mineral oil once a week for three weeks. A challenge dose of 68 % w/w of the chemical in mineral oil was applied 27 days after the first induction dose and animals were scored for erythema 24 and 48 hours later. Three and five animals out of 20 had a positive erythematous response 24 and 48 hours after the test dose, respectively. However, the test dose was noted to elicit irritation in naive (non-induced) animals and therefore the challenge dose was reduced to 45 % w/w in mineral oil. This dose did not elicit any erythematous reactions at 24 or 48 hours and therefore was not considered to induce sensitisation in the Buehler test (REACHa).

Bioaccessibility studies conducted in artificial sweat have shown that low levels of Ni^{2+} (less than 0.1 % of nickel) are released from nickel oxide powder (sample ID - N46) (Mazinanian et al, 2013). While this finding supports the animal studies, the bioaccessibility studies suggest that release of Ni^{2+} differs based on the nickel oxide material tested (Mazinanian et al, 2013; REACHb) . For example, nickel oxide (sample ID - N105) released 1.84 % of nickel in artificial sweat (REACHb). Given the known sensitising potential of the Ni^{2+} ion, there is the possibility that long term exposure may cause allergic reactions (EU

RAR, 2008). Therefore, in the absence of more comprehensive information on the materials tested in animals and bioaccessibility studies on a range of nickel oxide materials there is inadequate data to amend the classification.

Repeated Dose Toxicity

Oral

No data are available. However, considering the low absorption of nickel oxide via the oral route (ATSDR, 2005) the chemicals in this group are not expected to cause serious damage to health by prolonged exposure if swallowed. Furthermore, data from nickel sulfate (NICNASa), which is more bioavailable than nickel oxide through the oral route, suggest that classification is not warranted.

Dermal

No data are available. 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.

Inhalation

The National Toxicological Program (NTP) has carried out 13 week and two year inhalation exposure studies (carried out similarly to OECD TG 413) in F344 rats and B6C3F$_1$ mice (NTP, 1996). The available data report a lowest observed adverse effect concentration (LOAEC) of 0.5 Ni/m^3 for lung effects (chronic lung inflammation) and this data supports a classification (refer to **Recommendation section**) to reflect the findings reported below.

Thirteen week studies

Male and female F344 rats and B6C3F$_1$ mice were exposed to 0.6, 1.2, 2.5, 5 or 10 mg of nickel oxide/m^3 (equivalent to 0.4, 0.9, 2.0, 3.9 or 7.9 mg Ni/m^3) for six hours a day for 13 weeks. There was no reported exposure related mortality in rats or mice at any dose.

In rats, there was a significant increase in absolute and relative lung weight in males exposed to ≥ 0.6 mg NiO/m^3, and relative lung weights in females exposed to ≥ 0.6 mg NiO/m^3. There were also exposure related non-neoplastic lung lesions in male and female rats at concentrations ≥ 2.5 mg NiO/m^3. Furthermore, alveolar macrophage hyperplasia was observed in the lungs of both sexes at the lowest dose (≥ 2.5 mg NiO/m^3) and chronic inflammation was evident at ≥ 5 mg NiO/m^3. Also, hyperplasia and pigmentation of the bronchial and mediastinal lymph nodes were observed at at ≥ 5 mg NiO/m^3. Analysis of haematology results indicated that females were affected more than males. The following haematological factors were significantly increased in males and females; haemoglobin (females ≥ 0.6 mg and males at 10 mg NiO/m^3), segmented neutrophils (females ≥ 0.6 mg NiO/m^3 and males ≥ 1.2 mg NiO/m^3) and lymphocytes (females only 2.5 mg NiO/m^3) (REACHa; NTP, 1996).

In mice, there was a significant increase in absolute lung weight in male and female mice at the highest dose administered, 10 mg NiO/m^3. There were also exposure related non-neoplastic lung lesions in male and female mice at concentrations ≥ 2.5 mg NiO/m^3. Furthermore, alveolar macrophage hyperplasia was observed in the lungs of both sexes at ≥ 0.6 mg NiO/m^3 although chronic active inflammation was not significantly increased in mice. Changes in haematology were reported as being similar to those observed in rats. Overall, the NTP reported that the species of mice used in this study were less sensitive than rats to the effects of inhaled nickel oxide (NTP, 1996).

