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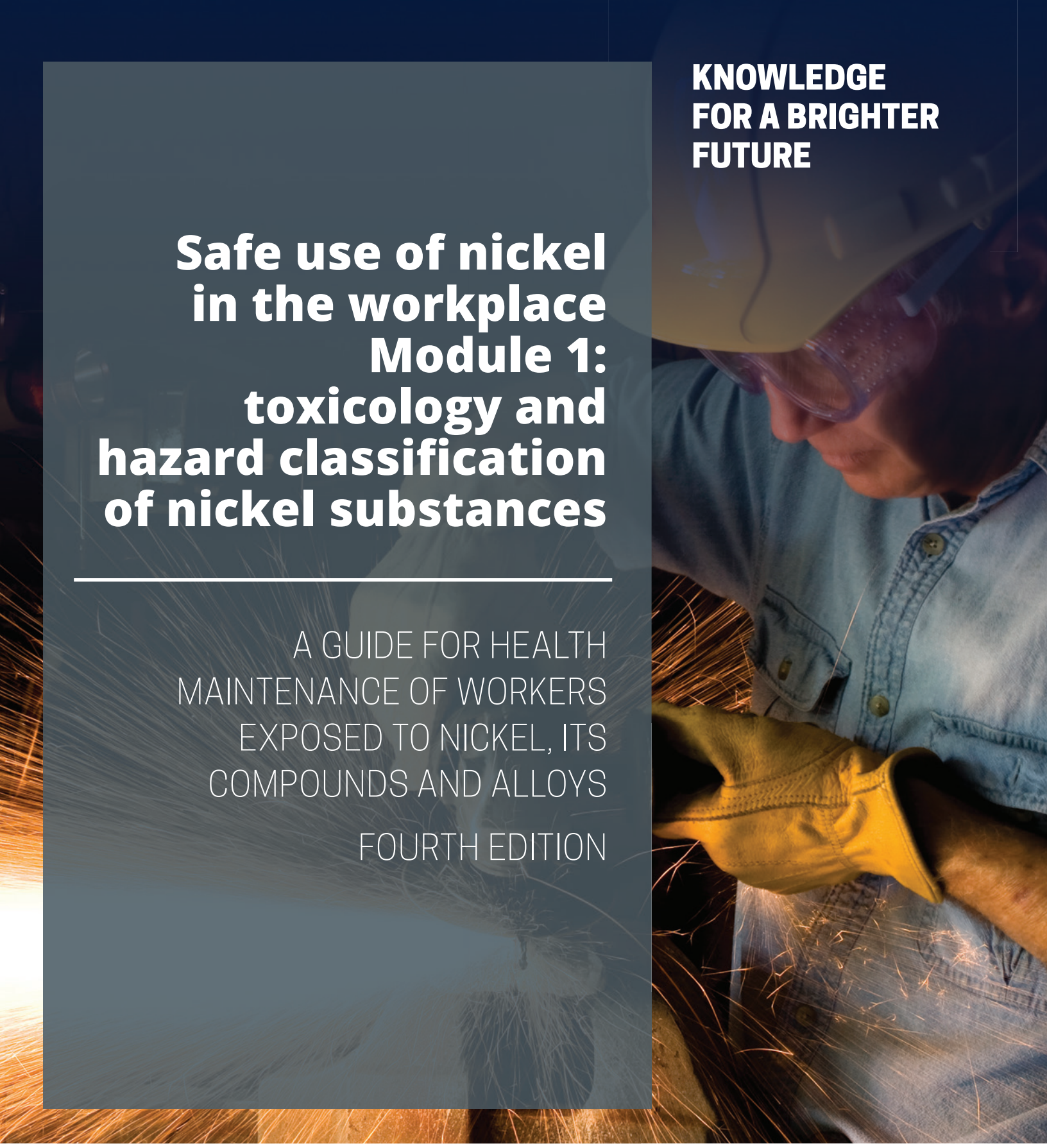
Safe use of nickel in the workplace Module 1: toxicology and hazard classification of nickel substances

A GUIDE FOR HEALTH MAINTENANCE OF WORKERS EXPOSED TO NICKEL, ITS COMPOUNDS AND ALLOYS

FOURTH EDITION



Nickel INSTITUTE

knowledge for a brighter future

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Contents

A guide for health maintenance of workers exposed to nickel, its compounds and alloys

1. ABOUT THIS GUIDE

Investigation into the toxicological effects of nickel salts on animals was first reported in 1826. Since that time, numerous reports and papers have been generated on the human health and environmental effects of nickel. The reported effects of nickel and its compounds on humans are wide ranging, comprising effects that are both beneficial – the probable essentiality of nickel in humans – as well as harmful – skin allergy and, in certain circumstances, respiratory cancer. Although nickel has been studied extensively, there is still much to be learned about this ubiquitous metal. Given the role of nickel to industrialised societies, it is important to have a guide for evaluating workplace exposures and health risks in order to promote safe handling of nickel materials. The first edition of this Guide was prepared in 1993 by the Nickel Producers Environmental Research Association (NiPERA) in collaboration with the Nickel Development Institute (now the Nickel Institute). The second edition of the Guide was published in 1997. Subsequent to that printed edition, the Guide was published online and was revised in 2002, 2004 and 2008. The current version of the Guide, updated in 2021, is the fourth edition and it reflects the evolving nature of the knowledge about the health concerns associated with working with nickel, nickel compounds and alloys. The fourth edition is divided into two modules; Module 1, on the Toxicology and Hazard Classification of Nickel Substances, was updated in 2021 and Module 2, on the Exposure of Workers to Nickel Substances and Health Assessment, is to be updated in 2022. These two modules will allow independent updates in the future with new information on nickel toxicology or worker exposures and health assessment.

This Guide has been written for those individuals who are responsible for the health maintenance of workers exposed to nickel, its compounds, and alloys. As such, it is directed to a variety of individuals including operational managers, business managers, industrial hygienists, occupational health nurses, physicians, joint occupational health and safety committees, and other health professionals. Its purpose is not only to educate the reader about the potential hazards associated with exposure to various forms of nickel but also to instruct the reader in the safe handling of nickel-containing substances in the workplace. Like all scientific documents, the information contained within this Guide constitutes a "snapshot" and is subject to change as knowledge is gained about nickel. Further updates are necessary.

Certain conventions have been followed in preparing this Guide. Since it mainly addresses the health effects associated with occupational exposure to nickel and nickel-containing substances, evaluations are based predominantly on epidemiological and clinical studies, complemented by animal studies. Most evaluations are qualitative and reflect the overall weight-of-evidence reported from studies of nickel workers. Discussions of the health effects related to working with nickel compounds focus on specific forms of nickel when feasible. Because they are not present in most work environments, organometallic nickel compounds, with the exception of a brief discussion on the acute toxicity of nickel carbonyl, are not discussed within this Guide. Finally, unless noted otherwise, statements regarding the "solubility" of nickel compounds are made with respect to their solubility in biological fluids as opposed to water.

