Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Nickel niobium oxide ($NiNb_2O_6$)

Assessment statement (CA09609)

19 December 2024

Table of contents

AICIS assessment (CA09609)

Chemical in this assessment

Name	CAS registry number
Nickel niobium oxide ($NiNb_2O_6$)	12059-60-8

Reason for the assessment

An application for an assessment certificate under section 31 of the *Industrial Chemicals Act 2019* (the Act).

Certificate application type

AICIS received the application in a Health Focus type.

Defined scope of assessment

The chemical has been assessed:

- as manufactured in Australia at up to 0.5 tonnes/year as solid particles, with a primary particle size above 0.5 µm
- for the production of piezoelectric ceramics (articles) containing the assessed chemical at up to 5% concentration, for use by professional workers
- with disposal of trade wastewater to an onsite wastewater treatment plant to meet safety standards of ≤ 3 mg Ni/L before release to accredited waste management facilities in accordance with relevant Local, State, Territory and Federal regulations

Summary of assessment

Summary of introduction, use and end use

The assessed chemical will be manufactured in Australia as a neat powder to be used in the production of piezoelectric ceramics (articles). The powder will initially be stored in labelled packages at the manufacturing site. The packages will only be opened when the assessed chemical is to be used in the production of piezoelectric ceramics.

The assessed chemical will be mixed with other chemicals and this mixture will be pressed into shapes and sintered to appropriate density and dimension for use in end use articles. These end use articles will contain the assessed chemical at up to 5% concentration (see **Supporting Information**).

The end use articles containing the assessed chemical will be used by professional workers only and will not be made available to the general public.

Human health

Summary of health hazards

The submitted toxicological data on analogue chemicals (see **Supporting information**) indicate that the assessed chemical is:

- of low acute oral toxicity (median lethal dose (LD50) > 4,000 mg/kg bw in rats)
- mildly irritating to the skin and eyes
- a skin sensitiser
- expected to cause serious systemic health effects following repeated oral exposure (statistically significant reduction in body weight of rats reported at 30 mg/kg bw/day in a 2-year study of an analogue chemical; the No Observable Adverse Effect Level (NOAEL) = 10 mg/kg bw/day (equivalent to 2.2 mg Ni/kg bw/day))

In a reproductive oral toxicity study, no adverse effects on reproductive function were observed in rats up to the highest tested dose (10 mg/kg bw/day). In a developmental inhalation toxicity study, adverse effects on foetal development (reduced body weights) were observed in rats (No Observable Adverse Effect Concentration (NOAEC) = 0.8 mg Ni/m^3).

Nickel compounds have been classified as Category 1 skin sensitisers on the Hazardous Chemical Information System (HCIS) of Safe Work Australia (SWA n.d.-a). Nickel compounds have also been classified as Category 1A carcinogenic substances and Category 2 germ cell mutagens with the risk statements of ‘May cause cancer by inhalation’ and ‘Suspected of causing genetic defects’, respectively, on the HCIS.

It is also noted that the International Agency for Research on Cancer (IARC) has classified nickel compounds as 'Carcinogenic to humans' (Group 1). IARC has highlighted studies showing an increased risk of lung cancer from exposure to nickel compounds, although these were often mixed exposures, either with soluble nickel or oxidic nickel compounds (IARC 2012).

Hazard classifications relevant for worker health and safety.

Based on the analogue data provided and the above information, the assessed chemical satisfies the criteria for classification according to the *Globally Harmonized System of Classification and Labelling of Chemicals* (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety as adopted for industrial chemicals in Australia.

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin sens. 1	H317: May cause an allergic skin reaction
Germ cell mutagenicity	Muta. 2	H341: Suspected of causing genetic defects
Carcinogenicity	Carc. 1B	H350i: May cause cancer by inhalation
Specific target organ toxicity - repeated exposure	STOT rep. exp. 1	H372: Causes damage to organs (lungs) through prolonged or repeated inhalation exposure
Reproductive toxicity	Repro. tox. 2	H361d: Suspected of damaging the unborn child

Summary of health risk

Public

The products containing the assessed chemical will not be available for use by the public. When introduced and used in the proposed manner, it is unlikely that the public will be exposed to the chemical.

This assessment does not identify any risks to public health that require specific risk management measures.

Workers

Limited occupational exposure is expected during manufacturing and production of end use products (articles) due to the use of engineering/enclosed systems. Only trained personnel will be involved in handling the assessed chemical. According to the applicant, worker exposure is expected to be further minimised through the use of dust/fume extraction and personal protective equipment (PPE) such as full-face respirators, impervious gloves, overalls and safety boots during handling of raw materials. Limited worker exposure is also expected during the handling of end use products containing the assessed chemical.

According to the applicant, regular testing of air contamination will be carried out along with regular blood testing of lead oxide levels in workers, which infers control of particulate exposure to all oxides at the manufacturing site, including the assessed chemical.

Considering the critical health effects possible through exposure to the assessed chemical, control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (see **Means for managing risk** section).

Environment

Summary of environmental hazard characteristics

As the assessed chemical is inorganic, it is excluded from categorisation under the *Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals* (DCCEEW 2022).

Environmental hazard classification

A dissolution test conducted on the assessed chemical following *Guidance on transformation/dissolution of metals and metal compounds in aqueous media, OECD Series on Testing and Assessment, No. 29* (OECD 2011) showed that only soluble nickel was detected. Therefore, the hazard classification for the assessed chemical is based on soluble nickel data. Accordingly, the assessed chemical satisfies the criteria for classification according to the GHS (UNECE 2017) as Chronic Category 4 (H413).

