

## NICKEL & NICKEL COMPOUNDS CARCINOGENICITY

**Nickel compounds** are classified under the European Union Classification, Labeling and Packaging (CLP) as *Carc 1A*, known to have carcinogenic potential to humans. A similar classification as *Group 1* carcinogens was given by IARC (International Agency for Research on Cancer). Only the inhalation route is associated with cancer and the tumors are local to the respiratory tract (sino-nasal and lung); oral route is not associated with cancer. The carcinogenicity of nickel compounds is mainly an occupational concern. Epidemiological evidence from workers refining and processing sulfidic ores have shown increased respiratory cancer risks associated with exposures to mixtures of water soluble and insoluble nickel compounds. Animal studies with pure compounds corroborate the respiratory carcinogenicity of insoluble nickel compounds. It is possible that soluble nickel compounds are not carcinogenic by themselves but promote the carcinogenicity of other nickel compounds.

Nickel compounds are weak mutagens with low affinity for DNA and a strong preferential interaction with proteins. The mode of action (MOA) for the carcinogenicity of nickel compounds is threshold-based and involves indirect genotoxic and non-genotoxic effects. Genotoxicity can be secondary to inflammation and dependent on the delivery of sufficient  $Ni^{2+}$  ions to intracellular target sites.

**Nickel metal** is classified as *Carc 2*, suspected human carcinogen (CLP) or *Group 2B* (IARC). Human and animal studies by relevant route of exposure have showed no evidence of respiratory carcinogenicity associated with exposures to nickel metal powders. Occupational Exposure Limit (OEL) for workplace exposure to nickel metals are therefore based on noncancer effects, such as respiratory toxicity. Thus, nickel and nickel compounds have different carcinogenic potentials. This difference, as well as the differences in carcinogenic potential among the various nickel compounds can be explained by the nickel-ion bioavailability model. This model considers that there are multiple factors that affect the amount of  $Ni^{2+}$  ions that can reach target cellular sites in respiratory tract epithelial cells, and this is reflected in the different carcinogenic potential of the different chemical forms of nickel.

In this fact sheet, we consider the evidence for carcinogenicity of nickel compounds and nickel metal from human occupational and animal studies. The MOA that underscores nickel carcinogenicity is also briefly considered. This fact sheet provides a high-level summary of the available data; for more detailed information, please consult the reference materials cited here.



*Nickel refining operation.\**

### 1 INTRODUCTION

Historically, occupational inhalation exposures to high levels of certain nickel compounds have been linked to respiratory cancer. Excess respiratory cancer has been associated with exposures to nickel compounds present during the refining and processing of sulfidic nickel ores but not with exposures in lateritic ore refineries, alloy manufacturing, or electroplating. Epidemiologic data from occupationally exposed nickel workers are usually complicated by the lack of a workplace with “pure” exposures to individual nickel compounds. Exposures are usually to a mixture of water soluble and insoluble compounds and nickel metal, as well as other inorganic compounds (arsenic, cobalt, strong acid mists) and organic combustion products. Additionally, historic exposure measurements, chemical speciation, and particle size information remain sparse. Confounding factors like cigarette smoking can also affect these assessments. A combination of modern exposure measurements, speciation and expert judgments has been applied in the last 30 years to obtain a clearer delineation of the carcinogenic risks associated with inhalation exposure to different nickel compounds.

A seminal comprehensive study by the International Committee on Nickel Carcinogenesis in Man (ICNCM) examining cancer risks in 10 cohorts of approximately 80,000 workers involved in nickel processing and nickel alloy production reported an association between exposure to nickel compounds (primarily sulfidic and certain oxidic nickel compounds) and respiratory cancer (lung and nasal sinus tumors); no association with exposure to metallic nickel

was identified (ICNCM, 1990). An association between soluble nickel and excess respiratory cancer was also reported, with soluble nickel exposures potentially enhancing the risks of exposure to insoluble compounds and cigarette smoking. Epidemiologic studies prior and after the ICNCM report have corroborated these general conclusions.