The Guide Module 1 has been organised into a summary followed by sections on production, pharmacokinetics, toxicology, and hazard classification.

1.1 SUMMARY

Nickel is a naturally occurring element that exists in nature mainly in the form of sulfide, oxide, and silicate minerals. Because it is ubiquitous, humans are routinely exposed to nickel in various amounts. "Zero exposure" to nickel is thus not possible. Nickel has been shown to be an essential element in certain microorganisms, animals, and plants. The generally held view is that nickel is probably an essential element for humans as well.

Nickel is an extremely important commercial element. Factors which make nickel and its alloys valuable commodities include strength, corrosion resistance, high ductility, good thermal and electric conductivity, magnetic characteristics, and catalytic properties. Its principle use is in stainless steels which are particularly valued for their hygienic properties. In some applications, nickel alloys are essential and cannot be substituted with other materials. Nickel plays important roles in environmental technologies to mitigate climate change, and alternative sources of energy. In recent years, the applications of nickel in the energy field, such as in electric batteries and energy storage, have increased. Given its many beneficial properties, nickel is used in a wide variety of products discussed below.

1.2 PRODUCTION AND USE

Nickel is produced from sulfide and laterite ores in mining and refining operations. Lateritic ore reserves occur in tropical and semi-tropical regions whilst sulfidic ore reserves occur in temperate regions. The estimated global nickel reserves in the earth's crust is about 300 million tons, with more in the sea. Annual world production of nickel in 2019 was estimated to be about 2,700 kilotonnes[1]. Primary nickel products are classified by the amount of nickel they contain. Class I products contain 99.8% or more nickel by weight, whereas Class II products contain less than 99.8% nickel by weight.

Nickel in one form or another has litreally hundreds of thousands of individual applications. Most primary nickel is used in alloys, the most important of which is stainless steels and the articles produced from them. Production of food contact materials, ranging from cutlery and pots/pans to preparation and bulk storage of foods and beverages, is a significant use of stainless steels. Other uses of nickel substances include electroplating and casting, as well as the production of catalysts, batteries, welding rods, coinage, and other miscellaneous applications. Recent advances in battery technologies for use in electric vehicles and other fields have increased nickel value in these technologies. The list of end-use applications for nickel is, for all practical purposes, limitless. Nickel is also found in transportation products, electronic equipment, medical devices, construction materials, oil and gas infrastructure, aerospace equipment, durable consumer goods, paints, and ceramics. From this list, it is evident that nickel is a critical metal to industrialised societies.

1.3 SOURCES OF EXPOSURE

Given its many uses and applications, the potential for exposure to nickel metal and nickel compounds, is varied and wide ranging. With respect to occupational exposures, the main routes of toxicological relevance are inhalation and, to a lesser extent, skin contact[2].

Workers engaged in nickel production may be exposed to a variety of nickel-containing substances and materials, depending upon the type of ore mined, the processes used to produce intermediate and primary nickel products, and the parts of the process in which the workers are assigned. Generally, exposures during nickel production are to moderately soluble and insoluble forms of nickel. In the nickel-producing industry, soluble nickel compounds are more likely to be found in hydrometallurgical operations. Exposures in nickel-using industry sectors vary according to the products manufactured and include both soluble and relatively insoluble forms of nickel substances.

In the past, airborne occupational nickel concentrations were believed to have been quite high (> 10 mg Ni/m^3) in certain producing operations, with some estimates of exposures as high as 100 mg Ni/m^3 or more for Ni_3S_2 sintering (sometimes referred to as "matte" sintering). More recent estimates of exposure (post-1960) are much lower, with current measurements generally averaging < 1 mg Ni/m^3. Exposures to nickel substances in using industries have historically been much lower than in producing industries, with estimates generally averaging well below 1 mg Ni/m^3 [3, 4].

Dermal occupational exposures were also believed to be quite high in the past, but mostly in nickel producing and

using industries involving soluble nickel substances, as evidenced by nickel allergic skin reactions in some of these facilities. Exposure reduction measures (e.g. improved containment of processes and PPE) have decreased occurrence of occupational nickel allergic reactions to very low levels. Measurement of dermal exposure levels in various nickel production and use industries showed median total nickel levels as high as 17.4 µg Ni/cm^2 (face) in nickel powder packing areas to 0.06 µg Ni/cm^2 (chest) in electrowinning/electrolysis areas [5]. When the different nickel species are accounted for, comparing the derived no effect level (DNEL) and the exposure level for the chemical form (90th percentile of the exposure distribution) demonstrated no excessive risk from dermal exposure in these scenarios [6].

1.4 PHARMACOKINETICS OF NICKEL

The major routes of nickel intake are dietary ingestion and inhalation. In the general public, diet constitutes the main source of nickel exposure. The average chronic dietary intake of nickel is between 2.0–13.1 µg/kg bw/day [7]. Nickel levels in drinking water (averages ranging from < 0.001 to 0.01 mg Ni/L) and ambient air (averages ranging from 1 to 60 ng Ni m^3) are generally quite low. Other sources of nickel exposure to the general public include contact with nickel-containing articles such as jewelry, medical applications, and tobacco smoke. The chemical forms of nickel in these exposures are varied and affect absorption.

For individuals occupationally exposed, total nickel intake is likely to be higher than that of the general populace. Whether diet or workplace exposures constitute the main source of systemically absorbed nickel in workers depends upon a number of factors. The factors that influence what part of the respiratory tract and in what amounts the particles are deposited include the size of the particles and their density, the concentration of the nickel in the breathing zone, the minute ventilation rate of a worker, whether breathing is nasal or oronasal, the use of respiratory protection equipment, personal hygiene practices, and general work patterns (for example, length of exposure).

Toxicologically speaking, inhalation is the most important route of nickel exposure in the workplace, followed by dermal exposure. Deposition, absorption, and retention of nickel particles in the respiratory tract will depend on many of the factors noted above. In general, only a fraction of the total airborne particle concentration will be inhaled into the nose and/or mouth during breathing. Depending on the air speed at the workplace, the 50% cut-point for penetration in the respiratory tract is 100 µm in non-calm air conditions (0.2 m/s $< w \leqslant 4$ m/s) and > 100 µm for calm air conditions ($w \leqslant 0.2$ m/s). It is believed that this efficiency may decline rapidly for particles with an aerodynamic diameter >100 µm (i.e., inhalable aerosol fraction). Of the particles inhaled, a 50% cut-point of 10 µm aerodynamic diameter is for fractions reaching beyond the larynx (i.e., thoracic aerosol fraction), and a 50% cut-point of 4 µm aerodynamic diameter for the fractions reaching the alveolar region (i.e., respirable aerosol fraction) [8].