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (long-term)	Aquatic Chronic 4	H413: May cause long lasting harmful effects to aquatic life

Summary of environmental risk

The assessed chemical containing nickel is manufactured in Australia to produce piezoelectric ceramics. The wastewater containing nickel from the manufacturing process will be treated at an onsite wastewater treatment plant before release to domestic sewers and then further treated at a centralised sewage treatment plant (STP) prior to deep ocean discharge. Based on the calculated Risk Quotient (RQ) value < 1 for the ocean compartment, it is expected that the environmental risk from the introduction of the assessed chemical can be managed.

Means for managing risk

Workers

Recommendation to Safe Work Australia

- It is recommended that Safe Work Australia (SWA) update the *Hazardous Chemical Information System* (HCIS) to include classifications relevant to work health and safety (see **Hazard classifications relevant for worker health and safety**).

Information relating to safe introduction and use

The information in this statement, including recommended hazard classifications should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

The following control measures could be implemented to manage the risk arising from exposure to the assessed chemical during manufacturing and production of end use articles:

- Use of engineering controls such as
  - Enclosed and automated systems where possible
  - Adequate workplace ventilation to avoid accumulation of dusts, mists or aerosols

- Use of safe work practices to
  - Avoid contact with skin and eyes
  - Avoid inhalation of dusts, mists or aerosols

- Use of personal protective equipment (PPE)
  - Impervious gloves
  - Protective clothing
  - Respiratory protection

- The storage of the assessed chemical should be in accordance with the Safe Work Australia *Code of Practice for Managing Risks of Hazardous Chemicals in the Workplace* (SWA 2023) or relevant State or Territory Code of Practice.

- Atmospheric monitoring should be conducted to measure workplace concentrations of nickel during manufacturing of the assessed chemical and end use products containing the assessed chemical. Manufacturing workers should ensure that the exposure standard for nickel, as detailed in Safe Work Australia's health monitoring guide for nickel and its inorganic compounds (SWA n.d.-b), is not exceeded for any areas where the assessed chemical is present.

- As the assessed chemical is a skin sensitiser and carcinogen, control measures need to be supplemented with health monitoring for any worker who is at significant risk of exposure to the assessed chemical, if valid techniques are available to monitor the effect on the worker's health.

- A copy of the Safety Data Sheet (SDS) should be easily accessible to workers.

Environment

Information relating to safe introduction and use

During the manufacturing processes, the wastewater containing the assessed chemical must be treated at an onsite wastewater treatment plant to meet trade wastewater safety standards of ≤ 3 mg Ni/L before release to domestic sewers. Solid waste containing the assessed chemical is classified as hazardous waste and must be disposed of by an accredited waste management facility in accordance with relevant Local, State, Territory and Federal regulations.

Conclusions

The Executive Director is satisfied that the risks to human health or the environment associated with the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under s 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	Nickel niobium oxide ($NiNb_2O_6$)
CAS No.	12059-60-8
Synonyms	Nickel niobate(V) ($NiNb_2O_6$)
Molecular formula	Nb.Ni.O
SMILES (canonical)	[O].[Ni].[Nb]

Chemical description

The assessed chemical has a purity greater than 99%.

Relevant physical and chemical properties

Physical form	Yellow powder
Melting point	> 1,400 °C
Density	5320 – 5380 kg/m^3
Water solubility	0.006 x 10^{-3} g Ni/L
Particle Size (coarse)*	Inhalable fraction (< 100 µm): < 4% Respirable fraction (< 10 µm): 0
Particle Size (fine)*	Inhalable fraction (< 100 µm): 100% Respirable fraction (< 10 µm): > 90 (Mass median aerodynamic diameter = 3.41 µm)
log K_D**	2.74 (Janik et al. 2015; NICNAS 2020)

*The manufactured nickel niobium oxide powder (primary particles) readily agglomerates into coarse particles. The fine particles were obtained by ultrasonication for testing of particle sizing.

**K_D: partition coefficients for sorption from water onto soil

Human exposure

Workers

Manufacturing

The assessed chemical will be manufactured from raw nickel oxide and niobium oxide in a batch process. The raw material will be weighed by workers wearing PPE (full-face respirator,

gloves, overalls and safety boots) under vacuum extraction, transferred to a hopper and then into mills to be milled wet, producing a slurry. After milling, the slurry will be dewatered using a filter press to produce a solid filter cake containing less than 20% water. The filter cake will then be transferred via a trolley to a calcine kiln and loaded into the kiln by hand, with the operators wearing appropriate PPE. The filter cake will be heated to elevated temperatures to form hard clumps of material. This material will be transferred via sealed drums to a hammer mill and pulverised into a powder. The pulverised powder will be collected via gravity feed into drums, sealed and manually transferred to a second wet milling step by an operator wearing appropriate PPE. The second wet milling process will be done under enclosed systems. After milling, the slurry will be transferred via pumps to a holding tank from where it is then spray-dried and stored in closed buckets.

The ceramic powder, containing the assessed chemical at up to 5%, is formed into the desired shape via a pressing operation. The pressed article will then undergo an organic removal cycle and the shaped part will be individually loaded into a sintering kiln and heated to elevated temperatures, after which it will become a solid article. The parts are machined to the desired dimensions and eventually incorporated into the end use products. Limited occupational exposure to the assessed chemical is expected during production of solid articles and machining as these procedures will be conducted in enclosed systems or with appropriate PPE.

Health hazard information

The applicant has not submitted data on the assessed chemical for toxicological endpoints. However, the applicant has submitted toxicological data on suitable analogues, which were appropriate for read across to the assessed chemical.

Toxicokinetics

No toxicokinetic data were available for the assessed chemical. Based on the low water solubility (0.006 x 10^{-3} g Ni/L), the potential for absorption across biological membranes is expected to be limited.

