# nickel, metal and insoluble COMPOUNDS (as ni)

| CAS number: | 7440-02-0 (Nickel metal) |
| --- | --- |
| Synonyms: | — |
| Chemical formula: | Ni |
| Structural formula: | — |

Workplace exposure standard (amended)

| TWA: | **0.1 mg/m3 (Ni, as inhalable)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Carc, 2, DSEN** |
| IDLH: | **10 mg/m3** |
| |  | | --- | | **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.1 mg/m3 is recommended to protect for inflammation of the airways and to minimise the potential for lung and nasal cancer in exposed workers.

## Discussion and conclusions

Major uses of nickel metal and divalent salts include production of stainless steel, corrosion- and heat resistant alloys, catalysts for hydrogenation of fats and oils, electro-plating, coinage and alkaline batteries. This evaluation covers insoluble nickel compounds including nickel metal, nickel powder and sulfide roasting fume and dust.

The critical effects of exposure are respiratory (nasal and lung) cancer and inflammatory responses in the lung. Several agencies have classified nickel compounds as carcinogenic, causing cancer in the lungs and nasal cavity based on observational studies in workers and evidence in animals. Carcinogenic risk is considered greater when there is exposure to mixed species of nickel (ACGIH, 2018; DFG, 2010; IARC, 2012; SCOEL, 2011). Nickel and nickel compounds are not directly mutagenic and carcinogenicity is due to mechanisms that are not directly genotoxic (AIOH, 2016; DFG, 2010; SCOEL, 2011). As such, insoluble nickel compounds are considered to have a threshold in terms of carcinogenicity.

AIOH (2016) cited a study of 2,521 refinery workers with more than five years employment and relatively high historic exposures to airborne nickel. An overall non‐significant excess of lung cancer in workers employed after 1952 and a significant excess was noted in this study for one specific sub-group exposed in the range of 1 to 10 mg/m3. As the workers were tracked over time and exposures were greatly reduced, follow‐up studies demonstrated negligible risks from “total nickel” at concentrations less than 0.2 mg/m3 (AIOH, 2016). Evidence of carcinogenicity in rats is demonstrated with significant increase in lung carcinomas and adenomas at and above 0.15 mg/m3 nickel subsulfide (Ni3S2) (equivalent to 0.11 mg/m3 Ni). However, no evidence of carcinogenicity is identified in mice at 0.8 mg/m3 as Ni (ACGIH, 2018; AIOH, 2016). Pronounced inflammatory reactions including fibrosis are seen in rats exposed for two years at 0.11 mg/m3 (Ni3S2) and 0.5 mg/m3 (Nickel Oxide (NiO)) (SCOEL, 2011).

Negligible risk of cancer is reported in workers at concentrations less than 0.2 mg/m3 (Ni), an increase of lung carcinomas is observed in rats at 0.11 mg/m3 (Ni) and there is evidence of a threshold for carcinogenicity. Based on this, the TWA of 0.1 mg/m3 derived by AIOH (2016) is recommended to minimise the potential for cancer in the lungs and naval cavity and to protect for inflammatory responses.

## Recommendation for notations

Classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitiser and not a respiratory sensitiser according to the GHS.

There are insufficient data to recommend a skin notation.