Animal studies using physiologically relevant routes of exposure have confirmed the respiratory carcinogenesis of certain nickel compounds (NTP, 1996a, b, c). Rats appear to be a sensitive species to study the carcinogenicity of nickel substances, with positive results found for nickel subsulfide and nickel oxide while studies in mice have been generally negative. Importantly, rat studies failed to confirm an association between inhalation exposure to soluble nickel compound by themselves and excess respiratory cancer risk (NTP, 1996a). In addition, oral exposure to soluble nickel compounds in rats did not produce cancer effects (Heim et al., 2007). Animal inhalation exposure studies have also confirmed the lack of association between metallic nickel and respiratory cancer (Oller et al., 2008). Based on the negative inhalation and oral rat results, it is possible that soluble nickel compounds may not be carcinogenic by themselves but may have a cancer promoter effect, when exposures are mixed. Further assessments and discussion of the respiratory carcinogenicity of soluble nickel compounds have been published (Goodman et al., 2009; Oller, 2002; Grimsrud et al., 2002; Oller, et al., 1997).

It is important to emphasize here that different chemical forms of nickel also have different chronic respiratory toxicity and potentials. For example, a water-soluble nickel compound like nickel sulfate hexahydrate has the highest respiratory toxicity of the nickel compounds, while nickel subsulfide has somewhat lower toxicity and high temperature calcining nickel oxide has the lowest toxicity of all compounds tested.

Different chemical forms of nickel vary in physical and chemical complexities (e.g., water solubility, surface charge), however these differences, alone, do not account for the different carcinogenic potentials of nickel and nickel compounds. It is differences in the bioavailable nickel ions (Ni<sup>2+</sup> ions) from the different nickel species at the nucleus of target respiratory epithelial cells (i.e., nickel-ion bioavailability model) that most aptly explains the differences in carcinogenicity hazard of the different chemical forms of nickel (Goodman et al., 2011).

Whilst there is an incomplete understanding of the mechanisms for nickel carcinogenicity, MOA studies have indicated very plausible pathways by which nickel causes cancer. Nickel compounds do not have a strong, direct mutagenic effect nor a strong, direct interaction with DNA. Both carcinogenic and MOA studies of nickel compounds have suggested thresholds for indirect genotoxic and/or non-genotoxic effects. Chronic inflammation, oxidative damage, impaired DNA repair, histone modifications, increased cell proliferation are some of the proposed mechanisms underlying nickel carcinogenicity.

## 2 WHAT IS THE CANCER HAZARD CLASSIFICATION FOR NICKEL AND NICKEL COMPOUNDS?

Hazard classifications for nickel carcinogenicity under the European Union CLP (Table 1), which is aligned with the United Nations Globally Harmonized System (GHS) for classification and packaging of chemicals, are based on the nature of the cancer evidence (human or animal), a weight-of-evidence (WOE) assessment of the existing data, and consideration of additional factors. The evaluations for classification are supposed to be based on reliable peer-reviewed publications and other data acceptable by regulatory standards. Route-specific classifications can be assigned when warranted (e.g., cancer by other routes of exposure can be excluded).

Carcinogen Classification	CLP	IARC
Soluble Nickel Compounds	Carc. 1A	Group 1
Insoluble Nickel Compounds	Carc. 1A	Group 1
Metallic Nickel	Carc. 2	Group 2B
Nickel Tetracarbonyl	Carc. 2	Group 2B

**Table 1:** Carcinogen hazard classification of nickel metal and nickel compounds

Many soluble and insoluble nickel compounds are classified as *Carc 1A* under the EU CLP. Category 1A classification implies these nickel compounds are *known to have carcinogenic potential for humans* based largely on human evidence. The CLP specifies inhalation as the only route of concern (H350i) given that the respiratory carcinogenicity of nickel compounds is associated only with inhalation exposure (considered in further detail below); the risks for cancer by other routes, such as oral exposure, has been excluded. The water soluble and sulfidic (water insoluble) nickel

compounds are also classified as *Muta 2, suspected of causing genetic defects*.