In an oral distribution study, 10 mg (in 5% saline) of 8 different nickel compounds of varying solubility, including nickel oxides and metallic nickel, were administered by gavage to rats. The rats were sacrificed 24 hr after exposure and the concentration of nickel was measured in the organs, blood and urine. Of the 8 compounds examined, green nickel oxide was the least soluble (~ 1 µg/mL), followed by nickel metal and then black nickel oxide (~ 3.9–4.5 µg/mL). Following exposure to green nickel oxide, the concentration of nickel in the organs and blood was not significantly different from control animals. Exposure to black nickel oxide resulted in a significant increase in nickel levels in the lungs and kidneys. In total, 0.01% and 0.04% of green and black nickel oxide, respectively, were measurable (i.e. absorbed) based on nickel levels in the organs, blood and 24 hr urine. The authors concluded that the kinetic behaviour of orally administered nickel compounds is closely related to the solubility of the compounds and that solubility is one of the important factors in determining the health effects of nickel compounds (Ishimatsu et al. 1995).

Acute toxicity

Oral

In an acute oral toxicity study (OECD TG 425), Sprague Dawley (SD) rats (n = 1, 2 or 3 females/dose) were administered a single dose of an analogue chemical (nickel hydroxide) at 3,200, 4,000, 5,000 or 6,300 mg/kg bw in distilled water by oral gavage.

No signs of toxicity or gross abnormality were observed in the animals treated with 3,200 or 4,000 mg/kg bw of the analogue chemical. Of the 3 animals treated with 5,000 mg/kg bw of the analogue chemical, 2 animals died following treatment, with necropsy revealing discolouration of the intestines and/or liver. Both animals treated with 6,300 mg/kg bw of analogue chemical died following treatment, with necropsy revealing red intestines. In the 2 highest dose groups, clinical signs noted in some animals prior to death included hypoactivity, soft faeces, ano-genital staining and/or reduced faecal volume.

Under the conditions of this study, the acute oral LD50 of the analogue chemical was calculated to be > 4,000 mg/kg bw in female rats (Henderson et al. 2012). Therefore, the assessed chemical is expected to be of low acute oral toxicity.

Corrosion/Irritation

Skin irritation

In a dermal irritation study (OECD TG 404), a single dose of 0.63 g of an analogue chemical (nickel hydroxide; 80% w/w) was topically applied semi-occlusively for 4 hours to the trunks of 3 New Zealand White (NZW) rabbits. Mild irritation in the form of slight erythema was observed within an hour of patch removal, which resolved within 24 hours (NICNAS 2014). Under the conditions of the study, the analogue chemical was mildly irritating to the skin, and therefore, the assessed chemical is considered a mild skin irritant.

Eye irritation

In an eye irritation study (OECD TG 405), 0.1 g of an analogue chemical (nickel hydroxide) was instilled into one eye of each of 3 female NZW rabbits. All treated eyes showed signs of iritis and conjunctivitis 1 hour after instillation. The severity of irritation decreased with time and had completely resolved by the end of the 7-day study (NICNAS 2014). Under the conditions of the study, the analogue chemical was mildly irritating to the eyes of rabbits, and therefore, the assessed chemical is considered a mild eye irritant.

Sensitisation

Skin sensitisation

The skin sensitisation potential of an analogue chemical (nickel sulfate) was tested using a guinea pig maximisation test (GPMT) (similar to OECD TG 406). Female albino guinea pigs (n = 120) were divided into 18 test groups of 6 animals and a control group of 12 animals. The concentrations of the analogue chemical used for induction ranged from 0.01–3.0% intradermally (day 0) and 0.25–10% topically (on day 7). Concentrations of 1% and 2% were used for topical challenge (on day 21), based on the absence of skin irritation in a pilot study.

The study authors reported that the maximum number of skin reactions at 48 hours were noted in the groups with 3% intradermal induction followed by 0.5% (2/6), 2% (3/6) and 10% (3/6) topical induction. The reactions had decreased by 72 hours. Statistical analysis of the results showed a linear dose-response relationship dependent on the intradermal induction concentration only, with no effect of variation in the topical induction concentration. The best fitting dose-response curve for the 48-hour data indicated a maximum sensitisation rate of 42% at 3% intradermal induction. The authors noted that the sensitisation obtained in this study was short-lasting and not convincing. The authors also stated that this GPMT was not an efficient animal model for testing nickel contact allergy, as it was not possible to achieve a strong and lasting sensitisation in most of the test animals (Rohold, Nielsen and Andersen 1990).

The applicant concluded that although the results in the study described above are not conclusive, other studies have proposed that nickel compounds are likely to have moderate skin sensitisation potential. It is noted that the analogue chemical (nickel sulfate) is also classified for skin sensitisation (Category 1) (HCIS, SWA n.d.).

Based on the analogue data provided, the assessed chemical is considered to be a skin sensitiser, warranting hazard classification for skin sensitisation (Category 1).

Repeat dose toxicity

Oral

In an oral carcinogenicity study (OECD TG 451), an analogue chemical (nickel sulfate) was administered daily by oral gavage to Fischer 344 rats (n = 60/sex/dose) for a period of 2 years. Based on data from a 90-day range-finding study, exposure levels of 0 (control), 10 (low dose), 30 (medium dose) and 50 mg/kg bw/day (high dose) were selected.

While an effect of treatment on mortality was not noted in male animals, a significantly higher mortality rate was noted in female animals at medium and high doses: 43% and 45% respectively, compared to 23% in controls and 33% at the low dose. Body weights were decreased in a dose-dependent manner in the medium and high dose males (-11% and -12% respectively) and females (-8% and -10% respectively), relative to the respective control groups. Reductions in weight gain relative to control group at study week 103 reached biological significance (i.e., > 10% decrease) in the medium and high dose males and the high dose females.

Some statistically significant differences in the haematology parameters were observed in the treated animals. However, none of these differences was suggestive of a hyperplastic (i.e., leukemia) response and none of the changes were considered toxicologically meaningful since they were small and did not follow a consistent exposure-related pattern. Numerous gross necropsy findings were observed for animals in the control and treated groups; however, the non-neoplastic gross and histopathological findings were either considered to be secondary to toxicity or incidental background occurrences, rather than a direct effect of treatment with the analogue chemical.

