Workplace Exposure Standard (WES) review

NICKEL METAL
(CAS NO: 7440-02-0)

NICKEL SULPHIDE
(CAS NO: 16812-54-7)

March 2018

New Zealand Government

WORKSAFE
NEW ZEALAND | MAHI HAUMARU AOTEAROA

CONTENTS

appendices

tables

1.0
Introduction

This WorkSafe New Zealand (WorkSafe) review considers whether the WES for nickel should be changed.

It considers the potential for exposures to nickel in New Zealand workplaces, the health effects and risks, exposure standards from other jurisdictions around the world, and the practicability of measuring nickel exposures.

The review includes a recommendation to change the current WorkSafe **WES**, which are the following **WES-TWA** (WorkSafe New Zealand, 2017):

- 1 **mg/m³** for nickel metal
- 0.1 mg/m³ for soluble nickel compounds (as nickel)
- 1 mg/m³ nickel sulphide (roasting, fume and dust, as nickel)

Terms that are **bold** (first occurrence only) are further defined in the Glossary.

2.0 Physical and chemical properties

Nickel is a lustrous, hard metal.

Chemical and physical properties of nickel are summarised in Table 1.

CAS number	Nickel 7440-02-0, Nickel sulphide 16812-54-7
Molecular weight	58.71 (nickel)
Specific gravity	8.902 at 25°C (nickel)
Formula	Ni (nickel) NiS (nickel sulphide)
Boiling point	2730°C (nickel)
Solubility	Nickel – insoluble in water. Slightly soluble in hydrochloric and sulphuric acid, and soluble in nitric acid. Dissolves slowly in dilute sulphuric acid
HSNO classifications[1]	Nickel – 6.5B (contact sensitiser), 6.7B (suspected human carcinogen), 9.1A (All) (very ecotoxic in the aquatic environment), 9.2C (harmful in the soil environment)

TABLE 1:
Chemical and physical properties of nickel

[1] (**EPA**, 2017).

3.0
Uses

Nickel is used in the production of stainless steels, corrosion and heat-resistant alloys, catalysts for hydrogenation of fats and oils, electroplating, coin making and NiCad batteries (**ACGIH**®, 2001).

Exposures may also occur in scrap metal recycling (**NLM**, 2010).

Inhalation is considered the principal route of exposure to nickel in the workplace, although ingestion of nickel dust from contaminated skin may also be a route of exposure (NLM, 2010).

In New Zealand workplaces the main exposures would be expected to be nickel fumes during the welding of stainless steel, electroplating, and in foundries where alloys based on a mixture of copper and zinc are mixed with small quantities of other metals including nickel and cast into billets which are subsequently extruded through dies into lengths of rod, bar, tube and sections.

4.0 Health effects of nickel

IN THIS SECTION:

Nickel can be absorbed via inhalation, ingestion and to a very limited extent following dermal exposure.

The absorption of nickel is related to the solubility of the compound, with absorption increasing with increasing solubility. Nickel compounds that are soluble in water include nickel chloride and nickel sulphate; insoluble nickel compounds include nickel oxide, nickel sulphide and nickel subsulphide (**PHE**, 2009).

The respiratory tract is the primary site of toxicity following inhalation of nickel and its compounds (PHE, 2009).

Nickel and nickel compounds have been extensively reviewed by, among others, the International Agency for Research on Cancer (**IARC**), the United States Department of Health and Human Services, National Toxicology Programme Report on Carcinogens (**RoC**), the United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (**ATSDR**), the European Scientific Committee on Occupational Limits (**SCOEL**), Public Health England (PHE) and the World Health Organisation (**WHO**). Consideration is also given to the Australian Institute of Occupational Hygienists, Inc. (**AIOH**) Position Paper – Nickel and its compounds (AIOH, 2016). These reviews assessed studies on human occupational exposure and experimental animal available at the time of review. An additional literature search was conducted in March 2017. The following comments are summarised from these publications, specific supporting references are cited within the aforementioned documents.

4.1 Non-cancer

Humans

Acute ingestion of nickel compounds may cause nausea, vomiting, diarrhoea, headache, cough and can cause death. Following exposure, there can be an asymptomatic period after which pulmonary symptoms become apparent. Inhalation exposure can result in rhinitis, sinusitis and eventually perforation of the nasal septum (PHE, 2009). Respiratory tract cellular changes have been suggested in humans. Nickel and nickel compounds are potent skin sensitisers with consequent contact dermatitis (PHE, 2009).

Animals

Health effects of acute exposure of experimental animals to nickel and nickel compounds by the inhalation route are comparable to those seen in humans. They can include pulmonary effects including oedema, intra-alveolar haemorrhage and fibrosis. Rats appear to be more sensitive than mice. Oral exposure indicated soluble nickel compounds to be the most toxic (PHE, 2009).

Chronic inhalation exposure results in a variety of pulmonary changes and lesions at all levels of the respiratory tract ranging from irritation of mucous linings to lung inflammation and fibrosis, emphysema and pneumoconiosis. Immunological and lymphoreticular changes have also been reported. Pulmonary changes have also been reported following chronic oral exposure to nickel compounds (PHE, 2009).

Nickel and nickel compounds are skin sensitisers. Repeat dermal exposure in rats results in skin atrophy, acanthosis and hyperkeratinisation (PHE, 2009).

Reproduction and developmental studies resulted in increases in fetotoxicity and developmental malformations of offspring (exposure specifically to nickel carbonyl). These data were deemed sufficient in Europe to classify a number of nickel compounds as having the potential to cause harm to the unborn child (PHE, 2009).

4.2 Cancer

Humans

Occupational epidemiological studies have implicated exposure to nickel compounds in the development of cancer, particularly of the respiratory tract (nasal sinus) and lung. As the occupations from which much of the human data are derived are from industries in which there is exposure to a mixture of both soluble and insoluble nickel compounds it is not always clear which specific nickel compound is responsible (IARC, 2010).