Nickel metal is classified as *Carc 2, suspected human carcinogen*, based on insufficient evidence from human studies with suggestive evidence from animal studies (e.g., positive results by non-relevant routes of exposure, negative results via inhalation). Nickel tetracarbonyl is a volatile liquid at ambient temperature and pressure that can become a very toxic gas at higher temperatures (above 110°F). This compound is also classified as *Carc 2, suspected human carcinogen*, based on insufficient evidence from humans and/or animals (the high acute toxicity makes animal testing difficult) (ECHA, 2017).

Likewise, IARC (Table 1) classified both soluble and insoluble nickel compounds under *Group 1, carcinogenic to humans*, and metallic nickel and nickel alloys under *Group 2B, possibly carcinogenic to humans* (IARC, 2012).

## 3 WHAT IS THE HUMAN EVIDENCE FOR NICKEL CARCINOGENICITY?

The evidence for human carcinogenicity of nickel metal and nickel compounds comes from epidemiological studies of workers involved with mining, refining, and processing of sulfidic nickel ores. Only workers in sulfidic ore refineries with high exposures to mixtures of water soluble and complex insoluble nickel compounds, and/or arsenic, cobalt, and acid mists had excess respiratory cancer risks. No excess respiratory cancer risks in workers at lateritic ore refineries, alloy manufacturing, or electroplating have been observed. These studies indicated that inhalation is the relevant exposure route and the respiratory system (sino-nasal and lung) the relevant organ system for nickel cancer effects. No consistent associations between excess respiratory cancer risk and exposure to metallic nickel have been observed. Nickel and nickel compounds appear to have differing carcinogenic potentials in the human studies. Table 2 summarizes the human evidence for carcinogenicity of nickel metal and nickel compounds.

### 3.1 INHALATION ROUTE

The 1990 ICNCM report concluded that inhalation exposure to mixtures of water soluble nickel compounds (e.g., nickel sulfate, nickel chloride) and water insoluble nickel compounds (e.g., nickel subsulfide, nickel oxide, complex Ni-Cu oxides) were associated with excess respiratory cancer risk in workers. Much of the excess respiratory cancer risk was associated with exposure to high concentrations ( $\geq 1$  mg Ni/m<sup>3</sup>) of soluble compounds or ( $\geq 10$  mg Ni/m<sup>3</sup>) of a mixture of sulfidic and oxidic nickel compounds. Excess nasal and/or lung cancer risks have been observed in different cohorts of workers. More recently, analyses of dose-responses for the main chemical forms of nickel that included 13 cohorts of nickel workers, indicated that no excess cancer risk were observed in these studies when exposures to the inhalable aerosol fraction of oxidic, sulfidic and soluble nickel were kept  $\leq 2.0$  mg Ni/m<sup>3</sup>,  $\leq 0.2$  mg Ni/m<sup>3</sup>, and  $\leq 0.1$  mg Ni/m<sup>3</sup>, respectively (Oller et al., 2014).

The ICNCM report found no association between metallic nickel and excess risks of lung or nasal cancer. Subsequent studies have also found no association between metallic nickel and respiratory cancer (see Sivulka 2005 for review). In two reports where hints of possible correlations between excess cancer risk and nickel metal exposure have been indicated, failure of cross-validation of the test model and non-significant odds ratio after adjusting for confounding exposures suggest that the risks for metallic nickel may have been overestimated (Easton et al., 1992; Grimsrud et al., 2002). No

association has been found between increased respiratory cancer risk and inhalation exposure to metallic nickel outside the nickel refineries, when local populations were used as controls (Arena et al., 1998; 1999). Thus, there has been a consistent lack of increased respiratory cancer risk associated with metallic nickel exposures in humans.