Under the conditions of this study and based on the effects on body weight, the NOAEL for the analogue chemical was reported to be 10 mg/kg bw/day, equivalent to 2.2 mg Ni/kg bw/day. These results warrant classification of the assessed chemical for specific target organ toxicity (repeated exposure) (Category 1) based on the reduction in body weight.

Genotoxicity

The applicant provided a report describing multiple in vitro genotoxicity studies on analogue chemicals, from which they highlighted 7 studies as summarised below. The report did not state whether any of these studies conformed to OECD test guidelines (ATSDR 2023).

Two studies on bacteria – one using live *Bacillus subtilis* and one using purified *Salmonella typhimurium* DNA – found no evidence of DNA damage upon exposure to nickel compounds. However, in mammalian in vitro models, cellular transformation was induced by nickel compounds in human foreskin fibroblasts, baby hamster kidney (BHK-21) cells and Chinese hamster embryo (CHE) cells. In addition, an increase in gene mutation frequency at the grp locus was found in Chinese hamster ovary (CHO) AS52 cells after treatment with several nickel analogues. Nickel compounds were also found to cause DNA strand breaks in human peripheral lymphocytes and human alveolar epithelial (A549) cells.

In a non-guideline in vivo genotoxicity study, various nickel compounds, including both black and green nickel oxides, were administered to Wistar rats (n = 4–5/dose) by intratracheal instillation at a dose of 1 mg. The rats were sacrificed 48 hours after exposure and the lungs were harvested, homogenised, and cell nuclei isolated by centrifugation. DNA was isolated from the nuclei and 8-hydroxydeoxyguanosine (8-OH-dG) adduct levels were analysed by enzyme digestion and high performance liquid chromatography - electrochemical detection (HPLC-ECD). For comparative purposes, DNA from cultured HeLa cells treated with 10 ug/mL of the chemicals for 24 hours was also analysed.

Relative to control tissue, both black and green nickel oxide induced a statistically significant 3-fold increase in DNA damage (from approximately 0.78 to 2.33 8-OH-dG/dG×10^5). The study authors suggested that the genotoxicity may be a secondary effect of inflammation induced by the nickel oxide treatment, as no increase in 8-OH-dG levels was seen in cultured cells treated with the same chemicals (Kawanishi et al. 2002).

Based on the limited data provided on analogue chemicals and the classification of nickel compounds as germ cell mutagens on the HCIS (SWA n.d.-a; see **Summary of health hazards** section), the assessed chemical is likely to be genotoxic, warranting hazard classification (Germ cell mutagenicity – Category 2).

Carcinogenicity

Oral

The oral carcinogenicity of an analogue chemical (nickel sulfate) was assessed in a carcinogenicity study described in the **Repeat dose toxicity** section above.

Analysis of the tumour data revealed only one statistically significant ($p < 0.001$) increase in tumours, corresponding to keratoacanthoma (tail) in the low dose males. However, according to the study authors, this finding is of questionable toxicologic significance since there was no dose-response relationship. Furthermore, the incidence rate in the low dose males (15%) was only slightly higher than the upper end of the historical control incidence for this tumour type (0–14%) and the incidence rate in the remaining control and treated groups (0–7%) was within historical control ranges. No other tumour finding in this study was statistically significant (Heim et al. 2007).

The study authors concluded that the analogue chemical showed no evidence of carcinogenicity in this study.

Inhalation

In an inhalation carcinogenicity study (similar to OECD TG 453), Fischer 344 rats (n = 50/sex/dose) were exposed (whole body) to an analogue chemical (nickel oxide) in the form of an aerosol for 6 hrs/day, 5 days/week, for 2 years at concentrations of 0, 0.62, 1.25, and 2.5 mg/m^3 (equivalent to 0, 0.5, 1.0 and 2.0 mg Ni/m^3). Aerosol concentration was determined by taking three 2-hour filter samples throughout the exposure day. Chamber concentrations and aerosol size were determined analytically (mass median aerodynamic diameter: 2.2–2.5 µm).

No significant differences in clinical signs or mortality were observed between control and exposed animals. The final mean body weights of exposed animals were within 5–10% of control animals and therefore were not adversely affected by exposure to the chemical. By 15 months, lung weight was significantly increased in exposed animals at 1.25 mg/m^3 (+50% in males; +54% in females) and 2.5 mg/m^3 (+86% in males; +94% in females). The increase in lung weight was attributed to an inflammatory reaction in response to exposure to the analogue chemical.

Other noncarcinogenic effects of exposure included focal alveolar/bronchiolar (A/B) hyperplasia, inflammation and/or fibrosis of the lung, and lymphoid hyperplasia of the lung-associated lymph nodes. Pigment was also observed in the lungs of exposed animals and was thought to indicate deposited nickel. Analysis of lung burden showed accumulation of nickel in the lungs after exposure to the analogue chemical for 7 or 15 months.

Carcinogenic effects included an increase in the incidence of A/B adenomas/carcinomas combined (A/B neoplasms) in male and female rats exposed to the analogue chemical at concentrations of 1.25 and 2.5 mg/m^3. In males, A/B neoplasms were seen in 11% of rats at 1.25 mg/m^3 and 8% of rats at 2.5 mg/m^3 compared to 1.9% of rats in the control group. In females, A/B neoplasms were seen in 11% of rats at 1.25 mg/m^3 and 10% of rats at 2.5 mg/m^3 compared to 1.9% of rats in the control group. At the highest concentration, the incidence of A/B neoplasms was significantly higher than historical control rates (1.4% in males and 1.9% in females). The study authors concluded that the increased carcinogenic response was related to exposure to the analogue chemical, as the increased incidence of A/B neoplasms was noted in both the medium and high exposure groups relative to concurrent and historical control rates and the effects were observed in both male and female rats.