Two year studies

In a study, male and female F344 rats were exposed to 0, 0.62, 1.25 or 2.5 mg NiO/m^3 (equivalent to 0, 0.5, 1 or 2.0 Ni/m^3) for six hours a day for two years. Mortality was not affected in either rats or mice exposed to nickel oxide. Similar adverse effects to the 13 week study were reported, and consisted of significantly increased absolute lung weights in male and female rats exposed to ≥ 1.25 mg NiO/m^3, respectively (at the 15 month evaluation). Further effects reported at the end of the two year study included chronic inflammation in the lungs of males and females (≥ 0.62 mg NiO/m^3), alveolus pigmentation in males and females (≥ 0.62 mg NiO/m^3), bronchial lymph node pigmentation in males and females (≥ 0.62 mg NiO/m^3) and bronchial lymph node hyperplasia at ≥ 0.62 and ≥ 1.25 mg NiO/m^3 in males and females, respectively. There was a significant increase in hyperplasia of the adrenal medulla in female rats at the highest dose (2.5 mg NiO/m^3) (NTP, 1996).

In a two year study in mice, male and female B6C3F1 mice were exposed to 0, 1.25, 2.5 or 5 mg NiO/m^3 (equivalent to 0, 1, 2 or 3.9 mg Ni/m^3). Mortality was not affected in mice exposed to nickel oxide. In mice, absolute lung weights were significantly elevated in male and female mice at exposure concentrations ≥ 2.5 mg NiO/m^3. Further significant adverse effects reported in male and female mice at ≥ 1.25 mg NiO/m^3 included chronic lung inflammation, bronchiolisation, alveolus pigmentation and proteinosis, bronchial lymph node hyperplasia and pigmentation (NTP, 1996).

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemicals in this group do not warrant classification. While there are positive in vitro results, the in vivo genotoxicity data do not indicate that nickel oxide directly damages genetic material.

In vitro

In a mammalian cell transformation assay, a mouse embryo cell line was incubated with 50 - 1000 μM of nickel oxide (grey-black) for 48 hours. Nickel oxide induced significant morphological transformations in a dose dependent manner at doses ≥ 200 μM (REACHa). In a further study carried out according to OECD TG 476 (in vitro mammalian cell gene mutation test), mouse lymphoma cells were exposed to nickel oxide (green) ranging from 1 - 10 mM for 4 or 24 hours, with or without metabolic activation. In this study, nickel oxide with or without metabolic activation did not induce mutation or clastogenicity (REACHa). Further studies summarised in a report from the European Union Scientific Committee on Occupational Exposure Limits (SCOEL) have identified three studies which show a positive effect (morphological transformation and surface independent growth) and one study that indicates a negative effect (no increased chromosome aberrations in peripheral lymphocytes) (SCOEL, 2011).

In vivo

A study in Wistar rats assessed the intratracheal administration of nickel oxide (1 mg) on the formation of 8-hydroxydeoxyguanosine (8-OH-dg) in lung tissues. Both black and green nickel oxide increased DNA damage as assessed through quantification of 8-OH-dg. The study authors concluded that the increase in 8-OH-dg was secondary to nickel oxide induced inflammation in the lungs (REACHa). A study summarised in the SCOEL report showed that nickel oxide tested negative in the mammalian micronucleus test conducted in mice (SCOEL, 2011).

Human studies

The SCOEL report identified a higher incidence of metaphases with gaps, but no significant increases in chromatid exchanges in lymphocytes in workers exposed to oxidic nickel compounds in a nickel smeltery (SCOEL, 2011). Six workers exposed to 0.77 mg/m^3 (nickel oxide) had an increase in chromosomal aberrations in lymphocytes compared with only a weak response in workers exposed to soluble nickel compounds (mean exposure concentration 1.3 mg/m^3) (SCOEL, 2011).