Factors such as the amount deposited, solubility, surface area and charge of the particle will influence the clearance behaviour of particles once they are deposited in the lung. The smaller and more soluble the particle, the more rapidly it will be absorbed into the bloodstream and excreted. The residence time of nickel-containing particles in the lung is believed to be an important component of toxicity.

With respect to skin absorption, divalent nickel (Ni^{2+}) has been shown to penetrate the skin fastest at sweat ducts and hair follicles; however, the surface area of these ducts and follicles is small. Hence, penetration through the skin is primarily determined by the rate at which nickel is able to diffuse through the horny layer of the epidermis. Although the actual amount of nickel permeating the skin from nickel-containing materials is unknown, in studies using excised human skin, the% permeation was small, ranging from negligible to 0.23% (non-occluded skin) to 3.5% (occluded skin) of an administered dose of nickel chloride after 144 hrs. Marked differences in the rate of nickel permeation have been reported for nickel solutions, with nickel sulfate solutions permeating the skin at a rate 50 times lower than nickel chloride solutions [9].

Analyses of tissues from autopsy of non-occupationally exposed adults have shown highest concentrations of nickel in the lungs, thyroid gland, and adrenal gland, followed by lesser concentrations in kidney, liver, heart, spleen, and other tissues [10]. Excretion of absorbed nickel is mainly through urine, whereas unabsorbed nickel is

excreted mainly in feces. Nickel also may be excreted in sweat, hair, and human breast milk [2].

1.5 SUMMARY OF THE TOXICITY OF NICKEL SUBSTANCES

Just as the pharmacokinetics of nickel chemical species are influenced by their physical and chemical properties, concentration, and route of exposure, so too are the toxic effects of nickel. Although a number of nickel-related effects, including renal and reproductive effects have been reported in animals, the main effects noted in humans are respiratory and dermal local effects. Consequently, the major routes of toxicological relevance in the workplace are inhalation and skin contact.

In most work environments, the potential chronic toxicity of various nickel species is likely to be of more concern than acute effects, with the exception of nickel carbonyl. Long-term exposures to some nickel compounds have been associated with excess lung and nasal sinus cancers. The major source of evidence for this association comes from studies of workers who were employed in certain nickel-refining operations. On the whole, these workers were generally exposed to higher concentrations of nickel than those that exist in many workplaces today. These workers were also exposed to a variety of other potentially carcinogenic substances, including arsenic compounds, polyaromatic hydrocarbons (PAHs), and sulfuric acid mists. These concurrent exposures make a direct cause and effect interpretation of the data somewhat difficult, but in general, nickel compounds should be considered to have a carcinogenic hazard by inhalation. Summarised below are the respiratory and dermal effects associated with exposure to the main chemical forms of nickel.

1.5.1 Summary of the toxicity of metallic nickel

A determination of the health effects of metallic nickel is based mainly upon epidemiological studies of over 40,000 workers from various nickel-using industry sectors (nickel alloy manufacturing, stainless steel manufacturing, and the manufacturing of barrier material for use in uranium enrichment). These workers were examined for evidence of carcinogenic risk due to exposure to metallic nickel and, in some instances, accompanying oxidic nickel compounds and nickel alloys. No metallic nickel-related excess respiratory cancer risks have been found in any of these workers. Animal data on carcinogenicity are in agreement with the human data. A 2008 regulatory compliant study on the inhalation of metallic nickel powder was negative for respiratory carcinogenicity in rats. However, at levels at or above 0.1 mg Ni/m^3 (respirable aerosol fraction), chronic respiratory toxicity was observed in the animals [11].

Data relating to respiratory effects associated with short-term exposure to metallic nickel are very limited. One case report of a fatality has been recorded in a man spraying nickel using a thermal arc process. However, the relevance of the case to current occupational settings is questionable since the reported exposure to total nickel was extremely high (382 mg Ni/m^3), the size of particles was in nanometer range and the released particles may have been comprised primarily of nickel oxides [12]. Nevertheless, special precautions to reduce inhalation exposure to fine and ultrafine Ni-containing powders should be taken.

Collectively, animal and human data present a mixed picture with respect to the potential role that metallic nickel may play in non-malignant respiratory disease. There are no clear, definite reports of asthma associated with metallic nickel exposure, although there are thousands of workers exposed to water-insoluble metallic nickel and nickel compounds [2]. Furthermore, the overall litreature shows that past exposures to metallic nickel have not resulted in excess mortality from such diseases. However comprehensive studies of non-malignant pulmonary disease are lacking and additional studies on such effects (e.g., lung function) would be desirable.

Skin sensitisation to metallic nickel (as nickel metal powder and alloys) can occur wherever there is leaching of a sufficient amount (above threshold) of nickel ions from articles containing nickel onto exposed skin. Occupational exposures involving direct and prolonged skin contact with pure nickel metal powders may elicit cutaneous allergy (allergic contact dermatitis) in nickel-sensitised workers, but these exposures are rare. Nickel dermatitis occurs mainly as the result of non-occupational exposures, with direct and prolonged skin exposure to items such as rings, necklaces, earrings, watches, and clothing fasteners when they are made of high nickel-releasing materials.

1.5.2 Summary of nickel metal alloys

Nickel-containing alloys are specific mixtures of metals which are produced to have unique physico-chemical properties, including hardness, toughness, and corrosion resistance. The properties of the alloys differ from those of their pure ingredients and combinations of those ingredients simply mixed together. Accordingly, the United Nations Globally Harmonised System of Classification and Labelling of Chemicals (GHS) defines alloys as "… a metallic material, homogenous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means" [13]. The alloy matrix affects metal release from, as well as associated chemico-physical properties and toxicity of, the alloy in ways that cannot be predicted solely by their composition.

While there are no studies of nickel workers exposed solely to nickel alloys in the absence of metallic or oxidic nickel, studies on stainless steel and nickel alloy workers (who would likely have low level nickel exposures) suggest an absence of nickel-related excess respiratory cancer risk [14-16]. Intratracheal studies on animals have generally shown an absence of lung tumours in animals exposed to nickel alloys. Collectively, these studies suggest that nickel alloys do not act as respiratory carcinogens. For many alloys, this may be due to their corrosion resistance that results in reduced release of the metal ions to target tissues.

With respect to non-carcinogenic respiratory effects, a 28-day inhalation study with stainless steel AISI 316L (<4 µm, MMAD 2.5 – 3.0 µm) up to 1.0 mg/L did not show adverse toxicity effects [17] in rats, and the human studies that have looked at such endpoints have generally shown no increased mortality due to non-malignant respiratory disease.