### 3.2 ORAL AND DERMAL ROUTES

Beside respiratory cancer, there is currently no consistent and reliable epidemiological data to suggest that metallic nickel and/or nickel compounds cause excess cancer at other organ sites. Although excess of cancer of the buccal cavity and pharynx, stomach, and prostate have been observed in some workers exposed to nickel, these findings have been rare and have not been consistently reproduced. In dental patients with nickel-containing orthodontic appliances, equivocal and low genotoxic effects have been observed in exposure to nickel ions. There is presently no human study linking oral or dermal exposure to metallic nickel and/or nickel compounds with excess local or systemic cancer risks. For the oral route, this is corroborated by animal studies, as noted in [Section 4.2](#). For the dermal route, no skin cancers have been reported with exposure to nickel compounds or alloys, and the systemic absorption of nickel through the skin is very low ( $\leq 1\%$ ). Thus, the epidemiological data does not suggest an association between cancer and oral or dermal nickel exposure.

### 3.2 OTHER ROUTES

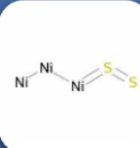
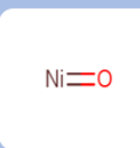
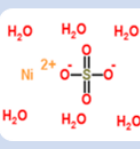

No consistent epidemiological data currently exists linking nickel exposure via other routes (e.g., implants) to cancer. Given the specificity of nickel cancer on the respiratory system, it is not expected that nickel cancer will be associated with routes other than inhalation.

## 4 WHAT ARE THE ANIMAL EVIDENCE FOR NICKEL CARCINOGENICITY?

Animal studies are useful in elucidating mechanisms of carcinogenesis and assigning the carcinogenicity observed in humans (mixed exposures) to specific substances. The relevant evidence for nickel carcinogenicity in animals comes from eight lifetime carcinogenicity studies in rats and mice. These animal studies support the conclusion from human studies that the inhalation route is the most relevant route for nickel and the respiratory tract is the target organ for cancer; they also suggest that the different nickel species have different carcinogenic potentials. [Table 2](#) summarizes the animal evidence for the carcinogenicity of nickel metal and nickel compounds. Nickel species have different carcinogenic potentials; in human studies, exposures are to mixtures of nickel compounds and other inorganic compounds but in animal studies, exposures are to a single form of nickel.

### 4.1 INHALATION ROUTE

Seven of the eight lifetime nickel carcinogenicity studies were conducted via the inhalation route in mice (3) and rats (4) (NTP, 1996a b, c; Oller et al., 2008; Dunnick et al., 1995). Nickel sulfate and nickel subsulfide induced no respiratory tumors in mice but nickel oxide had equivocal evidence of tumors in female mice. Perhaps mice are not very susceptible to the carcinogenic effects of nickel or mice have higher thresholds for the nickel cancer causing mechanisms. *Mice are not inherently non-susceptible to metal-induced tumorigenicity since other metals have been able to induce excess lung tumors in mice.* Early reports of metallic nickel inhalation in rats and mice, although compromised by high mortality, also suggested that metallic nickel did not cause cancer (Hueper, 1958).

	<p><b>Nickel Subsulfide</b></p> <ul style="list-style-type: none"> <li>• Humans: Evidence (mixed exposure) inhalation</li> <li>• Rats: Clear evidence (male, female) inhalation</li> <li>• Mice: No evidence (male, female) inhalation</li> </ul>
	<p><b>Nickel Oxide (green, high calcining temperature)</b></p> <ul style="list-style-type: none"> <li>• Humans: Evidence (mixed exposure) inhalation</li> <li>• Rats: Some evidence (male, female) inhalation</li> <li>• Mice: Equivocal evidence (female), No evidence (male) inhalation</li> </ul>
	<p><b>Nickel Sulfate Hexahydrate</b></p> <ul style="list-style-type: none"> <li>• Humans: Evidence (mixed exposure) inhalation</li> <li>• Rats: No evidence (male, female) inhalation</li> <li>• Rats: No evidence (male, female) oral</li> <li>• Mice: No evidence (male, female) inhalation</li> </ul>
	<p><b>Nickel Metal</b></p> <ul style="list-style-type: none"> <li>• Humans: No evidence, inhalation</li> <li>• Rats: No evidence, inhalation</li> </ul>

**Table 2:** Summary of evidence for carcinogenicity of nickel metal and nickel compounds from relevant human and animal studies

Nickel sulfate inhalation exposures in rats have not induced tumors, in alignment with the reports in mice. A plausible explanation for this is that nickel sulfate is not carcinogenic by itself at the exposure levels that can be tolerated by rats without overt toxicity. Green nickel oxide induced some tumors in rats but only at much higher exposures and with no clear dose-response. The lowest respirable nickel oxide concentration tested, which failed to induce any tumors, was >5000-fold higher than nickel concentrations in ambient air.