Evidence for elevated risk of lung cancer in humans was demonstrated specifically for nickel chloride, nickel sulphate, water-soluble nickel compounds in general, insoluble nickel compounds, nickel oxides, nickel sulphides, and metallic nickel (IARC, 2010).

Data have also indicated that nickel compounds can act as co-promoters for cancer and also induce cancers at sites distant from the site of exposure indicating that the nickel ion is the trigger (IARC, 2010).

The genotoxic effects seen in exposed humans manifest as elevated incidences of sister chromatid exchanges, chromosomal aberrations and chromosomal gaps (WHO, 2000).

The IARC classify nickel compounds and nickel metal as carcinogenic to humans (Group 1) (IARC, 2010). They concluded that as nickel metal dust can become solubilised and bioavailable after inhalation, separating nickel and nickel compounds for classification was considered unwarranted.

The New Zealand Environmental Protection Authority (EPA) classifies nickel metal as Class 6.7B (suspected human carcinogen) and nickel oxide as Class 6.7A (known or presumed human carcinogen) (**EPA**, 2017).

In 2011 SCOEL concluded that water soluble and poorly water soluble nickel compounds are Group C carcinogens (carcinogen with a practical threshold effect) (SCOEL, 2011). However, SCOEL also concluded that:

> "neither animal data nor epidemiological data point towards a carcinogenic action of nickel metal".

ECHA reported that:

> "It is assumed that nickel compounds can produce in vitro effects that could contribute to the appearance of respiratory tumours. Generally, there is consensus by different regulatory bodies that nickel and compounds are not directly mutagenic but can cause genotoxicity via indirect genotoxic mode of action such as interference with DNA repair systems and DNA methylation patterns as well as oxidative stress, which lead to clastogenicity and increased genomic instability (SCOEL 2011; EFSA 2015). IARC (2012) stated that based on the update and distribution in cells as described, the ultimate genotoxic agent is nickel (II). However, direct reaction of nickel (II) with DNA does not seem to be relevant under realistic exposure conditions" (ECHA, 2017).

Animals

Inhalation carcinogenicity studies in rats exposed to nickel subsulphide resulted in increased incidences of benign and/or malignant lung tumours and pheochromocytoma (adrenal gland) in both sexes. Nickel oxide induced an increased incidence of lung tumours in female mice. Rats appear to be more sensitive than mice. Exposure to metallic nickel resulted in an increased incidence of pheochromocytoma in male rats and in the adrenal cortex of female rats. There were also indications that metallic nickel was bioavailable systemically following inhalation. Inhalation of nickel carbonyl in rats resulted in an increase in lung tumours in both sexes. Oral exposure of rats and mice to nickel compounds did not induce increases in the normal tumour profile. Induction of tumours in experimental animals has also been reported following intratracheal, intraperitoneal and intraocular instillation studies. Nickel acetate crosses the placental barrier in experimental animals and is associated with the induction of pituitary tumours in offspring and renal tumours in male offspring. It should be noted that not all nickel compounds have been demonstrated to be carcinogenic (IARC, 2010).

Genotoxic effects demonstrated in test systems manifest as DNA damage but generally only occurring at comparatively high cytotoxic doses. Nickel was not mutagenic in bacterial assays and only weakly mutagenic in mammalian cells but can induce DNA damage, chromosomal aberrations and micronuclei in in vitro and in vivo test systems. Nickel compounds can also act as a co-mutagen with a variety of DNA damaging agents (as with smoking) thus indicating damage to the DNA repair mechanism. Inflammation may also contribute to nickel induced carcinogenesis (IARC, 2010).

The ultimate carcinogenic species is the nickel ion Ni (II) together with factors that promote localisation of high concentrations of nickel ions at critical tissue sites. Water soluble and poorly soluble nickel species are taken up in cells, the former by ion channels, the latter by phagocytosis. Nickel particulates are also taken up by phagocytosis. Cellular uptake results in an increase in nickel ions in the cytoplasm and nucleus. Epigenetic changes may be mediated by altered histone modification (IARC, 2010). It has been shown that histone proteins (which form the structure that enables DNA molecules to fold into chromosomes in the cell nucleus) can be tagged and thereby lead to DNA in the affected region being used or ignored (i.e. altered behaviour). A suggested mechanism is the replacement of iron by higher affinity nickel resulting in increased or decreased expression of specific genes depending on the affected pathway and the consequent potential for having extensive and varied effects on cell expression (Chervona et al, 2012).

4.3 Absorption, distribution, metabolism and excretion

Humans

In humans soluble nickel compounds are rapidly absorbed through the lungs and excreted mainly in urine. Insoluble nickel compounds result in elevated concentrations in plasma and urine but absorption is slow. The accumulation/ clearance of nickel following inhalation appears to be dependent on the stability and particle size of the nickel moiety. Nickel is taken up in cells and transported to the nucleus indicating the ultimate genotoxic agent is nickel ion (Ni II) (IARC, 2010).

Animals and experimental systems

Nickel is not metabolised. In rodents nickel salts and sulphides are absorbed through the lungs and excreted mainly in urine. Inhalation of green nickel oxide conversely is not distributed in extrapulmonary tissue and is excreted only in faeces. The lung clearance rate differs between nickel compounds following inhalation and is likely related to water solubility and particle size (IARC, 2012).

5.0 Exposure standards and guidance values in use around the world

IN THIS SECTION:

Table 2 below shows the nickel exposure standards from around the world.

This information is published by the Institute for Occupational Safety and Health of the German Social Accident Insurance (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung, 2017).