Because alloys are specifically formulated to meet the need for manufactured products that are durable and corrosion resistant, an important property of all alloys and metals is that they are relatively insoluble in water, depending on the alloy and the surrounding conditions. Alloys, however, may react (corrode) in the presence of other media. Of particular importance to dermal exposures are the potential of some alloys to corrode and the corrosion products to dissolve into nickel ions in sweat. The potential for nickel alloys to cause an allergic reaction in occupational settings (e.g., in tools) will depend on the amount of nickel released from the article, which is affected by the sweat resistant properties of the alloy, the amount of time that a worker is in direct and prolonged skin contact with an alloy, the site of contact, and whether the individual is already allergic to nickel. Alloys that release less than 0.5 µg/cm^2/week of nickel (2+) ions are generally believed to be protective of the majority of nickel-sensitised individuals and all non-nickel-sensitised individuals, when in direct and prolonged skin contact. Alloys that release greater than 0.5 µg/cm^2/week of nickel (2+) ions could, in theory, trigger elicitation of nickel allergic reactions in already sensitised individuals with prolonged contact. However, they may be used safely when not in direct and prolonged contact with the skin or where ample protective equipment is provided. It should be noted that there is a very small portion of the population that is hypersensitive to nickel, and they require special considerations which can be addressed by a dermatologist familiar with nickel allergy.

1.5.3 Summary of the toxicity of soluble nickel

Since the early 2000's, soluble and insoluble nickel compounds have been classified as human inhalation carcinogens in the European Union Classification, Labelling and Packaging regulation (EU CLP). However, the precise role of soluble nickel in human carcinogenicity is still uncertain as there are no large enough cohorts with exposure solely to soluble nickel available for study. Epidemiologic information suggests that an increased risk of respiratory cancer is associated with inhalable fraction exposure to soluble nickel compounds in refinery process at levels in excess of 0.1 mg Ni/m^3, when in the presence of ⩾ 0.2 mg Ni/m^3 sulfidic nickel and ⩾ 2.0 mg Ni/m^3 oxidic nickel [18].

Well-conducted inhalation animal studies where rats were exposed to soluble nickel (by itself) at workplace equivalent inhalable concentrations up to 0.7-1.0 mg Ni/m^3 did not show any evidence of carcinogenicity [19]. However, at workplace equivalent levels above 0.2 mg Ni/m^3, chronic respiratory toxicity was observed in animal studies. In workers, respiratory toxicity due to soluble nickel exposures may have enhanced the induction of tumours by less soluble nickel compounds or other inhalation carcinogens. This mode of action is in agreement with mechanistic information indicating that nickel ions from soluble nickel compounds will not be bioavailable at target respiratory nuclear sites

because they have inefficient cellular uptake and are rapidly cleared from the lungs.

With respect to non-malignant respiratory effects in humans, the evidence for soluble nickel salts being a causative factor for occupational asthma, while not overwhelming, is more suggestive than it is for other nickel species. Such evidence arises mainly from a small number of case reports in the electroplating industry and nickel catalyst manufacturing [2]. It should be noted, however, that exposure to soluble nickel can only be inferred in some of the cases and confounding factors (exposure to chromium, cobalt, and plating solutions of low pH) often have not been considered.

Aside from asthma, the only other non-carcinogenic respiratory effect reported in nickel workers is that of lung fibrosis even though these workers are not reported to experience pneumoconiosis to any significant extent. Evidence that soluble nickel may act to induce pulmonary fibrosis at the radiological level comes from a study of nickel refinery workers. While the presence of irregular opacities (ILO ⩾ 1/0) in the chest x-rays of these workers (4.5%) was not different from the 'normal' x-rays from a hospital (4.2%), a dose-response trend for 4 categories of cumulative exposure to soluble Ni was observed [20]. The significance of these results for the clinical diagnosis of fibrosis is not certain.

Dermal exposure to soluble nickel compounds is restricted to occupational settings of production and use of soluble nickel compounds. Historically, workplaces where prolonged contact with soluble nickel has been high, have shown high risks for allergic contact nickel dermatitis. For example, nickel dermatitis was common in the past among nickel platers. Due to improved industrial and personal hygiene practices, however, over the past several decades, reports of nickel sensitivity in workplaces, such as the electroplating industry, have been sparse.

1.5.4 Summary of the toxicity of oxidic nickel

Like the above-mentioned species of nickel, the critical health effect of interest in relation to occupational exposure to oxidic nickel is respiratory cancer. Unlike metallic nickel, which does not appear to be carcinogenic in humans or animals, and soluble nickel, whose carcinogenic evidence appears contradictory between humans and animals, the evidence for the carcinogenicity of certain oxidic nickel compounds is more compelling. That said, there is still some uncertainty regarding the forms of oxidic nickel that induce tumourigenic effects. Although oxidic nickel is present in most major industry sectors, it is of interest to note that epidemiological studies have not consistently implicated all sectors as being associated with respiratory cancer. Indeed, excess respiratory cancers have been observed only in refining operations in which nickel oxides were produced during the refining of sulfidic ores and where exposures were relatively high (> 5 mg Ni/m^3). At various stages in this process, nickel-copper oxides may have been formed. In contrast, no excess respiratory cancer risks have been observed in workers exposed to lower levels (< 2 Ni/m^3) of oxidic nickel free of copper during the refining of lateritic ores or in the nickel-using industry.

A high calcining temperature nickel oxide administered to rats and mice in a two-year inhalation study did show some evidence of carcinogenicity in rats but with much lower potency than Ni subsulfide [21]. In intramuscular studies, nickel-copper oxides appeared to be as potent as nickel subsulfide in inducing tumours at injection sites [22]. There is, however, no strong evidence to indicate that black (low temperature) and green (high temperature) nickel oxides differ substantially with regard to general toxicity.

There is no single unifying physical characteristic that differentiates oxidic nickel compounds with respect to their in vitro genotoxicity or carcinogenic potential. Some general physical characteristics of oxides which may be related to carcinogenicity include: particle size ⩽ 5 µm, a large particle surface area, presence of metallic or other metal impurities and/or amount of Ni (II), and the ability to induce reactive oxygen species. Solubility in biological fluids will also affect how much nickel ion is delivered to target sites (i.e., cell nucleus).

With respect to non-malignant respiratory effects, oxidic nickel compounds do not appear to be respiratory sensitisers. Based upon numerous epidemiological studies of nickel-producing workers, nickel alloy workers, and stainless-steel workers, there is little indication that exposure to oxidic nickel results in excess mortality from chronic respiratory disease. In the few instances where excess risks of non-

malignant respiratory disease did appear – for example, in refining workers in Wales – the excesses were seen only in workers with high nickel exposures (> 10 mg Ni/m^3), in areas that were reported to be very dusty. With the elimination of these dusty conditions, the risk that existed in these areas seems largely to have disappeared by the 1930s. In two studies of nickel workers using lung radiographs, there was no evidence that oxidic nickel dusts caused a significant fibrotic response at the radiological level.