# Appendix

### Primary sources with reports

| **Source Year set Standard** |
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| SWA 1991 TWA: 1 mg/m3 (as Ni) | |
|  |
| ACGIH 2001 TLV-TWA (inhalable nickel particulate mass): 1.5 mg/m3 (Elemental/Metal), 0.2 mg/m3 (Insoluble compounds) 0.1 mg/m3 (Nickel subsulfide) |
| TLV-TWA recommended for elemental and metal Ni to minimise the potential for dermatitis and pneumoconiosis.  TLV-TWA recommended for insoluble Ni compounds to minimise the potential for nasal and lung cancer.  TLV-TWA recommended for Ni3S2 to minimise the potential for nasal and lung cancer.  Summary of data:   * Insoluble Ni compounds identified in review: * metallic alloys 7440-02-0 * nickel oxide 1213-99-1 * nickel carbonate hydroxide 12607-70-4 * nickel hydroxide 12054-48-7 * nickel sulfide 1314-04-1 * nickel subsulfide 12035-72-2 * Monitoring data based primarily on “total” Ni particulate; recommends concentrations should expressed in terms of inhalable Ni particulate not total * TLV-TWA based on increased risk of lung and nasal sinus cancer among nickel refinery workers was associated with airborne exposures >10 mg/m3 for “total” aerosol of insoluble forms of nickel supported by evidence of pulmonary damage in animals exposed at 0.1–1.0 mg/m3 total aerosol (soluble and insoluble).   Human data:   * Ni and its inorganic compounds cause contact dermatitis in sensitised individuals;  2.5–5% prevalence of Ni sensitisation in the general public; no further information * Refers to ‘*International Committee on Nickel Carcinogenicity in* *Man’* reporting the following: * the available evidence suggests respiratory cancer risks in Ni refinery workers is primarily related to exposures >10 mg/m3 (insoluble Ni compounds) * more than one form of Ni gave rise to lung and sinus cancer * much of the respiratory cancer in Ni refinery workers could be attributed to exposure to a mixture of oxidic and sulfidic nickel at very high concentrations * no evidence that exposure to metallic nickel was associated with increased lung and nasal cancer risks * no evidence of increased risk of other forms of cancer * Large excess of cancer of the sinus and lung in 745 sinter plant workers exposed to sulfidic and oxidic Ni as high as 100 mg/m3; no evidence of inflammatory or fibrogenic response; no further information.   Animal data:   * 2 yr Ni3S2 inhalation study: * rats exposed at 0, 0.15 or 1 mg/m3 (equivalent to 0, 0.11 or 0.73 mg/m3 (Ni)) * mice exposed at 0, 0.6 and 1.2 mg/m3 (equivalent to 0, 0.44 or 0.88 mg/m3 (Ni)) * significant increases in lung carcinomas and adenomas in rats; no exposure provided * no evidence of carcinogenicity in mice at MTD of 0.88 mg/m3 (Ni) * A comparison inhalation study of rats and mice both exposed to Ni3S2 reported degeneration of the respiratory epithelium at 0.9 mg/m3 (Ni) in both species: * rats showed pulmonary inflammation at 0.4 mg/m3 (Ni) * In an inhalation study in rats, exposure at 0.13 mg/m3 Ni metal dust for 4 and 8 mo resulted in no structural changes but did produce increased phospholipids and phosphatidylcholines: * 0.13 mg/m3 considered a NOAEC (no further information) * Ni3S2 produced pulmonary carcinogenesis in 14/208 rats exposed at 0.97 mg/m3 for 78 wk, followed by a 30 wk observation period; no further details * Rats exposed for 2 yr to NiO, at 0.62 mg/m3 and mice at 1.0 mg/m3 showed inflammation and pigmentation in the lung; no further information. |
| DFG 2010 Not assigned |