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE (mg/m^3)	SHORT-TERM LIMIT VALUE (mg/m^3)
Nickel, metal		
Australia	1	
Austria	0.5	2
Belgium	1	
Canada – Ontario	1[2]	
Canada – Québec	1	
Denmark	0.05	0.1
Finland	0.01[3]	
France	1	
Germany (AGS)	0.006[3]	0.048[3]
Hungary	0.1	0.1
Ireland	0.5	
Israel	1.5	
Japan – JSOH	1	
Latvia	0.05	
New Zealand	1	
People's Republic of China	[1]	
Singapore	1	
South Korea	1	
Spain	1	
Sweden	0.5	
Switzerland	0.5[2]	
USA – NIOSH	0.015	
USA – OSHA	1	
Nickel, inorganic compounds, water-soluble		
Australia	0.1	
Austria	0.05[2]	0.1[2]
Belgium	0.1	

[2] Inhalable fraction.

[3] Calculated as Ni and measured as respirable fraction.

[4] Applied to workplaces using powder substances.

JURISDICTION OR ADVISORY BODY	8-HOUR LIMIT VALUE (mg/m^3)	SHORT-TERM LIMIT VALUE (mg/m^3)
Canada – Ontario	0.1[2]	
Canada – Québec	0.1	
Denmark	0.01	0.02
Hungary	0.1	0.1
Ireland	0.1	
Japan	0.5[4]	
New Zealand	0.1	
People's Republic of China	0.5	
Singapore	1	
South Korea	0.1	
Spain	0.1	
Switzerland	0.05[2]	
USA – NIOSH	0.015	
USA – OSHA	1	
United Kingdom	0.1	
Nickel, inorganic compounds, water-insoluble		
Austria	0.5	2[2]
Belgium	0.2	
Canada – Ontario	0.2[2]	
Canada – Québec	1	
Denmark	0.05	0.1
Ireland	0.5	
Japan	0.1[2]	
People's Republic of China	1	
Singapore	1	
South Korea	0.5	
Spain	0.2	
Switzerland	0.05[2]	
USA – NIOSH	0.015	
USA – OSHA	1	
United Kingdom	0.5	

TABLE 2: Nickel exposure standards from around the world

WorkSafe's WES for nickel has been unchanged since adoption in 1994 being: 1 mg/m^3 for nickel metal and nickel sulphide roasting (fume/dust), and 0.1 mg/m^3 for soluble nickel compounds.

5.1 Exposure standards with documentation

WorkSafe is unaware of documentation explaining the derivation of the non-WorkSafe exposure values given in Table 2. However other organisations not listed above do set exposure values and provide documentation. This includes the ACGIH®, **DFG**, ECHA, SCOEL and AIOH. Their WES values are discussed below and the values summarised in Table 3.

ORGANISATION AND YEAR OF REVIEW	ELEMENTAL/ METALLIC NICKEL	SOLUBLE INORGANIC NICKEL COMPOUNDS	INSOLUBLE/ POORLY SOLUBLE INORGANIC NICKEL COMPOUNDS	NICKEL SULPHIDE
ACGIH® (2001)	1.5[I]	0.1[I]	0.2[I]	0.1[I] (Ni_3S_2)
AIOH (2016)	0.1[I]	0.1[I]	0.1[I]	0.1[I]
ECHA (2017) (proposed values)	0.005[R]	0.02[I] 0.005[R]	0.02[I] 0.005[R]	
SCOEL (2011)	0.005[R]	0.01[I]	0.01[I]	
0.005[R]				
WorkSafe (1994)	1[I]	0.1[I]		0.1[I] (NiS)

All values in mg/m³, WorkSafe WES included for comparison.

TABLE 3: Exposure Standards mg/m³ with documentation

5.2 ACGIH®

The ACGIH® recommended the following **TLV-TWA**®s for *'nickel and inorganic compounds including nickel subsulfide (as Ni)*':

- Inhalable elemental/metal – 1.5 mg/m³ (A5 – not suspected as a human carcinogen).
- Inhalable soluble inorganic compounds – 0.1 mg/m³ (A4 – not classifiable as a human carcinogen).
- Inhalable insoluble inorganic compounds (not otherwise specified) – 0.2 mg/m³ (A1 – confirmed human carcinogen).
- Inhalable nickel subsulfide (A1 – confirmed human carcinogen) – 0.1 mg/m³ (ACGIH®, 2001).

The **TLV**® values are based on the following:

- For elemental nickel and metal – to minimise the potential for dermatitis and pneumoconiosis.
- For soluble nickel compounds – to minimise the potential for pulmonary damage, as well as dermatitis and suspected cancer risk.
- For insoluble nickel compounds – to minimise the potential for nasal and lung cancer.
- For nickel subsulfide – to minimise the potential for nasal and lung cancer.

The ACGIH® considered there was insufficient data available to recommend **skin** or **SEN** notations or a **TLV-STEL**.

[I] Inhalable.

[R] Respirable.

In 2001 the ACGIH® considered data published in the review by the International Committee on Nickel Carcinogenesis in Man (ICNCM, 1990) in which it was concluded that:

> "increased risk of lung and nasal sinus cancer among nickel refinery workers was associated with airborne exposures in excess of 1 mg/m^3 for soluble and 10 mg/m^3 for 'total' aerosol of insoluble forms of nickel" (ACGIH®, 2001).

The ACGIH® noted that almost all of the air monitoring data they report in their documentation on nickel was for 'total' particulate (using a closed faced 37-mm cassette) and when they set their TLVs® in 1996 they were based on measurement of 'total' particulate. The ACGIH® now consider the TLV-TWAs should be expressed as inhalable particulate rather than total particulate due to the association between some forms of nickel and sinus cancer. They stated that there were few published data to correlate 'total' particulate with inhalable particulate measurements. They used data from a study comparing 'total' particulate measurements to inhalable particulate measurements using an **IOM inhalable sampler** to develop their current TLV-TWAs for inhalable particulate (Tsai et al, 1996).