Dermal exposures to oxidic nickel are not believed to be of significant concern for toxicity to nickel workers. While no data are directly available on the effects of oxidic nickel compounds on skin, due to their very low solubility in water and synthetic sweat [23], little skin absorption of nickel ions from oxidic nickel is expected. As such, the risk of nickel sensitisation and systemic nickel effects is very low.

1.5.5 Summary of the toxicity of sulfidic nickel

Of all the nickel species examined in this document, a causal relationship for respiratory cancer can best be established for nickel subsulfide. The human data suggest that respiratory cancers have been primarily associated with exposures to less soluble forms of nickel (including sulfidic nickel). Animal data unequivocally point to crystalline nickel subsulfide as being carcinogenic.

Relative to other nickel compounds, nickel subsulfide may be the most efficient at inducing the heritable changes needed for the cancer process. In vivo, nickel subsulfide is likely to be readily phagocytised and dissolved by respiratory epithelial cells resulting in efficient delivery of nickel (II) to the target site within the cell nucleus. In addition, nickel subsulfide has relatively high solubility in biological fluids which results in the release of nickel (II) ions, with subsequent induction of cell toxicity and inflammation. Chronic cell toxicity and inflammation may enhance tumour formation by nickel subsulfide or other carcinogens (as discussed for soluble nickel compounds).

The evidence for non-malignant respiratory effects in workers exposed to sulfidic nickel has been mixed. Mortality due to non-malignant respiratory disease has not been observed in Canadian sinter workers. By contrast, increased mortality from non-malignant respiratory disease was observed in refinery workers in Wales for the earlier years of operation. With the elimination of the very dusty conditions that likely brought about such effects, the risk of respiratory disease disappeared in the Welsh workers by the 1930s. In a lung radiograph study of Norwegian nickel refinery workers, a potential increased risk of pulmonary fibrosis was found in workers with cumulative exposure to sulfidic nickel [20]. The significance of these results for the clinical diagnosis of fibrosis remains to be determined.

No relevant studies of dermal exposure have been conducted on workers exposed to sulfidic nickel. Likewise, no animal studies on dermal exposure have been undertaken. Although data for dermal exposure to sulfidic nickel compounds is not available, due to their low solubility in water and synthetic sweat [23], little skin absorption of nickel ions from sulfidic nickel is expected. Accordingly, the risk of nickel sensitisation and systemic nickel effects is low.

1.5.6 Summary of the toxicity of nickel carbonyl

The human data unequivocally show that nickel carbonyl is an agent which is extremely toxic to man; the animal data are in agreement with respect to this acute toxicity.

It is not possible to assess the potential carcinogenicity of nickel carbonyl from either human or animal data. Unless additional, long-term carcinogenicity studies in animals can be conducted at doses that do not exceed the Maximum Tolerated Dose (MTD) for toxicity, the database for the carcinogenicity of nickel carbonyl will remain unfilled. This issue may only be of academic interest since engineering controls and close monitoring of nickel carbonyl exposure to prevent acute toxicity greatly limit possible exposures to this compound.

Exposures to nickel carbonyl are usually confounded with exposures to other nickel compounds. However, for acute nickel carbonyl exposures urinary nickel can be used as a health guidance value to predict health effects and the need for treatment. Reasonably close correlations between the clinical severity of acute poisoning and urinary concentrations of nickel during the initial three days after exposure have been established as follows:

Symptoms	18-hr Urine specimen (µg Ni/l)
Mild	60-100
Moderate	100-500
Severe	>500

These values, however, are only relevant when urinary nickel is not elevated due to other nickel compound exposures.

Experience at a nickel carbonyl refinery has shown that the clinical severity of the acute nickel carbonyl exposure can also be correlated to nickel levels in early urinary samples (within the first 12 hrs of exposure). The use of an 8-hr post exposure urinary nickel specimen may also be helpful in categorising cases and determining the need for chelation therapy.

Due to the high toxicity of nickel carbonyl by inhalation exposure, nickel production facilities using this type of process minimise all types of exposures to nickel carbonyl. Therefore, dermal exposure would not be expected.

1.5.7 Summary of hazard classifications

The main human health hazards following acute and chronic exposure to nickel for which some nickel substances are classified, are for the most part, well established. The acute hazards for which many nickel substances are classified include acute toxicity, skin corrosion/irritation, serious eye damage/eye irritation, and the chronic health hazards include skin sensitisation, respiratory sensitisation, germ cell mutagenicity, carcinogenicity, and reproductive toxicity. Specific Target Organ Specificity (STOT) classifications cover hazard endpoints following single exposures (SE) or repeat exposures (RE) not covered by the other health hazard endpoints. Not all nickel substances are classified for the same hazards or in the same classification category. The hazard classifications discussed here focus on the European Union Classification, Labelling and Packaging (EU CLP) regulation for the nickel substances registered in the EU Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) by the Nickel Consortia.

Acute toxicity hazard refers to the adverse effects that occur following a single exposure or multiple exposures in a 24-hr period via oral or dermal routes, or a 4-hr inhalation exposure. In the EU CLP regulation, the most stringent classification for nickel acute toxicity is Acute Tox. 2 for inhalation exposure to nickel hydroxycarbonate. Acute Tox.4 (oral or inhalation) is the predominant classification for the rest of the classified nickel compounds. No nickel metal or nickel compound is classified for dermal acute toxicity. Skin corrosion refers to adverse damage to the skin that is irreversible while skin irritation or eye irritation refers to reversible damage to the skin or eye. The most stringent classifications in the EU CLP for the nickel substances registered under REACH are Skin Irrit. 2 for nickel chloride, sulfate, nitrate and hydroxycarbonate, Skin Corr. 1B for nickel bis (dihydrogen phosphate), Eye Damage 1 for nickel nitrate and bis (dihydrogen phosphate), and Eye Irrit. 2 for nickel hydroxycarbonate.

Classification for respiratory sensitisation or skin sensitisation of nickel is based on hypersensitivity of the lung airways following inhalation exposure or allergic response following dermal contact, respectively. Nickel metal, monoxide, subsulfide and sulfide are skin sensitisers and are thus classified for skin sensitisation (Skin Sens 1) in the EU CLP, but they are not classified for respiratory sensitisation. The soluble nickel compounds are considered as both skin and respiratory sensitisers and are classified as such in the CLP.

The hazard class 'Germ Cell Mutagenicity' is concerned with substances that cause a permanent change in the structure or amount of the germ cells of humans that can be transmitted to the offspring. Nickel metal and nickel oxide are not classified for germ cell mutation effects in the GHS and CLP. However, the sulfidic and soluble nickel compounds have shown weak, equivocal genotoxicity effects in various *in vitro* and *in vivo* assays, and are thus classified as category 2 mutagens (Muta. 2, suspected of causing genetic defects) in the CLP.