Nickel subsulfide was the most carcinogenic in the rat inhalation study. At the lowest concentration level at which increased tumors were detected, the incidence and severity of chronic lung inflammation in rats was similar between nickel sulfate and subsulfide, even though the tumor outcome was different. According to the nickel ion bioavailability model, nickel subsulfide has a high carcinogenic potential due to its low extracellular dissolution but high intracellular dissolution, resulting in the highest dose of bioavailable nickel ions in the nucleus of respiratory epithelial cells.

Metallic nickel failed to produce lung tumors in rats following inhalation exposure (Oller et al., 2008). While positive results have been found after intratracheal instillation of nickel metal in rats (Pott et al., 1987), the doses in that study were shown to not be achievable via the normal inhalation route, in addition to intratracheal instillation not being a physiologically relevant route of nickel exposure. Other inhalation studies in guinea pigs and hamsters have buttressed the negative carcinogenicity of metallic nickel.

## 4.2 ORAL AND DERMAL ROUTES

Nickel sulfate exposure via the oral route has not produced tumors in rats (Heim et al., 2007). Nickel chloride also failed to induce tumors in mice following oral administration (Uddin et al., 2007). No robust animal studies exist for oral administration of metallic or insoluble nickel compounds. However, the negative results with the most bioavailable of the nickel compounds via the oral route are also relevant for these less bioavailable substances. No cancer studies in animals using dermal administration of soluble, insoluble, or metallic nickel compounds have been conducted.

## 4.3 OTHER ROUTES

There are various studies assessing the carcinogenicity of the different nickel species following parenteral, intratracheal instillation, intraperitoneal and injection administrations. However, these routes of exposure are not appropriate nor physiologically relevant for metallic nickel and nickel compounds. For example, while local sarcomas at sites of injection of nickel metal powder were found, the relevance of these findings for a weight of evidence hazard assessment of nickel metal respiratory carcinogenicity in humans is highly questionable. The results of experimental studies of carcinogenicity of nickel metal powder using other routes of exposure were reviewed by Sivulka (2005).

## 5 WHAT IS THE CARCINOGENIC MOA OF NICKEL COMPOUNDS?

In general, carcinogenic substances can be divided into three main groups:

1. direct acting genotoxicants,
2. indirect acting genotoxicants, and
3. substances that cause cancer via non-genotoxic modes of action.

For the first group, all exposure levels are assumed to be associated with some degree of excess cancer risk. For the latter two groups, threshold exposure levels can be identified below which cancer risks are expected to be negligible.

Direct-acting genotoxic agents are positive in bacterial, germ cell, and mammalian cell mutagenicity tests and have a direct interaction with DNA. Nickel compounds have been consistently negative or showed weak effects in bacterial, *in vitro* and *in vivo* mutagenicity tests. Nickel ions have a weak interaction with DNA but a preferentially stronger interaction with proteins. For example, Ni<sup>2+</sup> has binding constants of 6.7 X 10<sup>-1</sup> M<sup>-1</sup> and 4.37 X 10<sup>9</sup> M<sup>-1</sup> for adenosine (nucleic acid) and cysteine (amino acid), respectively. Nickel and nickel compounds are therefore not considered to have a direct genotoxic mode of action.