It should be noted that nickel and inorganic compounds, including nickel subsulfide are listed in the 'Chemical Substances and Other Issues Under Study' section of the current ACGIH® TLVs® and BEIs® book (ACGIH®, 2017). The ACGIH® website lists the nickel group as Tier 2 (ie *"will not move forward with an NIC [Notice of Intended Change] proposal in 2018"*).

5.3 AIOH

In 2016 the AIOH published a position paper following a review of nickel and nickel compounds. The AIOH recommended an exposure standard for all forms of nickel of 0.1 mg/m^3 (inhalable) (AIOH, 2016).

The AIOH concluded that:

- "The animal data for fibrotic effects of sulphidic, oxidic and soluble nickel (NTP, 1994a; 1994b; & 1995) and for metallic nickel (Oller et al, 2008) are unconvincing when viewed in the light of human epidemiology.
- For nickel compounds in general, the main adverse health effects that need to be considered in setting an **OEL** are respiratory cancer (of the lung and nasal cavity and para-nasal sinus) and sensitisation leading to contact dermatitis. The AIOH regards respiratory cancer (lung and nasal) as the main health effect to derive an OEL recommendation.
- The compounds principally implicated in causing respiratory cancer are sulphidic nickel, particularly nickel sub-sulphide (Ni_3S_2) and oxidic nickel, which includes a range of insoluble nickel compounds. There is debate about whether soluble nickel compounds are carcinogenic, although respiratory cancer risk is greater when there is exposure to mixed species of nickel.
- The occurrence of multiple nickel species in most work environments and the difficulty of speciation suggests that a common limit be set for all nickel species.
- Reproductive outcomes, either animal or human, do not occur at the exposure levels of interest.

- Lung fibrosis drives the SCOEL OEL for metallic nickel of 0.005 mg/m^3 in respirable dust based on the animal study of Oller et al (2008). Review of the literature of human exposure to metallic nickel, and in fact all nickel species, presents a different picture. Berge and Skyberg (2003) in a study of pulmonary fibrosis at Kristiansand found a prevalence of 4.5% of workers with pulmonary fibrosis at greater than ILO category 1/0, although only 6 of the 1046 workers reviewed exceeded ILO category 1/1. Pulmonary fibrosis was significantly associated with exposure to soluble and sulphidic nickel but not to metallic nickel. It should be noted that 74 workers were identified as having pleural plaques suggesting asbestos exposure. Twenty one of the 47 workers diagnosed with pulmonary fibrosis also had pleural plaques." (AIOH, 2016).

5.4 DFG

In 2006 the DFG concluded that no **NOAEL** for carcinogenicity can be derived from the epidemiological and animal studies, and thus no **MAK** value can be established for nickel and nickel compounds as a whole. They say there is sufficient evidence of sensitizing effects on the respiratory tract for water-soluble nickel compounds (DFG, 2006). They stated that the following conclusions can be drawn from data of animal studies:

- "The epidemiological data contribute little to the assessment of a no observed effect level (NOAEL) for the respiratory toxic effects of nickel and nickel compounds, since the exposure cannot be established accurately enough and since the studies are in most cases limited to tumours as the end point.
- As a result of the NTP studies on nickel oxide (NTP 1994a) (sic), nickel subsulfide (NTP 1994b) (sic) and nickel sulfate (NTP 1996c), nickel sulfate is regarded as the most toxic nickel compound among the compounds tested.
- The following effects were found in F344/N rats after exposure to ≥ 0.06 mg Ni/m^3: chronic, active pneumonia, hyperplasia of the macrophages, alveolar proteinosis, fibrosis, hyperplasia of the bronchial lymph nodes and atrophy of the olfactory epithelium. Similar inflammatory reactions were observed in B6C3F1 mice after exposure to ≥ 0.11 mg Ni/m^3 (NTP 1996c).
- The NOAEL was thus 0.03 mg Ni/m^3 (0.12 mg nickel sulfate/m^3) in rats and 0.06 mg Ni/m^3 (0.25 mg nickel sulfate/m^3) in mice. If the lowest NOAEL from test animals were used as a basis, a threshold value for inflammatory reactions of the lungs of about 0.01 mg Ni/m^3 would be obtained for humans. Since nickel metal and the other inorganic nickel compounds also release nickel ions in vivo, the same threshold should be established for nickel and inorganic nickel compounds as a whole. This value does not take into account the sensitizing effects of nickel and nickel compounds".

5.5 ECHA

In 2017 the ECHA publicised a document proposing exposure values for nickel and compounds (ECHA, 2017). Their final decision (after public consultation) will be published in March 2018. In their report they extensively discussed exposure limits for nickel set by other organisations, and proposed the following exposure limits:

- 0.005 mg/m^3 (respirable) for nickel metal and nickel compounds
- 0.02 mg/m^3 (inhalable) for nickel metal and nickel compounds

- No STEL is proposed as this group of substances is neither known to be acutely toxic nor irritating.
- As nickel and its compounds are skin and respiratory sensitisers a 'sensitisation notation' is warranted.
- Absorption of nickel following dermal contact to various nickel compounds is low therefore nickel and its compounds do not warrant a skin notation.