| Reviewed undertaken as a group ‘*Nickel and its compounds (in the form of inhalable dusts/aerosols*)’.  Summary of data:   * No NOAEL for carcinogenicity can be derived from the epidemiological and animal studies and therefore no MAK can be recommended * Carcinogenicity of Ni compounds is probably due to mechanisms that are not directly genotoxic: * mutagenicity is only weak and mechanistic studies have shown an inhibition of DNA repair and a stimulation of cell proliferation   Human data:   * Ni allergies are predominantly non-occupational in origin caused by fashion jewellery; individuals already sensitised may experience contact eczema from occupational exposures * Cancer mortality studied in a cohort of 31,165 Ni alloy workers from 13 plants: * approximate mean exposure concentrations for specific work areas: * powder metallurgy 1.5 mg/m3 * grinding operations 0.3 mg/m3 * hot working areas with 0.1 mg/m3 * compared with the cancer mortality data of the total US population and found increased risk of lung cancer mortality was found among workers * compared also with two other reference populations, a population in the proximity of the Ni plants and a steel worker cohort from a different study and found pattern of risk for the various work areas and subgroups of sex or race are similar across all three comparison groups * no increased risk for lung cancer is noted compared with that of local populations * DFG concludes indications of carcinogenic effects of metallic Ni from epidemiology but not conclusive * NiO, NiO2, Ni2O3, NiS and Ni3S2 classified as carcinogenic based on evidence of carcinogenicity in humans. No further information * Increased risks of lung and nasal cancers among persons exposed to sulfidic and oxidic Ni: * workers with relatively low exposure to oxidic and soluble Ni and high exposure to sulfidic Ni, the lung cancer risk was clearly higher than among those with lower exposure to sulfidic Ni.   Animal data:   * Intratracheal instillation of Ni powder (99.9% Ni) induced malignant lung tumours in: * 10/39 rats over 20 administrations of 6 mg * 8/32 rats over 10 administrations of 9 mg * 0/40 control animals * IP injection of Ni powder (100% Ni) induced local, malignant lung tumours in rats in relation to the dose * NiO and Ni3S2 (cited by DFG) found to be carcinogenic by inhalation in animal studies. No further information. |
| SCOEL 2011 TWA: 0.005 mg/m3 (respirable fraction), 0.01 mg/m3 (inhalable fraction of water soluble as well as poorly water soluble nickel compounds, excluding metallic nickel) |
| TWA based on protection from inflammatory effects in the lung. Available evidence indicates protection for Ni-induced carcinogenicity; review of Ni and inorganic Ni compounds.  Summary of additional data:   * Review based primarily on documentations from IARC (1990), ICPS (1991) and the DFG (2006) * Exposure to Ni compounds associated with an increased cancer risk in the lung and nasal cavity, as well as with inflammatory responses/fibrosis in the lung * Mechanistic data indicate an indirect genotoxic mode of action; hence, a carcinogen with a practical threshold * Explanation for the derivation of respirable fraction OEL (TWA 0.005 mg/m3): * NOAEL 0.03 mg/m3 (Ni) (water-soluble NiSO4) no consistent inflammatory effects in rats * corresponds to an equivalent human concentration of 0.016 mg/m3; no further information * only considers deposited dose and not long-term chronic retained dose * particle size of NiSO4 of 2.5 µm MMAD; proposed value corresponds to the respirable fraction * derives a TWA of 0.005 mg/m3; no further details * Supporting evidence for respirable fraction OEL: * pronounced inflammatory reactions including fibrosis seen at 0.11 mg/m3 (Ni) for Ni3S2 and 0.5 mg/m3 (Ni) for NiO; details as follows: * rats exposed to NiO for 2 yr at 0, 0.62, 1.25 or 2.5 mg/m3 (0, 0.5, 1.0, 2.0 mg/m3); chronic inflammation and alveolar pigmentation was observed at high incidence in all animals at all concentrations * rats exposed 6 h/d, 5 d/wk for 2 yr to Ni3S2 at 0, 0.15 or 1 mg/m3 (0, 0.11 or 0.73 mg/m3 (Ni)) (cited by ACGIH, 2018), fibrosis, inflammation and alveolar hyperplasia in the lungs were observed with a high incidence in practically all animals * longer retention half-times in humans as compared to rats for Ni3S2 and NiO; both poorly water-soluble nickel compounds * Estimated 2-3-fold higher deposition of Ni in the lungs after exposure to NiO in humans as compared in rats. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2003 Not assigned |
| Review of developmental and reproductive effects; no additional data. |