The human epidemiological and animal carcinogenicity evidence for sulfidic and oxidic nickel are compelling. For soluble nickel, the epidemiological evidence implicates it as a respiratory carcinogen, while the animal inhalation/oral cancer bioassay does not support soluble nickel by itself as a respiratory/systemic carcinogen. Regardless, all nickel compounds (soluble, sulfidic and oxidic nickel) are classified as human carcinogens in the CLP (category 1A, Carc. 1A), by IARC (Group 1) and in the NTP RoC (*known to be human carcinogens*).

Nickel metal is classified as a category 2 carcinogen (suspected human carcinogen) in the CLP. IARC assessed nickel metal as *possibly carcinogenic to humans* (Group 2B) whilst the U.S. EPA National Toxicology Report on Carcinogens (NTP RoC) listed nickel metal as *reasonably anticipated to be a human carcinogen*. These classifications are mainly based on animal studies by non-relevant routes of exposure.

Finally, the last two human health hazards discussed in this guide are reproductive toxicity and STOT. Reproductive toxicity is divided into 1) adverse effects on fertility and sexual function, and 2) adverse effects on development. Nickel metal, oxidic nickel, sulfidic nickel and soluble nickel compounds are not classified for fertility and sexual function adverse effects in the CLP and GHS, but soluble nickel compounds are classified for developmental toxicity (Repr. 1B). Nickel metal and nickel compounds are classified as STOT RE 1 (inhalation, respiratory tract as target organ) based on animal inhalation studies, but they are not classified for STOT following single exposure (SE) in the CLP.

2. PRODUCTION AND USE

Apart from unusual sources, such as massive nickel in meteorites, nickel from natural sources is usually found at modest concentrations and occurs in conjunction with a wide variety of other metals and non-metals. Although nickel is a ubiquitous metal in the natural environment, industrialisation has resulted in increased concentrations in both rural and urban environments.

Nickel-bearing particles are present in the atmosphere as constituents of suspended particulate matter and, occasionally, of mist aerosols. The primary anthropogenic stationary source categories that emit nickel into ambient air are: (1) combustion and incineration sources (heavy residual oil and coal burning units in utility, industrial, and residential use sectors, and municipal and sewage sludge incinerators), (2) high temperature metallurgical operations (steel and nickel alloy manufacturing, secondary metals smelting, and co-product nickel recovery), (3) primary production operations (mining, milling, smelting, and refining), and (4) chemical and catalyst sources (nickel chemical manufacturing, electroplating, nickel-cadmium battery manufacturing, and catalyst production, use, and reclamation).

For purposes of this document, the main concern is nickel presence in occupational settings. The use of nickel, although concentrated in the traditional uses of stainless steels and high-nickel alloys, continues to find new uses, such as in batteries, based on electrical, magnetic, catalytic, shape-memory, electro-magnetic shielding, and other unique properties. Thus, more nickel in small quantities and in various forms will be used in more industries and applications. The contributions being made by nickel have never been greater and neither has the need for an understanding of nickel toxicity.

It is evident that industrial processes present potential for exposure of workers to higher concentrations of nickel and/or its compounds than those generally found in the natural environment. Occasionally, these exposures may be to a refined form of nickel, but usually they are mixed, containing several nickel substances and/or non-nickel substances. These "mixed exposures" often complicate the interpretation of health effects of specific nickel species and make it difficult to set substance-specific regulations.

2.1 NICKEL-PRODUCING INDUSTRIES

Workers engaged in nickel production – which may include mining, milling, concentrating, smelting, converting, hydrometallurgical processes, refining, and other operations – are exposed to a variety of nickel minerals and compounds depending upon the type of ore mined and the process used to produce intermediate and primary nickel products [2]. These production processes are often broadly grouped under the industry sectors of mining, milling, smelting, and refining.

Generally, exposures in the producing industry are to moderately soluble and insoluble forms of ores and nickel substances, such as pentlandite [(FeNi)9S8], nickeliferous pyrrhotite, (FeNi)1-xS, nickel subsulfide (Ni_3S_2), silicates (including garnierite and smelting slags), and oxidic nickel (including nickeliferous limonite, NiO, Ni-Cu oxides, and complex oxides with other metals such as iron and cobalt). Exposures to metallic and soluble nickel compounds are less common in early parts of the production processes but are found in refining. Soluble nickel compounds are more likely to be found in hydrometallurgical operations, such as leaching and electrowinning [24].

Primary nickel products produced from the above operations are often characterised as Class I and II. Class I products are pure nickel metal in massive or dispersible forms, defined as containing ⩾ 99.8% Ni by weight (*Table 2-1*). Class II products have <99.8% Ni by weight and encompass three different types of products: metallic nickel in various product forms, nickel oxides, ferronickels and nickel pig iron (*Table 2-2*).

Class I products are marketed in a variety of forms including pure electrolytic full-plates, nickel squares, rounds, or crowns, spherical pellets, briquettes of consolidated pure nickel powder compacts, and several different pure nickel powders. The metallic nickels in Class II are electrolytic nickel products and briquettes containing >99.7% Ni, but <99.8% Ni and utility nickel shot containing >98.7% Ni. The oxide products in Class II include rondelles – partially reduced nickel oxide compacts containing about 90% Ni – and compacts of nickel oxide sinter containing approximately 75% Ni. The ferronickel products contain about 20% to 50% Ni. Nickel pig iron (NPI) ranges in concentration from about 2% up to less than 15% Ni.

While the production processes differ, they may be broadly classified into two groups: (1) those in which nickel is recovered from sulfidic ores (generally, but not always, found in the temperate zones of the earth's crust) and (2) those which are recovered from lateritic ores (commonly present in areas that currently are, or geologically were, tropical and semi-tropical areas). Traditionally, primary nickel production from the sulfidic ores dominated but that has changed; primary nickel production is now more dependent on lateritic ores, a trend likely to continue in the future. It is important to note, however, that secondary sources of nickel – overwhelmingly in the form of scrap stainless steels and nickel alloys but also including spent catalysts, batteries and other products – constitutes a large and ever-increasing percentage of world nickel supply.

With the exception of inhalable nickel powders, all the above products are massive and cannot be inhaled. However, in some instances, inhalable particles may be generated as a result of the degradation of briquettes, rondelles, and sinters during production, handling, packaging, shipping, unpacking, or subsequent treating or processing of these products.