They noted:

- "The particle size of nickel compounds determines the deposition fraction in the respiratory tract of rats and humans. The particle sizes of the aerosols used in the animal inhalation bioassays were small, with most measures near a mass median aerodynamic diameter (MMAD) of 2 **µm**. The human deposition characteristics of aerosols indicate that all of these particles would be of respirable size in humans (Oller and Oberdorster, 2010). Nickel containing aerosols with larger particles (eg >20 µm MMAD), such as those in workplaces, contain a relatively smaller proportion of respirable-size nickel. Human occupational exposure concentrations were often much higher than those tested in the inhalation bioassays, but resulted in equivalent exposures to respirable-size nickel as in the animal bioassays (ie resulted in the same deposited dose in the pulmonary region per unit of surface area) (Goodman et al 2011). Therefore, two different threshold based exposure limits, for the inhalable and the respirable fraction, respectively are proposed in order to give sufficient worker protection" (ECHA, 2017).

For the respirable fraction exposure limit they reported that:

- "A practical approach is proposed for OEL setting for nickel metal and all nickel compounds based on the most sensitive endpoint in animal data which is inflammatory reactions in the lungs. In the inhalation toxicity study in rats with nickel sulfate an **NOAEC** of 0.027 (~0.03) mg/m^3 for inflammatory effects were (sic) observed. However, for less soluble nickel subsulfide and nickel oxide, a LOAEC of 0.11 and 0.05 mg/m^3 respectively, were identified for inflammatory effects and lung fibrosis in NTP (1996) studies, but no NOAEC.
- Inflammatory effects in the respiratory tract are not seen in humans. Therefore the PODs (Points of Departure) are the NAEC-HECs (No Adverse Effect Concentration–Human Equivalent Concentration) for soluble and poorly soluble nickel compounds as well as for nickel metal, as calculated by **NiPERA** (2017). An assessment factor of 3 is applied for the LOAECs of 0.11 and 0.05 mg/m^3 for nickel subsulfide and nickel oxide, respectively, and HECs are calculated for soluble and poorly soluble nickel compounds resulting in a HEC of [about] 0.03 mg/m^3 for respirable particles.
- The HEC calculations already take possible differences in toxicokinetics into account and an additional AF [assessment factor] for toxicokinetic differences is therefore not considered. Since the rat is generally the most sensitive species for the local lung effects of particulates, an AF of 1 is considered for toxicodynamic differences between rats and humans.

- By considering the AF of 5 for intra-worker variation and applying this to the calculated NAEC-HEC [0.03 mg/m³], acceptable exposure limits of 0.006 mg/m³ and 0.004 mg/m³ for nickel compounds and nickel metal, respectively are proposed. Since the derived values for both metallic nickel and nickel compounds are almost the same, the value of 0.005 mg Ni/m³ is recommended by the dossier submitter ECHA as an OEL for the respirable fraction of both nickel metal and nickel compounds. The choice of 0.005 mg Ni/m³ instead of 0.006 mg/m³ is also in accordance with the general practise of OEL setting which usually uses the decimals of the integers 1, 2 or 5 **ppm** or mg/m³, if scientific reasons do not suggest a more specific value (further see SCOEL key documentation from 2014). This avoids giving wrong impression on the preciseness in cases in which uncertainties related to the limitations of the database do not justify such a precision.
- Although nickel compounds are considered to have a practical threshold for its carcinogenicity, it should be noted that the residual cancer risk cannot to be totally excluded at the exposure levels below the proposed occupational exposure level of 0.005 mg/m³." (ECHA, 2017).

For the inhalable fraction exposure limit they reported that:

- "Since nickel compounds have shown (sic) to increase also the risk of sinonasal cancer in humans, an OEL for inhalable fraction is considered appropriate. Anttila (1998) found in Finnish workers exposed to concentrations of [about] 0.25 mg/m³ soluble nickel sulphate an excess of bronchial cancer and two cancers of the sinuses in the nasal cavity. However the low observed absolute numbers of cases make nasal cancer less amenable to quantitative dose response assessment. However comparing the overall lung and nasal cancer incidence/mortality in the available cohort studies indicates that there is no cohort were (sic) the risk of nasal cancer would be statistically significantly increased if the risk of lung cancer was also not statistically significantly increased. Consequently the quantitative dose-response for lung cancer can be used as a surrogate. In epidemiological data from Norwegian refinery workers (Kristiansand cohort) a significant increase in lung cancer incidence for water soluble nickel is observed at a cumulative exposure of 1.6 mg/m³ x years. Since the average exposure of the cohort was 13 years, this corresponds [to] an average exposure to 0.123 mg Ni/m³ (Grimsrud et al., 2002; 2003). However, since workers can be potentially exposed for 40 years to nickel, this needs to be taken into account. In 40-years occupational exposure 1.6 mg/m³ x years corresponds an exposure level of 0.04 mg/m³. A standard AF [assessment factor] of 3 is used for the LOAEC to NOAEC extrapolation resulting in a value of 0.013 mg/m³. When a correction factor of 2 for sampler efficiency is applied this results in lowest inhalable exposure 0.027 mg/m³". See further points below on sampler correction factor.
- "The starting point represents the lowest estimate for an increased nasal cancer risk and it is derived from the epidemiological data from a worker cohort which is considered to adequately address the variability among workers. Therefore, no additional AF for interindividual variation is considered to be required. The value of 0.027 mg/m³ can be rounded to 0.02 mg/m³ following the general principles of setting an OEL [SCOEL preferred value approach]. Thus, the value of 0.02 mg/m³ is proposed by the dossier submitter ECHA as an OEL for inhalable fraction.
- Since metallic nickel is very poorly soluble and have not shown to cause effects in the upper respiratory tract, no separate value for inhalable fraction of metallic nickel is needed" (ECHA, 2017).