### Secondary source reports relied upon

| **Source** |  | **Year** | **Additional information** |
| --- | --- | --- | --- |
| AIOH |  | 2016 | * Recommends a TWA for Ni (including both readily soluble and sparingly soluble (insoluble) compounds) of 0.1 mg/m3 (inhalable aerosol fraction) * Regards respiratory cancer (lung and nasal) as the main health effect to derive an OEL recommendation * Notes differences in the literature and between organisations on critical effects to derive exposure limits * Carcinogenic risk is greater when there is exposure to mixed species of Ni * Clear evidence of nasal and lung cancer in a study of 2,521 refinery workers with more than 5 yr employment between 1902 and 1969 and relatively high exposures to airborne Ni: * follow up studies with greatly reduced exposures provided little evidence of elevated lung cancer risks associated with exposures at <0.2 mg/m3 total Ni * Difficulties and uncertainties in using epidemiological data to estimate levels and types of Ni that correspond to increased respiratory cancer risk in refinery workers * Evidence of carcinogenicity in rats at ≥0.1 mg/m3 for Ni3S2 (cited by ACGIH, 2018). |
| NICNAS |  | 2014 | * A case report of a fatal incident in a worker exposed by inhalation to an estimated concentration of 382 mg/m3 * No epidemiological evidence for carcinogenicity in humans exposed to metallic Ni alone; insufficient evidence to support a recommendation to amend the current carcinogenicity classification * Based on available data from animal studies, there is a concern the current occupational exposure standard of 1 mg/m3 (inhalable fraction) for 'Nickel, metal' may not sufficiently protect worker health. |
| IARC |  | 2012 | * Sufficient evidence in humans for the carcinogenicity of mixtures that include Ni compounds and Ni metal * Sufficient evidence in experimental animals for the carcinogenicity of NiO, Ni(OH)2, NiS, Ni3S2 * Ni compounds are carcinogenic to humans (Group 1). |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | No |
| --- | --- |
| **The chemical is not a non-threshold based genotoxic carcinogen.** |  |

## Notations

| **Source** | **Notations** |
| --- | --- |
| SWA | — |
| HCIS | Carcinogenicity – category 2, Skin sensitisation – category 1 |
| NICNAS | Carc. Cat. 3 (as Ni) |
| EU Annex | Carcinogenicity – category 2 |
| ECHA | NA |
| ACGIH | Carcinogenicity – A5 (inhalable Ni particulate mass – Elemental/Metal)  Carcinogenicity – A1 (inhalable Ni particulate mass – Insoluble compounds) |
| DFG | Carcinogenicity – 1, Sh (dermal sensitiser), Sa (respiratory sensitiser) |
| SCOEL | Carcinogenicity – C |
| HCOTN | — |
| IARC | Carcinogenicity – Group 2B |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
| --- |
| There are insufficient data to recommend a skin notation. |

### IDLH

| Is there a suitable IDLH value available? | Yes |
| --- | --- |

## Additional information

|  |  |
| --- | --- |
| Molecular weight: | 58.71 (Metal) |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = Number mg/m3; 1 mg/m3 = Number ppm |
| This chemical is used as a pesticide: |  |
| This chemical is a biological product: |  |
| This chemical is a by-product of a process: |  |
| A biological exposure index has been recommended by these agencies: | ACGIH  DFG  SCOEL |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Australian Institute of Occupational Hygienists (AIOH) Australian Institute of Occupational Hygienists (AIOH) (2016) Position paper Nickel and its compounds – potential for occupational health issues.

Deutsche Forschungsgemeinschaft (DFG) (2010) Nickel and its compounds (in the form of inhalable dusts/aerosols) – MAK value documentation.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2011) Recommendation from the Scientific Committee on Occupational Exposure Limits for nickel and inorganic nickel compounds. SCOEL/SUM/85.

Health Council of the Netherlands (HCOTN) (2003) Nickel and its compounds. Evaluation of the effects on reproduction, recommendation for classification. The Hague: Health Council of the Netherlands; publication no. 2003/05OSH.

International Agency for Research on Cancer (IARC) (2012). Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100C ‐ Arsenic, Metals, Fibres and Dusts – Nickel and Nickel Compound

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) Nickel: Human health tier II assessment – IMAP report.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – nickel metal and other compounds (as Ni).