TABLE 2-1: Class I primary nickel products, 99.8% nickel or more by weight

Product name	Nickel content, wt%	Form	Principal impurity
Electro – electrolytic nickel squares, rounds, crowns	99.8 – 99.99	Massive	Various
Pellets – from nickel carbonyl	> 99.97	Massive	Carbon
Briquettes – metallized powder compacts	⩾ 99.8	Massive (possibility of some powder formation during transport and handling)	Cobalt
Powders – by carbonyl decomposition or by precipitation	⩾ 99.8	Dispersible	Carbon

TABLE 2-2: Class II primary nickel products, less than 99.8% nickel by weight

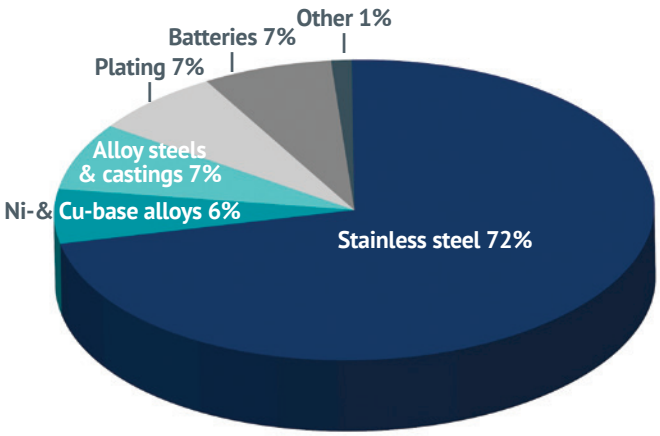
Product name	Nickel content, wt%	Form	Principal impurity
Form	Principal Impurity		
Electro	> 99.7	Massive	Cobalt
Briquettes	> 99.7	Massive (possibility of some powder formation during transport and handling)	Cobalt
Utility – shot	> 98.7	Massive	Iron
Sinter – nickel oxide and partially metallized	~75 – 90	Massive (possibility of some powder formation during transport and handling)	Oxygen
Ferronickel – ingots, cones, shot, granules	~20 – 50	Massive	Iron
Nickel pig iron – ingots	~2 – 15	Massive	Iron

The primary nickel industry is growing and evolving. There are a number of new entrants and a number of established producers are now part of some of the largest mining companies in the world. Smelting or refining operations take place in more than a dozen countries and are fed with concentrates from many more locations. The volumes in domestic and international trade are increasing, as are the ways in which the intermediate and finished products are packaged and transported.

2.2 NICKEL-USING INDUSTRIES

Various public and private statistical services track the production and end-use of nickel. The divisions vary and all percentages are "best estimates". The numbers given below provide breakdowns for 2020.

Figure 1 Nickel first use by product form

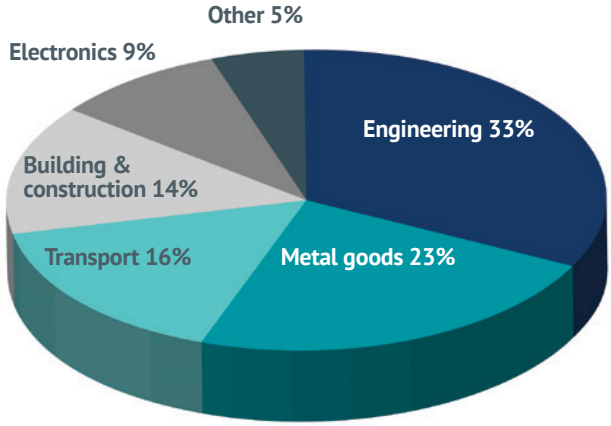


Data: Roskill

Figure 1 (Nickel Institute https://nickelinstitute.org/about-nickel/#04-first-use-nickel) shows nickel substance use by industry sector. It indicates that about 85% of all nickel substances are used in the production of different stainless and alloy steels, other nickel alloys and foundry products. About 7% is used in plated products, 7% in batteries, and the remaining 1% into other applications, such as coinage, pigments, catalysts, and litreally thousands of other small chemical uses.

New uses for nickel arise continually. For instance, nickel is present in critical applications that mitigate climate change and provide other environmental benefits. Most of the plating and "other" applications are "end-uses" of nickel; that is to say, the products are used directly by the customer or "end-user." The steels and other nickel alloys, on the other hand, are "intermediate" products that are further processed or "transformed" into end-use products in a number of industrial or consumer applications. These applications include building and construction materials; tubes; metal goods; transportation, electrical and electronic; engineering; and consumer and other products (*Figure 2* Nickel Institute https://nickelinstitute.org/about-nickel/#04-first-use-nickel).

Figure 2 Nickel end-use by sector



Data: Roskill

Only the most superficial description of nickel production and use are given here to provide context for the occupational health management issues that are the focus of this publication. For more information on nickel production and use, including end-of-life management, of nickel and nickel-containing materials and products, contact the Nickel Institute at: www.nickelinstitute.org

3. PHARMACOKINETICS OF NICKEL COMPOUNDS

Factors of biological importance to nickel, its compounds, and alloys include solubility, chemical form (species), physical form (e.g., massive versus dispersible), particle size, surface area, concentration, and route and duration of exposure. Where possible, the relationship of these factors to the intake, absorption, distribution, and elimination of nickel is discussed in this section. Independent factors that can also affect the biokinetic activity of nickel species, such as disease states and physiological stresses, are briefly noted.

3.1 INTAKE

The major routes of nickel intake are dietary ingestion and inhalation. In most individuals in the general public, including some who are occupationally exposed, diet constitutes the main source of nickel intake. Nickel levels in food are generally between 0.01–0.1 mg/kg [25]. The average acute and chronic dietary intake of nickel for toddlers to elderly in Europe range from 1.89–14.6 µg/kg bw/day and 1.57–14.6 µg/kg bw/day, respectively [7]. In the USA, the average daily dietary nickel intake is 69–162 µg Ni/day [26-29]. However, consumption of foodstuffs naturally high in nickel, such as oatmeal, cocoa, chocolate, nuts, and soy products, may result in higher nickel intake [2, 30].

Nickel in potable water also is generally quite low, averaging from < 0.001 to < 0.010 mg Ni/L [31]. In the USA and in Europe, nickel concentration in drinking water is generally ⩽ 0.020 mg/L [25, 32]. Nickel concentrations in groundwater may be higher, depending on the pH, soil use, and proximity to nickel refinery plants. Assuming an intake of 2 L/day, either as drinking water or water used in beverages, nickel in water may typically add 0.002 to 0.02 mg Ni to total daily intake.