In regard to sampling correction factors they stated:

- "Parallel to the process improvements there were also changes in the sampling and analytical techniques used to monitor exposure. Oller and Oberdörster (2010) have pointed out that comparisons of measurements in various nickel industries using the old 37 mm sampler and the IOM sampler indicate that the 37 mm sampler captured on average about half of the nickel mass captured by the IOM inhalable sampler. Thus a correction factor would be needed when 37 mm sampler had been used in assessing exposure in the epidemiological cohorts which would have underestimated the exposure levels linked to the identified risk levels.
- SCOEL based the lung cancer practical threshold (OEL of 0.01 mg Ni/m^3 for the inhalable fraction) on one cohort (5,000 workers) where exposures were collected with a 37-mm sampler, which is known to undersample the nickel mass in the inhalable aerosol fraction. SCOEL reported exposures both in terms of 37-mm samplers and equivalent inhalable samplers, but did not consider that these samplers differ by about 2-fold in sampling efficiency. Therefore, the final OEL did not incorporate a conversion to inhalable aerosol (ECHA, 2017)

5.6 SCOEL

SCOEL recommended the following 8 hour WES-TWAs:

- 0.005 mg/m^3 (respirable) for nickel metal and poorly soluble inorganic nickel compounds
- 0.01 mg/m^3 (inhalable) for soluble and poorly soluble inorganic nickel compounds (excluding metallic nickel) (SCOEL, 2011).

They stated that these values are based on protection from inflammatory effects in the lung, and according to available evidence should also protect against carcinogenic effects.

SCOEL reported that exposure to nickel compounds is associated with an increased cancer risk in the lung and nasal cavity, as well as with inflammatory responses/fibrosis in the lung. They were of the view that since mechanistic data indicate an indirect genotoxic mode of action, nickel is considered a carcinogen group C (carcinogen with a practical threshold) (SCOEL, 2011).

In setting the WES values they considered:

- A rat study in which an NOAEL of 0.03 mg/m^3 was demonstrated for water soluble nickel sulphate (equivalent human concentration is 0.016 mg/m^3). Since this conversion only takes into account the deposited dose and not the long-term chronic retained dose as well as potential toxicodynamic differences, an 8 hour WES-TWA of 0.005 mg/m^3 was recommended. As the particle size of nickel sulphate of 2.5 µm mass median aerodynamic diameter (MMDA) was applied in the rat study, the proposed value corresponds to the respirable fraction.
- That no NOAELs were demonstrated in other experimental animal studies.
- That in addition to chronic inflammation of the lung, the proposed exposure standards also need to protect from nickel-induced carcinogenicity. Since epidemiological evidence suggests not only the induction of lung tumours, which may be provoked by respirable particle sizes, but also of nasal tumours, and particles at the workplace are not limited to the respirable fraction, exposure towards inhalable nickel particles needs to be limited for carcinogenic nickel species as well.
- That excluding metallic nickel from the inhalable WES was appropriate as neither animal data nor epidemiological data point towards a carcinogenic action of nickel metal.

- That increased frequencies of chromosomal aberrations in humans were observed at exposure levels above 0.5 mg/m^3.
- The reproductive system is regarded as a target organ for nickel compounds but effects were seen at levels well above the proposed exposure limits.
- Exposure to nickel and nickel salts in the workplace might evoke contact dermatitis and contact urticarial. In contrast, cases of occupational asthma by exposure to nickel are rare and co-exposure (eg to chromium, cobalt or hard metals usually occurred) indicating that nickel is not a significant respiratory sensitizer.
- That the general consensus is that lung tumours seen in rats under conditions of particle overload can occur with a range of respirable poorly-soluble low-toxicity substances and that their lung tumour-inducing potency is more closely related to particle size and particle-surface properties rather than mass.
- Epidemiological evidence suggests not only the induction of lung tumours, which may be provoked by respirable particle sizes, but also of nasal tumours, and particles at the workplace are not limited to the respirable fraction, exposure towards inhalable nickel particles needs to be limited for carcinogenic nickel species as well.

6.0 Analytical methods for the assessment of airborne nickel

A common practice in New Zealand to measure airborne nickel is a modification of NIOSH Method 7303 (NIOSH, 2003).

Using this method an air sample is collected onto a PVC or cellulose ester membrane filter using a sampling train set at a flow rate between 1 and 4 litres of air per minute. Following exposure of the filter for an appropriate period of time, the filter is subjected to acid digestion followed by analysis using **ICP**. The detection limit of this modified method has been quoted by a New Zealand analytical laboratory as 0.05 µg per sample for nickel.

This would allow a minimum concentration of 0.00005 mg of nickel per m^3 of air to be quantified over a collection period of 8 hours using a typical flow rate for a respirable cyclone sampler set at 2.2 litres of air per minute.

It would also allow a minimum concentration of 0.00005 mg of nickel per m^3 of air to be quantified over a collection period of 8 hours using a flow rate for an inhalable dust sampler of 2 litres of air per minute.

7.0
Discussion and recommendation

WorkSafe proposes to change the current WES for nickel and nickel compounds.

7.1 Metal/elemental nickel

The reviews discussed in Sections 5.2 to 5.6 indicate different views on whether elemental/metallic nickel should be measured using an inhalable/respirable method. The range of WES (inhalable) values were 0.1 to 1.5 mg/m^3. SCOEL considers it appropriate to measure using the respirable method and their WES is 0.005 mg/m^3. All except the ACGIH® are lower than the current WorkSafe WES. Based on these reviews WorkSafe does not consider its current WES-TWA of 1 mg/m^3 for elemental nickel or roasting fumes is acceptable.

7.2 Soluble versus insoluble/poorly soluble WES

Only ACGIH® has a different WES value for soluble versus insoluble compounds. SCOEL, AIOH and ECHA all recommend the same WES value whether the compound is soluble, poorly soluble or insoluble. WorkSafe currently has only a WES value for soluble nickel compounds (with the exception of nickel sulphide which is poorly soluble).