A carcinogenic response was also seen in the adrenal medulla of exposed rats, which reached statistical significance at the highest exposure concentration (2.5 mg/m^3). An increase in benign or malignant pheochromocytoma was noted in both males (+30%) and females (+450%), however, the mechanism for this response was unclear (Dunnick et al. 1995).

Under the conditions of this study conducted on an analogue chemical, the assessed chemical is likely to be carcinogenic by inhalation, warranting hazard classification (Carcinogenicity - Category 1B).

Reproductive and development toxicity

Oral

In a two-generation reproductive toxicity study (OECD TG 416), an analogue chemical (nickel sulfate) was administered to F_0 (parental) and F_1 Wistar rats (n = 28/sex/dose) by oral gavage at dose levels of 0, 1.0, 2.5, 5.0 and 10.0 mg/kg bw/day. Dosing of the F_0 animals began 10 weeks prior to mating. Dosing of the F_1 animals began on postpartum day 22 and continued

until the day prior to euthanasia. Adult F_1 females and their pups were euthanised and necropsied after 16 and 18 weeks of treatment, respectively.

Oral administration of the analogue chemical over the course of two generations at up to 10.0 mg/kg bw/day had no effect on F_0 or F_1 survival, growth, mating behaviour, fertility, gestation, parturition or lactation. No treatment-related mortality or clinical signs of toxicity were observed in F_0 or F_1 rats or their offspring at any tested dose. The viability and growth of F_1 and F_2 pups were not affected by treatment. Furthermore, toxicologically meaningful differences were not noted among the groups with respect to reproductive parameters in F_1 animals. Absolute and/or relative liver weights were significantly reduced in F_0 males at 10.0 mg/kg bw/day and in F_1 males at 5.0 and 10.0 mg/kg bw/day. However, these differences were not regarded as toxicologically significant as the relative liver weights were less than 10% different from the respective control weights and there was no evidence of treatment-related adverse histopathological changes in the liver. Furthermore, histopathological examination also did not reveal any treatment-related changes in the reproductive organs or other tissues examined. Based on the results of this study, the NOAEL for reproductive/developmental toxicity of the analogue chemical is > 10.0 mg/kg bw/day (equivalent to 2.2 mg Ni/kg bw/day), as no adverse effects were reported up to the highest tested dose.

Inhalation

In a non-guideline study, pregnant female Wistar rats (n = 10–13/dose) were continuously exposed to an aerosol of analogue chemical (nickel oxide) at concentrations of 0.8, 1.6 and 3.2 mg Ni/m^3 for 21 days. On day 21, foetuses were removed by caesarean section and examined. Maternal blood, serum and urine as well as foetal blood were also collected for examination.

In the maternal rats, significant reductions were observed in body weight (all exposure groups), wet weights of kidneys, erythrocyte count (medium and high exposure groups) and serum urea levels (high exposure group only). Significant increases were observed in wet weight of lungs (all exposure groups), haematocrit (high exposure group), mean corpuscular volume (medium and high exposure groups) and leukocyte numbers (low exposure group only). No changes were observed in liver weights in any treatment group (ATSDR 2023).

In the foetuses, body weights were reduced in the medium (-9%) and high (percentage reduction unknown) exposure groups. Leukocytes and serum urea levels in the medium exposure group were increased. No effects of exposure were observed for the number of foetuses or placentas, wet weight of placentas, haemoglobin, haematocrit, erythrocytes, mean corpuscular volume or alkaline phosphatase in serum.

Based on this study, the NOAEC for developmental toxicity of the analogue chemical is 0.8 mg Ni/m^3, as decreased foetal body weight was reported at higher doses. Therefore, under the conditions of this study conducted on an analogue chemical, the assessed chemical is suspected of inducing developmental toxicity by inhalation, warranting hazard classification (Reproductive toxicity - Category 2).

Observation in humans

Epidemiological studies have found that maternal occupational exposure to water-soluble nickel compounds was not associated with an increased incidence of newborns with genital malformations. The study authors warned that this result should be interpreted with caution as there were very few cases in the high exposure groups (Vaktskjold et al. 2006). Similarly, no statistical correlation between nickel exposure during pregnancy and rates of spontaneous abortions, small-for-gestational-age newborns or congenital musculoskeletal defects was seen

in the same cohort of women (Vaktskjold et al. 2007, Vaktskjold et al. 2008a, Vaktskjold et al. 2008b).

Environmental exposure

The assessed chemical is manufactured in Australia in batch processes. The raw materials are milled and then dewatered using a filter press. The filter cake is heated to elevated temperatures and forms hard clumps of material. The material is then transferred via sealed drums to an enclosed hammer mill which pulverises the powder. The pulverised powder is collected via gravity feed into drums, sealed and transferred to a second wet milling step. After milling the slurry is transferred via pumps to a holding tank from where it is then spray dried and stored in closed buckets. The powder is then formed into the desired shape via a pressing operation. The pressed article then undergoes an organic removal cycle and parts are individually loaded into the sintering kiln and heated to elevated temperatures after which time it becomes a solid article. From here the parts are generally machined to desired dimensions from where they will eventually be incorporated into the end products.

Significant releases of the assessed chemical to the environment are not expected during manufacture as the wastewater containing the assessed chemical will be treated at an onsite wastewater treatment plant to meet trade wastewater safety standards specified by the local water utility operator before release to domestic sewers. The wastes will be then further treated at a centralised sewage treatment plant (STP) prior to deep ocean discharge.

Solid waste containing the assessed chemical is classified as hazardous waste and will be disposed of by an accredited waste management facility in accordance with relevant Local, State, Territory and Federal regulations. Release of the materials and products containing the assessed chemical due to accidental spills are to be collected and disposed of in accordance with relevant Local, State, Territory and Federal regulations.