Carcinogenicity

Nickel oxide (CAS No. 1313-99-1) is classified as hazardous—Category 1 carcinogenic substance—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 nickel compounds as 'Carcinogenic to humans' (Group 1). The available data support this classification.

Epidemiological Studies

In nickel producing plants/factories, nickel oxide exposure can occur from the calcination of nickel sulfide containing ores; therefore, the data presented include a working population exposed to both nickel sulfide and nickel oxide (SCOEL, 2011; IARC 2012). Cohort studies assessing workers exposed to oxidic nickel have shown a significant increase in the incidence of lung and nasal cancers (SCOEL, 2011; IARC 2012).

Analysing specific cohorts, such as workers from the roasting, smelting and calcining departments at the Kristiansand nickel refinery, showed that long-term (15 years) exposure to oxidic nickel at concentrations of 5 mg Ni/m^3 was associated with an increased incidence of lung cancer. This risk was greatest in those workers who had also been exposed to soluble forms of nickel (nickel sulfate). Compared with workers exposed to soluble nickel compounds, exposure to oxidic nickel was a stronger hazard for nasal cancer (Andersen et al, 1996; Grimsrud, 2000). Further analysis of workers in Welsh and Canadian nickel refineries also showed an increased risk of lung and nasal cancers. However, workers from the Canadian nickel refineries were also exposed to sulfidic nickel. Workers from Welsh and Canadian refineries were exposed to some of the highest reported levels of nickel (10 mg Ni/m^3) (Roberts et al. 1989; IARC, 2012).

In contrast, workers exposed to lower concentrations of nickel oxide (2 mg Ni/m^3) via inhalation showed no increased risk of nickel-related respiratory cancer. These studies were carried out in miners as well as smelter workers in New Caledonia and Oregon respectively (Goldberg et al, 1992; Cooper & Wong, 1985). Furthermore, analysis of workers in nickel-using industries such as nickel-cadmium factories have not shown an increased risk of nickel-related respiratory cancers (Andersson et al, 1984; Jarup et al, 1998).

Animal Studies

The NTP has conducted two year inhalation exposure studies (carried out similarly to OECD TG 453) in F344 rats and $B6C3F_1$ mice (NTP, 1996). Nickel oxide was administered to rats and mice for six hours a day, five days a week for two years; further methodological details of the NTP study are available in the **Repeat Dose Toxicity - Inhalation** section of this report.

No tumours were observed in rats administered with the lowest dose (0.6 mg Ni/m^3) for two years. Adenomas or carcinomas were reported in rats exposed to 1 mg Ni/m^3 (12/106 rats) and 2 mg Ni/m^3 (9/106 rats). Based on this observation, it was concluded that there was some evidence of carcinogenicity in rats. In contrast, male mice did not develop tumours at any of the exposure concentrations (1, 2 or 4 mg Ni/m^3). Tumours were reported in female mice exposed to 1.0 mg Ni/m^3, but not any of the higher exposure concentrations (REACHa; NTP, 1996).

Further data are available from studies using methods of exposure not following OECD TGs (intratracheal or intramuscular injection). For example, in a study conducted in male Wistar rats, animals were administered a single 10 mg intratracheal dose of nickel oxide and followed up for 30 months. The mean time to mortality in rats administered nickel oxide was 224 days. Autopsy of exposed animals showed tumours (sarcomas in the pleural cavity) in 31/32 rats exposed to nickel oxide and 9/32 rats exposed to the positive control (crocidolite) (REACHa). In a further study, Wistar rats administered a single dose (20 mg) of nickel oxide intramuscularly developed muscle tumours (rhabdomyosarcomas and fibrosarcomas) within 302 days, and all but five animals survived up to the end of the 595 day study (REACHa).