7.3 Sampling method

The reviews discussed in Sections 5.2 to 5.6 indicate different views on whether nickel compounds (excluding metal) should be measured using inhalable or respirable methods. For those organisations providing an inhalable WES they range from 0.01 to 0.2 mg/m^3 (WorkSafe WES is 0.1 mg/m^3 for soluble). For those organisations providing a respirable WES (SCOEL and ECHA) they are both 0.005 mg/m^3 (no WorkSafe WES).

Based on these reviews WorkSafe questions whether it is appropriate to have both and inhalable and respirable WES for soluble compounds, and what an acceptable WES value should be.

7.4 Nickel sulphide and nickel subsulphide compounds

The reviews discussed in Sections 5.2 to 5.6 indicate only WorkSafe has a specific WES for nickel sulphide. The ACGIH® has one for nickel subsulphide. Nickel sulphides are poorly soluble, and it is to be assumed that SCOEL, AIOH and ECHA treat nickel sulphides in the ‘poorly soluble’ group and do not make a separate distinction for the sulphides.

7.5 Proposed WorkSafe WES

It is proposed that WorkSafe:

- With the exception of elemental nickel, do not have different WES values for soluble and insoluble/poorly soluble nickel compounds. The reason being that multiple nickel species can occur in work environments and the difficulty of speciation suggests that a common limit be set for all nickel species (AIOH, 2016).
- Have a respirable WES-TWA for elemental/metallic nickel as it is poorly soluble and does not cause effects in the upper respiratory tract, therefore no separate value for inhalable fraction of metallic nickel is needed (ECHA, 2017).
- Have both a respirable and inhalable WES-TWA for inorganic nickel compounds (soluble, poorly soluble and insoluble) to protect from chronic inflammation of the lung (respirable WES-TWA) and nickel-induced carcinogenicity (inhalable WES-TWA).
- Delete reference to 'nickel sulphide roasting fume and dust' in the WES book.
- Retain the 'sen' notation for nickel and its compounds.

As such Worksafe proposes the following WES-TWA values:

- Elemental/metal – WES-TWA of 0.005 mg/m^3 (respirable).
- Inorganic nickel compounds – WES-TWA of 0.005 mg/m^3 (respirable) and WES-TWA of 0.02 mg/m^3 (inhalable) – based on the most recent review (ECHA, 2017).

Appendices

IN THIS SECTION:

Appendix 1: Glossary

TERM	MEANING
ACGIH®	The American Conference of Governmental Industrial Hygienists (ACGIH®) is a 501(c)(3) charitable scientific organization, established in 1938, that advances occupational and environmental health. Examples of this include their annual edition of the TLVs® and BEIs® book and Guide to Occupational Exposure Values.
AIOH	Australian Institute of Occupational Hygienists, Inc.
ATSDR	Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services.
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation), the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Federal Republic of Germany. The science-based MAK values are recommended to the German Minister of Labour and Social Affairs for possible adoption under the German Hazardous Substances Ordinance.
ECHA	The European Chemical Agency (an Agency of the European Union).
EPA	New Zealand Environmental Protection Authority.
HSNO	Hazardous Substances and New Organisms Act, New Zealand.
IARC	The International Agency for Research on Cancer – an agency of the World Health Organisation, whose mission is to coordinate and conduct research on the causes of human cancer and to develop scientific strategies for cancer prevention and control.
ICP	Inductively coupled plasma – a powerful method used in analytical chemistry to detect metals and some non-metal species.
IOM Inhalable Sampler	A particulate sampling head that samples the inhalable fraction in accordance with the ISO/CEN definition of inhalable dust fraction.
MAK	The maximum permissible concentration of a substance in air at the workplace – a DFG term.
mg	Milligram or one thousandth of a gram.
mg/m³	Milligrams of substance per cubic metre of air.
NIOSH	The National Institute for Occupational Safety and Health (NIOSH) is the United States federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. NIOSH is part of the Centers for Disease Control and Prevention (CDC) within the U.S. Department of Health and Human Services.
NiPERA	Nickel Producers Environmental Research Agency – an independently incorporated division of the Nickel Institute, an international organisation dedicated to all aspects of nickel product development and stewardship.
NLM	National Library of Medicine, US Department of Health and Human Services.
NOAEC	No observable adverse effects concentration.
NOAEL	No observable adverse effects level.
OEL	Occupational Exposure Limit.
OSHA	Occupational Safety and Health Administration is an agency of the Department of Labor, United States Government responsible for setting and enforcing standards for working conditions
PHE	Public Health England is an executive agency for the protection of health and wellbeing sponsored by the United Kingdom Government
ppm	Parts of vapour or gas per million parts of air.
RoC	The Report on Carcinogens is a mandated report identifying substances that pose a hazard to people in the United States. It is prepared by the National Toxicology Programme for the United States Department of Health and Human Services.

TERM	MEANING
SCOEL	The Scientific Committee on Occupational Exposure Limits is a committee of the European Commission, established in 1995 to advise on occupational health limits for chemicals in the workplace within the framework of Directive 98/24/EC, the chemical agents directive, and Directive 90/394/EEC, the carcinogens at work directive.
SEN	A notation indicating the subject substance is a sensitiser. DSEN and RSEN are used in place of SEN when specific evidence of sensitisation by the dermal or respiratory route, respectively, is confirmed by human or animal data. An ACGIH® term.
sen	A substance that can 'sensitise' the skin or respiratory system, inducing a state of hypersensitivity to it, so that on subsequent exposures, an allergic reaction can occur (which would not develop in non-sensitised individuals). It is uncommon to become sensitised to a compound after just a single reaction to it. A WorkSafe term.
Skin	A notation indicating the potential for significant contribution to the overall exposure, by the cutaneous route, including mucous membranes and the eyes, by contact with vapours, liquids and solids. An ACGIH® term.
TLV®	Threshold Limit Value (see TLV-STEL and TLV-TWA below). An ACGIH® term.
TLV-STEL	TLV®-Short-Term Exposure Limit; a 15 minute TWA exposure that should not be exceeded at any time during a work day, even if the 8-hour TWA is within the TLV-TWA. An ACGIH® term.
TLV-TWA	TLV® – Time-Weighted Average; the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed to, day after day, for a working lifetime without adverse effect. An ACGIH® term.
WES	Workplace Exposure Standard – WESs are values that refer to the airborne concentration of substances, at which it is believed that nearly all workers can be repeatedly exposed to, day after day, without coming to harm. The values are normally calculated on work schedules of five shifts of eight hours duration over a 40 hour week. A WorkSafe term.
WES-TWA	The average airborne concentration of a substance calculated over an eight-hour working day. A WorkSafe term.
WHO	The World Health Organisation – its primary role is to direct international health within the United Nations system and to lead partners in global health responses.
µm	Micrometre, or millionth of a metre.