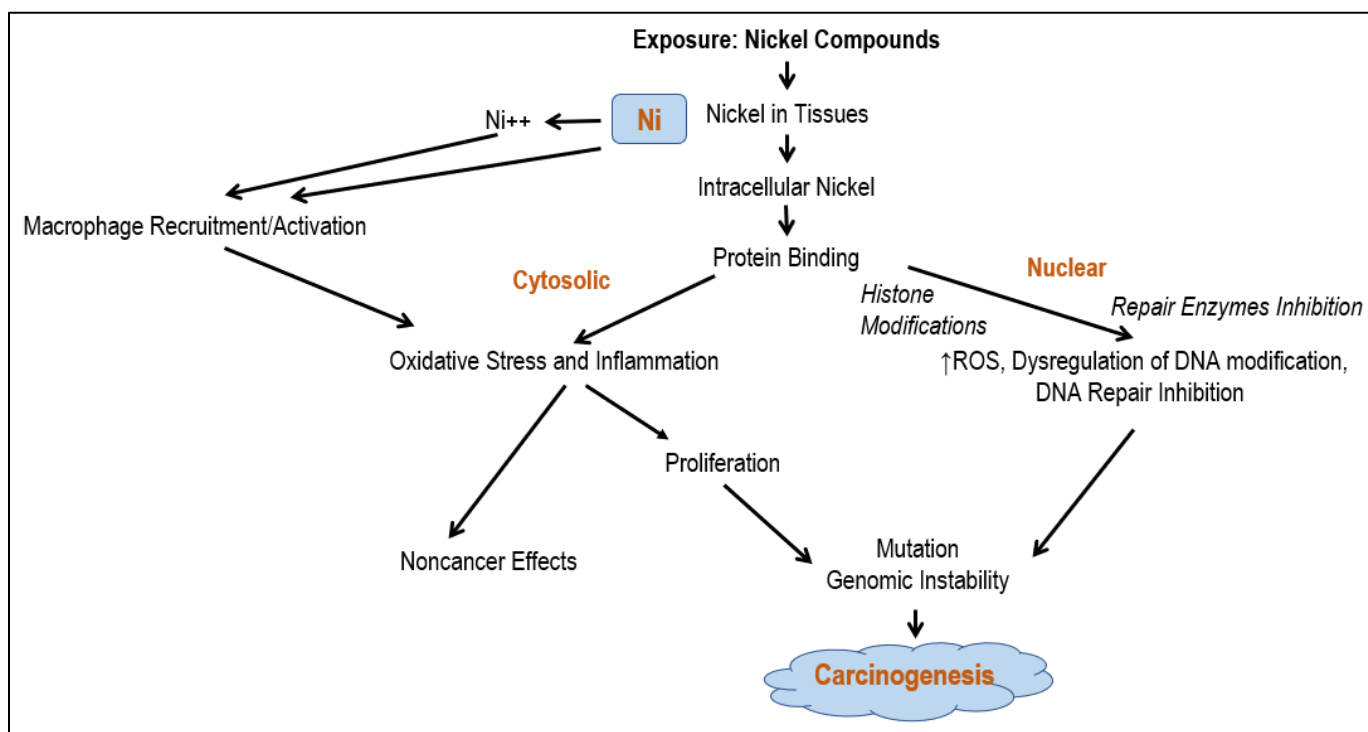
Indirect genotoxicants can damage DNA via secondary mechanisms like generation of reactive oxygen species (ROS) or inhibition of repair. The indirect genotoxic mechanisms have shown thresholds. *In vitro* nickel compounds have been shown to cause DNA damage (such as fragmentation, single-strand breaks) indirectly through increased formation of oxidative radicals. Nickel compounds enhanced the induction of sister chromatid exchange, chromosomal aberrations and micronucleus formation *in vitro*. Nickel compounds also caused increased formation of DNA-Protein crosslinks.

Additionally, nickel compounds are known to inhibit DNA repair enzymes *in vitro*; Ni<sup>2+</sup> ions competitively inhibit the repair enzyme ABH2 by binding to the same site as Fe<sup>2+</sup> (Chen et al., 2010). DNA repair inhibition may also occur via inhibition of DNA ligation and post replication repair. Non-genotoxic modes of action include the induction of epigenetic effects that can affect gene expression. Nickel compounds can increase histone phosphorylation (H3S10), methylation (H3K4), ubiquitination (H2B and H2A) and decrease histone acetylation (H4) through decreased histone acetyltransferase activity. Nickel compounds can induce selective fragmentation or decondensation of heterochromatic long arms of X-chromosomes. [Figure 1](#) outlines the proposed carcinogenic MOA of nickel compounds.