The IARC has concluded that there is "sufficient evidence" in humans for the carcinogenicity of nickel compounds. Nickel compounds are reported to cause cancers of the lung, nasal cavity and paranasal sinuses. With respect to animal data, IARC concluded that there was "sufficient information" for the carcinogenicity of nickel monoxide (IARC, 2012).

Reproductive and Developmental Toxicity

No reliable data on reproductive and/or developmental toxicity are available for this group of chemicals. Based on the available evidence, no classification is warranted for this group of chemicals.

In a developmental study, Wistar rats were exposed to nickel oxide aerosol (0.8, 1.6 and 3.2 mg/m^3) on gestation days 1 - 21. Maternal toxicity was apparent through significant reductions in weight (all exposure groups), significant reductions in kidney weight and erythrocyte count (at 1.6 and 3.2 mg/m^3 chemical) and a significant increase in lung weights (all exposure groups). Pups had a decreased foetal body weight at maternally toxic exposure levels of 1.6 mg/m^3 and higher (REACHa).

Data available from repeat dose toxicity studies (inhalation) reported that exposure to nickel oxide (CAS No. 1313-99-1) (0.6 -10 mg Ni/m^3) for 13 weeks showed no significant effect on vaginal cytology. However, a significant decrease in the concentration of epididymal spermatozoa was reported in rats exposed to the highest dose (10 mg Ni/m^3). This dose (10 mg Ni/m^3) caused severe lung effects (ATSDR, 2005; NTP, 1996).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local long-term effects (carcinogenicity) and local acute effects (skin sensitisation). This group of chemicals may also cause harmful effects (chronic lung inflammation and alveolar hyperplasia) following repeated exposure through inhalation.

Public Risk Characterisation

The chemicals in this group have site-limited uses in Australia. Overseas, the chemicals have commercial and site-limited uses. Although, the public may come into contact with articles/coated surfaces containing these chemicals, it is expected that the chemicals 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 these chemicals, dermal, ocular and inhalation exposure of workers to the 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 local long-term and local acute health effects, the chemicals in this group may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical 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**). There is also a concern that there is currently no recommended exposure standard in the HSIS. Based on data for nickel oxide, and considering the concentration of 0.5 mg/m^3 nickel identified in the inhalation repeated dose toxicity studies at which adverse effects are observed, there is a concern that the absence of exposure controls in the HSIS may not be protective of the health of workers. The Scientific Committee on Occupational Exposure Limits (SCOEL) in the EU has proposed an exposure standard (0.005 mg/m^3 - respirable fraction) for 'poorly soluble nickel chemicals' which includes nickel oxide, nickel subsulfide and nickel metal (SCOEL, 2011). The differences between rats and humans with respect to particle deposition in the alveolar region should be determined and quantified in considering appropriate exposure controls (SCOEL, 2011).

NICNAS Recommendation

A Tier III assessment may be necessary to provide further information to determine the adequacy of protection to workers under the current exposure control framework.

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 chemicals in this group are 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]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	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)
Carcinogenicity	Carc. Cat 1 - May cause cancer by inhalation (T; R49)*	May cause cancer - Cat. 1A (H350i)

[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 oxide 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;
- 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.

References

Agency for Toxic Substances & Disease Registry (ATSDR) Toxicological Profile for Nickel (2005). Accessed September 2013 at **http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=44**

Andersen A, Engeland A, Berge SR& Norseth, T (1996). Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occupational and Environmental Medicine 53 pp. 708-713.

Andersson K, Elinder C G, Hogstedt C, Kjellstrom T& Spang G (1984). Mortality among cadmium and nickel exposed workers in a Swedish battery factory. Toxicology and Environmental Chemistry 9, pp 53-62.

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed October 2013 at **http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/ns2004criteriaforclassifyinghazardous**

Cooper, W C& Wong O (1981). A study of mortality in a population of nickel miners and smelter workers in Oregon. Scandanavian Journal of work, Environment and health 11 pp. 331 345.

European Chemicals Agency (ECHA), Classification& Labelling Inventory. Accessed September 2013 at **http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database**

European Union Risk Assessment Report (EU RAR). Background document in support of individual risk assessment reports of nickel compounds (2008). Accessed January 2014 at **http://esis.jrc.ec.europa.eu/**.