Appendix 2: References

ACGIH® (2017). TLVs® and BEIs® book. Copyright 2017. Reprinted with permission. www.acgih.org/store

ACGIH® (2001). Nickel and Inorganic Compounds, including Nickel Subsulfide. From ACGIH® documentation of the Threshold Limit Values and Biological Exposure Indices, 7th Edition. Copyright 2001. Reprinted with permission.

AIOH (2016). Australian Institute of Occupational Hygienists, Inc. Nickel and it's compounds, Potential for Occupational Health Issues Position Paper.

Chervona et al (2012). Carcinogenic Metals and the Epigenome: Understanding the effect of Nickel, Arsenic and Chromium. Metallomics 4(7): 619–627.

DFG (2006). Deutsche Forschungsgemeinschaft -The MAK-Collection Part I, MAK Value Documentations, Nickel and its Compounds (in the form of inhalable dusts/aersols). http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb744002vere0022/pdf

ECHA (2017). Proposal by the European Chemical Agency (ECHA) in support of occupational exposure limit values for nickel and its compounds in the workplace. www.pssewloclawek.pl/pliki/aktualnosci/dokumentacja_rac/dokumentacja%20RAC%20dla%20niklu%20i%20jego%20zwiazkow.PDF

EPA (2017). New Zealand Environmental Protection Authority. www.epa.govt.nz/search-databases/Pages/controls-details.aspx?SubstanceID=2723&AppID=3287

IARC (2010). Nickel and nickel compounds. Monographs Volume 100C, 169-218. https://monographs.iarc.fr/ENG/Monographs/vol100C/mono100C-10.pdf

ICNCM (1990). Report of the International Committee on Nickel Carcinogenesis in Man. Sir R.Doll Chair. Scandanavian Journal of Work and Environ. Health 16:1(Special issue).

Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung. (2017). Retrieved from http://limitvalue.ifa.dguv.de

NIOSH (2003). Elements by ICP. Method 7030, Issue 1. www.cdc.gov/niosh/docs/2003-154/pdfs/7303.pdf

NiPERA (2017), 2017-Workplace nickel DNEL derivation prepared by the Nickel REACH Consortia Secretariat (Nickel Institute-NiPERA) (Appendix C2 – Background Documents in Support of Long-Term Inhalable DNELs for Nickel and Nickel Compounds). www.nickelconsortia.eu/dnel-derivation.html

NLM (2010). Hazardous Substances Data Bank. U.S. Department of Health and Human Services National Toxicology Information Program, National Library of Medicine, Bethesda, MD. https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~5r1ZAR:3

NTP (1996a) Toxicology and carcinogenesis studies of nickel oxide in F344/N rats and B6C3F1 mice. Technical report series No. 451, US Department of Health and Human Services, Washington, DC, USA.

NTP (1996b) Toxicology and carcinogenesis studies of nickel sub-sulphide in F344/N rats and B6C3F1 mice. Technical report series No. 453, US Department of Health and Human Services, Washington, DC, USA.

NTP (1996c) Toxicology and carcinogenesis studies of nickel sulphate hexahydrate in F344/N rats and B6C3F1 mice. Technical report series No. 454, US Department of Health and Human Services, Washington, DC, USA.

Public Health England (2009). Nickel Toxicological Overview. Prepared by the

Toxicology Department.

SCOEL (2011). Recommendation from the Scientific Committee on Occupational Exposure Limits for Nickel and Inorganic Nickel Compounds SCOEL/SUM/85.

Tsai PJ, Werner MA, Vincent JH, Maldonado G (1996). Worker Exposure to Nickel-Containing Aerosol in Two Electroplating Shops: Comparison Between Inhalable and Total Aerosol. Appl. Occup. Environ. Hyg. 11:484-492.

World Health Organisation (2000). Air quality guidelines for Europe, second edition. European Series 91, Chapter 6.10 Nickel. www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/pre2009/who-air-quality-guidelines-for-europe,-2nd-edition,-2000-cd-rom-version

WorkSafe New Zealand (2017). Workplace Exposure Standards and Biological Exposure Indices, 9th Edition.

Disclaimer

WorkSafe New Zealand has made every effort to ensure the information contained in this publication is reliable, but makes no guarantee of its completeness. WorkSafe may change the contents of this guide at any time without notice.

This document is a guideline only. It should not be used as a substitute for legislation or legal advice. WorkSafe is not responsible for the results of any action taken on the basis of information in this document, or for any errors or omissions.

Published: March 2018 Current until: 2020

PO Box 165, Wellington 6140, New Zealand

www.worksafe.govt.nz

WSNZ_2988_MAR 2018

WORKSAFE
NEW ZEALAND | MAHI HAUMARU AOTEAROA

Level 6, 86 Customhouse Quay
PO Box 165, Wellington 6140
0800 030 040 worksafe.govt.nz