Products containing the assessed chemical will be used in piezoelectric ceramics and will be in service for many years. During use, the piezoelectric ceramics will be housed in a rubber/plastic/metal casing and will not be in direct contact with the environment. At the end of their service life, the products will be disposed of by an accredited waste management facility in accordance with relevant Local, State, Territory and Federal regulations.

Environmental fate

A dissolution test conducted on the assessed chemical following *Guidance on transformation/dissolution of metals and metal compounds in aqueous media, OECD Series on Testing and Assessment, No. 29* (OECD 2011) showed that only dissolved nickel was detected. Therefore, the environmental fate data are read across from ionic nickel(2+). A detailed discussion of the environmental fate of ionic nickel(2+) is available in the IMAP Environment Tier II Assessment for water soluble nickel(2+) salts (NICNAS 2020). A summary of fate characteristics is presented below.

Dissolution, speciation and partitioning

The behaviour of the nickel(2+) ion is strongly dependent on the chemistry of the environmental compartment into which it is released.

In natural waters (pH 5–9), nickel(2+) ions may adsorb to iron/manganese oxides or dissolved organic matter (DOM), or form complexes with inorganic ligands (OH , SO , Cl or NH) (IPCS 1991). These interactions produce a complex mixture of nickel species and compounds that

are largely determined by the chemistry of the aquatic compartment. In aquatic systems, > 90% of nickel is associated with particulate matter or sediments (Hart 1982). However, this distribution between phases is affected by pH. At pH > 6, nickel(2+) readily adsorbs to suspended organic matter or precipitates with iron and manganese hydroxides (ANZECC 2000a). Conversely, in acidic waters (pH < 6), adsorption of nickel(2+) to organic matter plays a minor role and ionic nickel is relatively mobile (ANZECC 2000a).

The partitioning of nickel in soil has a complex dependence on soil properties, but is mainly determined by soil pH, cation exchange capacity (CEC) and the concentration of both clay and DOM (Danish-EPA 2015). Recently, the median partition coefficient (log K_D) value for nickel of 2.74 was reported in a large-scale European geochemical survey of 500 soils with varying physical and chemical properties (Janik et al. 2015).

Degradation

No information on the degradation of the assessed chemical was provided. The assessed chemical is inorganic, and therefore excluded from persistence classification.

Bioaccumulation

Conventional measures of bioaccumulation as applied to organic chemicals are not appropriate for metal ions. However, nickel does not bioaccumulate to a significant extent in aquatic or terrestrial organisms (ECB 2008; NICNAS 2020). Although data are limited for the biomagnification of nickel, most studies indicate that biomagnification does not occur in aquatic (ECB 2008) or terrestrial (Commonwealth of Australia 2011) food chains.

Predicted environmental concentration (PEC)

The wastewater containing nickel from manufacturing processes will be treated at an onsite wastewater treatment plant to meet trade wastewater safety standards specified by the local water utility operator of 3 mg Ni/L. The effluent from the onsite wastewater treatment plant will be released to the domestic sewer system and further treated by a centralised STP prior to deep ocean discharge. According to the trade waste agreement between the applicant and the local water utility operator, the maximum discharge volume from the onsite wastewater treatment plant is 4 m^3/day while the centralised STP has a treatment volume of 336,000 m^3/day, so the treated effluent from the onsite wastewater treatment plant will be diluted about 84,000 times at the centralised STP. The centralised STP is primary treatment only. Assuming no removal of nickel during centralised STP process as a worst case, and applying a dilution factor of 10 for deep ocean discharge, a predicted environmental concentration (PEC) is estimated as 3 mg Ni/L ÷ 84,000 ÷ 10 = 0.004 µg Ni/L.

Environmental effects

A dissolution test conducted on the assessed chemical following *Guidance on transformation/ dissolution of metals and metal compounds in aqueous media, OECD Series on Testing and Assessment, No. 29* (OECD 2011) showed that only soluble nickel was detected. Therefore, soluble nickel is expected to be the primary toxicity concern of the assessed chemical and the environmental effects data are based on read across information from ionic nickel (2+). A detailed account of the ecotoxicity of ionic nickel is available in the IMAP Environment Tier II Assessment for water soluble nickel(2+) salts (NICNAS 2020). The relevant data are summarised in this section.

Effects on aquatic Life

Bioavailable forms of nickel(2+) are very toxic to aquatic life in short and long term exposures. The toxicity of ionic nickel to aquatic organisms varies considerably between species and is strongly influenced by water chemistry.

Acute toxicity

The acute toxicity of nickel to aquatic organisms varies at both the interspecies and intraspecies level. Differences in intraspecies acute nickel toxicity can be attributed to abiotic and biotic factors including water hardness, pH and dissolved organic carbon (DOC) (Deleebeeck et al. 2009). In addition, fish age is also an important factor influencing toxicity where older fish are more tolerant than younger fish. The IMAP Environment Tier II Assessment for water soluble nickel(2+) salts identified a 48 hour median effective concentration (EC50) value on the invertebrates Daphnid as the most sensitive endpoint for the acute toxicity of ionic nickel at 35 µg Ni_{diss}/L (NICNAS 2020).

Chronic toxicity

The chronic toxicity of nickel is strongly dependent on the bioavailability of nickel(2+) which is influenced by three key parameters: pH, water hardness and concentration of DOC. In general, nickel toxicity is greatest in waters with alkaline pH, low water hardness and a low concentration of DOC. The IMAP Environment Tier II Assessment for water soluble nickel(2+) salts identified a 10 day 10th-percentile effective concentration (EC10) value on the invertebrates Daphnid as the most sensitive endpoint for the chronic toxicity of ionic nickel at 9 µg Ni_{diss}/L (NICNAS 2020).