The *in vivo* genotoxic effects of nickel compounds in the lung are observed following inflammation and macrophage activation that results in indirect oxidative DNA damage. *Preventing inflammation would therefore prevent the indirect genotoxic effects and prevent tumor formation.* [Table 3](#) summarizes some of the relevant *in vitro*, *in vivo*, and human genotoxicity and carcinogenicity data with nickel compounds.

The indirect genotoxic and non-genotoxic effects of nickel compounds have thresholds below which these effects are not observed; this suggests that nickel carcinogenesis depends on the delivery of sufficient amounts of Ni<sup>2+</sup> ions to the cell nucleus of respiratory epithelial cells (see [Table 4](#), nickel-ion bioavailability model). Bioavailability of Ni<sup>2+</sup> depends on overall toxicity, lung fluid solubility, clearance, cellular uptake, and dissolution. The balance of these factors predicts high bioavailability of nickel subsulfide, low bioavailability for nickel oxide and even lower (below threshold) bioavailability for nickel sulfate and nickel metal (Goodman et al., 2011).

Taken together, the totality of the data supports an indirect genotoxic and/or non-genotoxic MOA with thresholds for nickel compounds.



**Figure 1:** Proposed cancer & non-cancer MOA of nickel compounds. The interplay between cytosolic and nuclear events is important for nickel carcinogenesis. DNA and chromosomal changes are secondary to macrophage recruitment/activation, inflammation, and oxidative stress.

	<i>In Vitro</i> Studies	Animal Studies	Human Studies Workers, Patients
Available Studies	Many studies have looked at the mutagenic and genotoxic effects of nickel compounds	Studies on gene mutation, micronucleus (MN, oral), chromosomal aberrations (CA, oral), and tumor induction (inhalation, oral) have been conducted	Genotoxicity studies in buccal mucosa of patients with dental appliances; CA and Sister Chromatid Exchange (SCE) studies in peripheral blood; cancer mortality-morbidity studies in workers
Main Results	Positive for a variety of effects: DNA damage, reactive oxygen generation, histone modification, DNA methylation, inhibition of repair, etc.  Negative for gene mutation  Mixed results (+/-) for MN and CA	Positive and negative for CA and MN induction in mice and rats via oral, subcutaneous or intraperitoneal injection routes; overall genotoxicity weak  Negative cancer in mice for all compounds via inhalation; positive cancer in rats via inhalation (except sulfate); sulfate via oral also negative	Studies of active and retired workers had inconclusive results for CA & SCE; no clear correlation with plasma or urine nickel  Increased nasal and lung cancer risk associated with high exposures to the nickel compounds found in sulfidic ore refinery operations
Presence of Thresholds	Many of the studies show thresholds  Thresholds also observed for nickel delivery to nuclear sites	Several of the genotoxicity studies were negative, indicating thresholds  Carcinogenicity studies showed thresholds in rats (sulfate and oxide); most mice studies were negative (possible thresholds)	Joint analyses of cancer mortality studies show thresholds

**Table 3:** Comparison of genotoxicity and carcinogenicity studies with nickel compounds *in vitro*, *in vivo*, and in humans

## 6 WHAT IS THE CORRELATION BETWEEN THE HUMAN AND ANIMAL EVIDENCE?

In interpreting nickel carcinogenicity studies, it is important to realize that exposures in animal studies are to a “pure” nickel compound (a single nickel compound) whilst exposures in human studies are to mixtures of nickel compounds (plus other inorganic compounds). Any potential co-carcinogenic or promoting effect of the different nickel compounds in the human studies will not be detected in the single exposure animal studies.