Galleria Chemica. Accessed at October 2013 at **https://jr.chemwatch.net/galleria/**

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at **http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html**

Goldberg M, Goldberg P, Leclerc A, Chastang J, Marne M, Gueziec J, Lavigne F, Dubourdieu D& Huerre M (1992). A seven-year survey of respiratory cancers among nickel workers in New Caledonia (1978-1984). Advances in environmental science and technology 25(11) pp. 649-657.

Grimsrud T, Berge S, Resmann, F, Norseth T& Andersen A (2000). Assessment of historical exposure in a nickel refinery in Norway. Scandanavian Journal of Work, Environment and Health 26(4) pp. 338-345.

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed on October 2013 athttp://toxnet.nlm.nih.gov.

Henderson R G, Durando J, Oller A R, Merkel D J, Marone P A& Bates H K 2012. Acute oral toxicity of nickel compounds. Regulatory Toxicology and Pharmacology 62 (2012) pp. 425 - 432.

International Agency for Research on Cancer (IARC) 2012. IARC monographs on the evaluation of carcinogenic risks to humans. Nickel and Nickel Compounds. Volume 100c (A review of Human Carcinogens: Arsenic, metals, fibres and Dusts). Accessed September 2013 at **http://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-10.pdf**

Jarup L, Bellander T, Hogstedt C& Spang G (1998). Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occupational and Environmental Medicine 55, pp 755-759.

Mazinanian N, Hedberg Y& Wallinder I O 2013. Nickel release and surface characteristics of fine powders of nickel metal and nickel oxide in media of relevance for inhalation and dermal contact. Regulatory Toxicology and Pharmacology 65 (2013), pp 135-146.

National Industrial Chemical Notification and Assessment Scheme (NICNASa). Tier II Human health assessment for Nickel sulfate. Australian Government Department of Health. Accessed December 2013 at **http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments**

National Toxicology Program (NTP) 1996. Technical Report on toxicity studies of nickel oxide (CAS No. 1313-99-1) in F344/N Rats and B6C3F1 Mice (inhalation studies). U.S. Department of Health and Human Services. Accessed September 2013 at **http://ntp.niehs.nih.gov/**

REACH Dossier. Nickel hydroxide (12054-48-7) (REACHb). Accessed December 2013 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

REACH Dossier. Nickel oxide (1313-99-1) (REACHa). Accessed December 2013 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

Reagan E L 1992. Acute oral LD50 study in rats with nickel hydroxide. International Journal of Toxicology 11 pp 684.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Annex XVII (2009). Accessed September 2013 at **http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:164:0007:0031:EN:PDF**

Roberts R, Julian J, Sweezey D, Muir D, Shannon H& Mastromatteo E (1989). A study of mortality in workers engaged in the mining, smelting, and refining of nickel. I: Methodology and mortality by major cause groups. Toxicology and Industrial Health, 5 pp. 957-974.

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed October 2013 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

Safe Work Australia (SWA). Model Work Health and Safety Regulations. Accessed September 2013 at **http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/model-whs-regulations**

Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendation on occupational exposure limits for nickel and nickel compounds (June, 2011). Accessed October 2013 at **http://ec.europa.eu/social/keyDocuments.jsp?advSearchKey=recommendation&mode=advancedSubmit&langId=en&policyArea=&type=0&country=0&year=2011**

Last Update 07 February 2014

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Nickel oxide, (NiO)** Nickel oxide Black nickel oxide Green nickel oxide Nickel monoxide Nickel protoxide
CAS Number	1313-99-1
Structural Formula	
Molecular Formula	NiO
Molecular Weight	74.69

Chemical Name in the Inventory and Synonyms	**Nickel oxide**
CAS Number	11099-02-8
Structural Formula	

	No Structural Diagram Available
Molecular Formula	Unspecified
Molecular Weight	N/A

Share this page