Effects on terrestrial Life

Bioavailable forms of nickel(2+) are toxic to terrestrial organisms (NICNAS 2020). The bioavailability and toxicity of nickel in soil is strongly influenced by soil properties, especially cation exchange capacity (NiPERA 2015). Soil Quality Guidelines have been derived for nickel in Australian soils (Commonwealth of Australia 2011). The guidelines were derived from no-observed effect concentration (NOEC) and EC10 values for plants, microbial processes and invertebrates exposed to nickel in the form of nickel metal, nickel sulfate, nickel chloride, nickel nitrate or nickel carbonate (CAS RN 3333-67-3). Over 330 toxicity data points were available, with the majority relating to microbial processes and enzymes. The lowest NOEC/EC10 values for nickel toxicity to plants, microbial processes and invertebrates are 26.9 mg Ni/kg (*Spinacia oleracea*, spinach), 81.3 mg Ni/kg (nitrification) and 103 mg Ni/kg (*Eisenia veneta*, earthworm), respectively (geometric mean values) (Commonwealth of Australia 2011).

Effects on sediment dwelling life

Bioavailable forms of nickel(2+) can have some toxic effects on sediment-dwelling organisms (NICNAS 2020). The chronic toxicity of nickel is influenced by several physico-chemical properties of sediments including total organic carbon (TOC), total recoverable iron, the concentration of acid-volatile sulfides (AVS) and CEC (Besser et al. 2013; Schlekat et al. 2016). These characteristics of sediments can mitigate the toxicity of nickel to sediment-dwelling organisms. Chronic toxicity values for the effects of nickel on sediment-dwelling invertebrates have been obtained for amphipods, insects, oligochaetes and mussels (ECB 2008; Vangheluwe et al. 2013). Based on a worst-case scenario (low sediment AVS and TOC), a 28 d EC20 of 149 mg Ni/kg was obtained for the amphipod *Hyalella azteca*. Under the same exposure conditions, the most tolerant sediment-dwelling species were midges (*Chironomus*

riparius and *Chironomus dilutes*) and mussels (*Lampsilis siliquoidea*), where the NOEC exceeded the highest nickel concentration (> 762 mg Ni/kg). An intermediate toxicity value was found for the freshwater oligochaete, *Lumbriculus variegates* (worm) (EC10 = 554 mg Ni/kg) (Vangheluwe et al. 2013).

Predicted no-effect concentration (PNEC)

The environmental effects of the assessed chemical could be caused by the release of nickel(2+) ions from discharging treated effluent of the centralised STP to deep ocean. Therefore, a PNEC value from guidelines for the marine compartment is considered. The default guideline values published for nickel in the Australian and New Zealand Guidelines for Fresh and Marine Water Quality have been used. These values represent thresholds above which further assessment of potential toxicity may be required to ensure environmental quality and have been normalised using a water hardness of 30 mg $CaCO_3$/L. For the marine ecosystem, a high reliability guideline value for protection of 95% of marine species has been determined to be 7 µg Ni/L (ANZECC 2000b).

Categorisation of environmental hazard

As the assessed chemical is inorganic, it is excluded from categorisation under the *Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals* (DCCEEW 2022).

Environmental risk characterisation

Based on the PEC and PNEC values determined above, the Risk Quotient (RQ = PEC ÷ PNEC) has been calculated for release of the assessed chemical to ocean:

Compartment	PEC	PNEC	RQ
Ocean	0.004 µg Ni/L	7 µg Ni/L	0.0006

For the ocean compartment, an RQ less than 1 indicates that introduction of the assessed chemical, in line with the defined scope of assessment, is not expected to pose a significant risk to the aquatic environment. Biosolids from the centralised STP may contain a minor fraction of nickel which may be released to soil. However, the release of nickel to the environment in Australia from this introduction is expected to be a negligibly small fraction of the amount of nickel released from other sources including fossil fuel combustion. Furthermore, there are extensive national guidelines for nickel in biosolids and soils which can be used to identify and manage risks from anthropogenic nickel emissions. Adherence to these guidelines and requirements is sufficient to manage the risk to the terrestrial environments from uses of the assessed chemical containing nickel. As such, the risk from the introduction of the assessed chemical can be managed.

References

ANZECC (Australia and New Zealand Conservation Council & Agriculture and Resource Management Council of Australia and New Zealand) (2000a) *Australian and New Zealand Guidelines for Fresh and Marine Water Quality (Vol II) Aquatic Ecosystems — Rationale and Background Information (Chapter 8),* ANZECC, accessed 03 May 2024.

ANZECC (Australia and New Zealand Conservation Council & Agriculture and Resource Management Council of Australia and New Zealand) (2000b) *Australian and New Zealand Guidelines for Fresh and Marine Water Quality (Vol I). The Guidelines (Chapters 1-7)*, ANZECC, accessed 03 May 2024.

ATSDR (Agency for Toxic Substances and Disease Registry) (2023) *Toxicological Profile for Nickel [PDF 1.4 MB]*, ATSDR, accessed 28 August 2024.

Besser JM, Brumbaugh WG, Ingersoll CG, Ivey CD, Kunz JL, Kemble NE, Schlekat CE and Garman ER (2013) 'Chronic toxicity of nickel-spiked freshwater sediments: variation in toxicity among eight invertebrate taxa and eight sediments', *Environmental Toxicology & Chemistry*, 32(11): 2495-506, doi:10.1002/etc.2271.

Commonwealth of Australia (2011) *National Environment Protection (Assessment of Site Contamination) Measure*, Commonwealth of Australia website, accessed 03 May 2024.

Danish-EPA (Danish Environmental Protection Agency) (2015) *Part of the LOUS review, Environmental project No. 1723, Survey of nickel metal Danish Ministry of the Environment Environmental Protection Agency*, Danish-EPA, accessed 03 May 2024.

DCCEEW (Department of Climate Change, Energy, the Environment and Water) (2022) *Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals*, DCCEEW, accessed 03 May 2024.