There is generally a great correlation between the human occupational exposure studies and animal studies on the carcinogenicity of nickel and nickel compounds. The evidence from both human and animal studies point to the absence of carcinogenic effects of nickel metal but the presence of carcinogenic effects for sulfidic and oxidic nickel compounds. The only inconsistency between the human and animal evidence relates to the carcinogenicity of soluble nickel compounds. The animal studies have failed to show carcinogenic effect of pure soluble nickel compounds following inhalation and oral exposures. In the human studies, an association between exposure to soluble nickel (with additional exposures to insoluble nickel compounds) and/or smoking and lung cancer was observed in some groups of workers. According to the nickel ion bioavailability model, nickel sulfate has a low carcinogenic potential by itself, due to its high extracellular dissolution and clearance, and its low intracellular uptake; this combination results in low bioavailable nickel ions in the nucleus of respiratory epithelial cells. However, this does not preclude soluble nickel from enhancing carcinogenicity of insoluble compounds through inflammatory and proliferative effects.

## 7 CONCLUSIONS

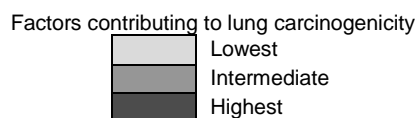
Nickel compounds are known human carcinogens and classified as such. Carcinogenicity is via inhalation exposure only; oral exposure is not associated with carcinogenicity. Carcinogenicity of nickel compounds is mainly an occupational concern. Workplace standards [such as Permissible Exposure Limits (PELs), Reference Exposure Limit (RELs), OELs] are set to protect workers from these effects. Nickel compounds have threshold MOA for carcinogenicity with indirect genotoxicity and non-genotoxicity effects. The different nickel compounds have different carcinogenic potentials. According to the nickel-ion bioavailability model, the differences in the carcinogenicity of the nickel species is due to differences in the delivery of sufficient amounts of Ni<sup>2+</sup> ion to the nucleus of respiratory epithelial cells. This has recently been considered by the Risk Assessment Committee (RAC) in their opinion on nickel compounds OELs. According to ECHA (2018), the mechanisms of nickel genotoxicity may involve:

1. “interference with cellular redox regulation and induction of oxidative stress;
2. inhibition of DNA repair systems; and
3. dysregulation of signaling pathways and alteration of the epigenetic landscape.”

By contrast, nickel metal which is classified as a suspected human carcinogen has been consistently negative in animal and human carcinogenicity studies. OEL for the protection of workers from risks associated with exposure to nickel metal are thus based on noncancer effects, such as respiratory toxicity.

Bioavailability Factors	Nickel Sulfide	Nickel Oxide	Nickel Sulfate Hexahydrate	Nickel Metal
Respiratory Toxicity	Intermediate	Low	High	Intermediate
Maximum Tolerated Dose, Rats Inhalation (mg Ni/m <sup>3</sup> )	0.7	2.0	0.11	0.4
Lung Clearance (retention half-time)	~5 Days	>100 Days	~2 Days	~30-100 Days
Extracellular Dissolution	Medium	Very Low	High	Low
Intracellular Uptake	High via (Particle) Endocytosis	Low via (Particle) Endocytosis	Very Low (Ni <sup>2+</sup> ) via Ion Channels	Very Low via (Particle) Endocytosis
Intracellular Dissolution	High	Low	Already dissolved	Low
Intranuclear Ni <sup>2+</sup> Bioavailability	Highest	Medium	Very Low	Very Low
Carcinogenic Potential (animals)	Highest	Medium	Not Detected	Not Detected

**Table 4:** Nickel-ion bioavailability model. The bioavailability of Ni<sup>2+</sup> ions in respiratory epithelial cell nucleus governs the carcinogenic potential of nickel metal and nickel compounds (modified from Goodman et al., 2011)



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### Fact Sheets on Nickel and Human Health

This is the second in a series of fact sheets addressing issues specific to the evaluation of risks to humans associated with nickel-containing substances and materials. The fact sheets are intended to assist the reader in understanding the complex issues and concepts associated with assessment of human health hazards, dose-response relationships, and exposure by summarizing key technical information and providing guidance for implementation.

NiPERA Inc. welcomes questions about anything stated in this fact sheet on nickel and nickel compounds carcinogenicity. For inquiries, please contact:

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