Deleebeeck NME, De Laender F, Chepurnov VA, Vyverman W, Janssen CR and De Schamphelaere KAC (2009) 'A single bioavailability model can accurately predict Ni toxicity to green microalgae in soft and hard surface waters', *Water Research*, 43(7): 1935-47, doi: 10.1016/j.watres.2009.01.019.

Dunnick JK, Elwell MR, Radovsky AE, Benson JM, Hahn FF, Nikula KJ, Barr EB and Hobbs CH (1995) 'Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung', *Cancer Res*, 55(22):5251-256.

ECB (European Chemicals Bureau) (2008), *European Union Risk Assessment Report: Nickel [PDF 14.7 MB]*, ECB, accessed 03 May 2024.

Hart BT (1982) *Australian water quality criteria for heavy metals, technical paper 77*, Australian Water Resources Council, Australian Government Publishing Service, Canberra, Australia.

Heim KE, Bates HK, Rush RE and Oller AR (2007) 'Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats', *Toxicol Appl Pharmacol*, 224(2):126-37, doi:10.1016/j.taap.2007.06.024.

Henderson RG, Durando J, Oller AR, Merkel DJ, Marone PA and Bates HK (2012) 'Acute oral toxicity of nickel compounds', *Regul Toxicol Pharmacol*, 62(3):425-432, doi:10.1016/j.yrtph.2012.02.002.

IARC (International Agency for Research on Cancer) (2012) *Arsenic, Metals, Fibres, and Dusts: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100C*, IARC, accessed 07 June 2024.

IPCS (International Programme on Chemical Safety) (1991), *Environmental Health Criteria 108: Nickel*, IPCS, accessed 03 May 2024.

Ishimatsu S, Kawamoto T, Matsuno K and Kodama Y (1995) 'Distribution of various nickel compounds in rat organs after oral administration', *Biological trace element research*, 49(1): 43–52, doi:10.1007/BF02789001.

Janik LJ, Forrester ST, Soriano-Disla JM, Kirby JK, McLaughlin MJ and Reimann C (2015) 'GEMAS: Prediction of solid-solution partitioning coefficients (K_D) for cationic metals in soils using mid-infrared diffuse reflectance spectroscopy', *Environmental Toxicology & Chemistry*, 34(2): 224-34, doi:10.1002/etc.2736.

Kawanishi S, Oikawa S, Inoue S, Nishino K (2002) 'Distinct mechanisms of oxidative DNA damage induced by carcinogenic nickel subsulfide and nickel oxides', *Environ Health Perspect*., 110 (Suppl 5):789-791, doi:10.1289/ehp.02110s5789.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2014) *IMAP Single Assessment Report – Nickel Hydroxide (Ni(OH)2): Human health tier II assessment [PDF 159 KB]*, NICNAS, accessed 03 June 2024.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2020) *IMAP Group Assessment Report – Water soluble nickel (2+) salts: Environment tier II assessment [PDF 238 KB]*, NICNAS, accessed 03 May 2024.

NiPERA (Nickel Producers Environmental Research Association) (2015) *Incorporation of Bioavailability in the Terrestrial Compartment*, NiPERA, accessed 03 May 2024.

OECD (Organisation for Economic Co-operation and Development) (2011) *OECD Series on Testing and Assessment, No. 29 - Guidance on transformation/dissolution of metals and metal compounds in aqueous media*, OECD.

Rohold AE, Nielsen GD and Andersen KE (1991) 'Nickel-sulphate-induced contact dermatitis in the guinea pig maximization test: a dose-response study', *Contact Dermatitis*, 24(1):35-9, doi:10.1111/j.1600-0536.1991.tb01627.x.

Schlekat CE, Garman ER, Vangheluwe MLU and Burton Jr. GA (2016) 'Development of a bioavailability-based risk assessment approach for nickel in freshwater sediments', *Integrated Environmental Assessment and Management*, 12(4): 735-46, doi: 10.1002/ieam.1720.

SWA (Safe Work Australia) (n.d.-a) *Hazardous Chemical Information System*, SWA website, accessed 03 May 2024.

SWA (Safe Work Australia) (n.d.-b) *Health monitoring guide for nickel*, SWA website, accessed 27 August 2024.

SWA (Safe Work Australia) (2023) *Code of Practice: Managing Risks of Hazardous Chemicals in the Workplace, Safe Work Australia*, SWA, accessed 03 July 2024.

UNECE (United Nations Economic Commission for Europe) (2017) *Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Seventh Revised Edition*, UNECE, accessed 19 June 2024.

Vaktskjold A, Talykova LV, Chashchin VP, Nieboer E, Thomassen Y, Odland JO (2006) 'Genital malformations in newborns of female nickel-refinery workers', *Scand J Work Environ Health*, 32(1):41-50, doi:10.5271/sjweh.975.

Vaktskjold A, Talykova LV, Chashchin VP, Odland JO, Nieboer E (2007) 'Small-for-gestational-age newborns of female refinery workers exposed to nickel', *Int J Occup Med Environ Health*, 20(4):327-338, doi:10.2478/v10001-007-0034-0.

Vaktskjold A, Talykova LV, Chashchin VP, Odland JO, Nieboer E (2008) 'Maternal nickel exposure and congenital musculoskeletal defects', *Am J Ind Med*., 51(11):825-833, doi:10.1002/ajim.20609.

Vaktskjold A, Talykova LV, Chashchin VP, Odland JO, Nieboer E (2008) 'Spontaneous abortions among nickel-exposed female refinery workers', *Int J Environ Health Res*., 18(2):99-115, doi:10.1080/09603120701498295.

Vangheluwe ML, Verdonck FA, Besser JM, Brumbaugh WG, Ingersoll CG, Schlekat CE and Garman ER (2013) 'Improving sediment-quality guidelines for nickel: development and application of predictive bioavailability models to assess chronic toxicity of nickel in freshwater sediments', *Environmental Toxicology & Chemistry*, 32(11): 2507-19, doi: 10.1002/etc.2373.