For individuals who are not occupationally exposed to nickel, nickel intake via inhalation is considerably less than dietary intake. The Ni concentration in particulate form and aerosol in the atmosphere of the United States ranges from 7–12 ng/m^3, or up to 150 ng/m^3 near point sources [33]. Average ambient air Ni concentrations in some Canadian cities range from <0.1 to 4.5 ng/m^3 (Alberta Environment, 2004). Ambient air Ni concentrations in remote areas globally range from 1 to 3 ng/m^3, but levels in rural and urban areas can range from 5 to 35 ng/m^3 [34]. Nickel concentrations in indoor air are typically ⩽10 ng/m^3 [33, 35, 36]. Higher nickel air values have been recorded in heavily industrialised areas and larger cities [37]. An average urban dweller (70 kg man breathing 20 m^3 of 20 ng Ni/m^3/day) would inhale around 0.4 µg Ni/day [38]. For rural dwellers, daily intake of airborne nickel would be even lower. Tobacco smoking may also be a source of nickel inhalation exposure. Some researchers have suggested that smoking a pack of 20 cigarettes a day may contribute up to 0.004 mg Ni/day[39]. While this would contribute little to total nickel intake, smoking cigarettes with nickel-contaminated hands can significantly increase the potential for oral nickel exposures. Ultimately, the general population absorbs the greatest amount of nickel through food.

For occupationally exposed individuals, total nickel intake is likely to be higher than that of the general population. Whether diet or workplace exposures constitute the main source of nickel intake in workers depends upon a number of factors. These factors include the aerodynamic size of the particle and whether it is inhalable, the concentration of the nickel that is inhaled, the minute ventilation rate of a worker, whether breathing is nasal or oronasal, the use of respiratory protection equipment, personal hygiene practices, and general work patterns.

Other sources of exposure include dermal contact with nickel-releasing items (e.g., jewelry), though the relative amount absorbed compared to any other route are much lower. Direct and prolonged dermal exposure to nickel-releasing articles constitutes one of the most toxicologically important routes of exposure for the general public with respect to nickel allergic contact dermatitis.

3.2 ABSORPTION

3.2.1 Respiratory tract deposition, absorption and retention

Toxicologically speaking, inhalation is the most important route of nickel exposure in the workplace, followed by dermal exposure. Deposition, absorption, and retention of nickel particles in the respiratory tract follow general principles of lung dynamics. Hence, factors such as the aerodynamic size of a particle and ventilation rate will largely dictate the deposition of nickel particles into the nasopharyngeal, tracheobronchial, or pulmonary (alveolar) regions of the respiratory tract.

Not all particles are inhalable. As noted in *Section 2 Production and Use*, many primary nickel products are massive in form, and, hence, are inherently not inhalable. However, even products which are "dispersible" may not necessarily be inhalable unless the particles are sufficiently small to enter the respiratory tract. Humans inhale only about half of the particles with aerodynamic diameters ⩾ 80 µm, and it is believed that this efficiency may decline rapidly for particles with aerodynamic diameters between 100 and 200 µm. Of the particles inhaled, only a small portion with aerodynamic diameters larger than 10 µm are deposited in the lower regions of the lung, with deposition in this region predominantly limited to particles ⩽4 µm [40-42].

Factors such as the amount deposited and particle solubility, surface area, and size will influence the behaviour of particles once deposited in the respiratory tract and will probably account for differences in retention and clearance via absorption or through mechanical means (such as mucociliary clearance). Physiological factors such as age and general health status may also influence the process. Unfortunately, little is known about the precise pharmacokinetics of nickel particles in the human lung.

Based largely upon experimental data, it can be concluded that the more soluble the compound, the more readily it is absorbed from the lung into the bloodstream and excreted in the urine. Hence, nickel salts, such as sulfate and chloride, are rapidly absorbed and eliminated. The total retention half-life of nickel in the lungs of rats exposed by inhalation has been calculated to be 4.2 days for nickel sulfate after 15-month exposure to 0.03 mg Ni/m^3 (MMAD = 2.2–2.5 µm), 28 days for nickel subsulfide after 15-month exposure to 0.11 mg Ni/m^3 (MMAD = 2.17 µm),39 days for nickel metal after 15-month exposure to 0.1 mg Ni/m^3 (MMAD = 1.7–1.8 µm), and 116–500 days for green nickel oxide after 6–12-month exposure to 0.5 mg Ni/m^3 (MMAD = 2.21 µm) [43].

The relatively insoluble compounds, such as nickel oxides, are believed to be slowly absorbed from the lung into the bloodstream, thus, resulting in accumulation in the lung over time (see Section 6.3). Dunnick et al. [44] found that equilibrium levels of nickel in the lungs of rodents were reached by 13 weeks of exposure to soluble $NiSO_4$ (as $NiSO_4 \bullet 6H_2O$) and moderately soluble Ni_3S_2, but levels continued to increase with exposure to NiO. There is also evidence that some of the nickel retained in lungs may be bound to macromolecules [45].

In workers presumably exposed to insoluble nickel compounds, the biological half-time of stored nickel in nasal mucosa has been estimated to be several years [46]. Some researchers believe that it is the accumulated, slowly absorbed fraction of nickel which may be critical in producing the toxic effects of nickel via inhalation. This is discussed in Section 5 of this Guide.

Workers occupationally exposed to nickel have higher lung burdens of nickel than the general population. Dry weight nickel content of the lungs at autopsy was 330±380 µg/g in roasting and smelting workers exposed to less-soluble compounds, 34±48 µg/g in electrolysis workers exposed to soluble nickel compounds, and 0.76±0.39 µg/g in unexposed controls [47]. In an update of this study, Svenes and Andersen [48] examined 10 lung samples taken from different regions of the lungs of 15 deceased nickel refinery workers; the mean nickel concentration was 50 µg/g dry weight. Nickel levels in the lungs of cancer victims did not differ from those of other nickel workers [49, 50]. Nickel levels in the nasal mucosa are higher in workers exposed to less soluble nickel compounds relative to soluble nickel compounds [46]. These results indicate that, following inhalation exposure, less-soluble nickel compounds remain deposited in the nasal mucosa.

Acute toxicokinetic studies of NiO or $NiSO_4 \bullet 6H_2O$ in rodents and monkeys and subchronic repeated inhalation studies in rodents have been conducted to determine the effects of nickel compounds on lung clearance [51]. Clearance of NiO from lungs was slow in all species. Impairment of clearance of subsequently inhaled radiolabled NiO was seen in rodents, particularly at the highest concentrations tested (2.5 mg NiO/m^3 in rats and 5.0 mg NiO/m^3 in mice). In contrast to the NiO-exposed animals, clearance of $NiSO_4 \bullet 6H_2O$ was rapid in all species, and no impaired clearance of subsequently inhaled radiolabeled $NiSO_4 \bullet 6H_2O$ was observed.

Measurements of deposition, retention, and clearance of nickel compounds are lacking in humans.

3.2.2 Dermal absorption

Percutaneous absorption of nickel is of negligible significance quantitatively but is clinically important in the pathogenesis of contact dermatitis [37]. The available data indicate that absorption of nickel following dermal contact to various nickel compounds can take place, but to a limited extent with a large part of the applied dose remaining on the skin surface or in the stratum corneum. Divalent (Ni^{2+}) nickel has been shown to penetrate the skin fastest at sweat ducts and hair follicles where it binds to keratin and accumulates in the epidermis. However, the surface area of these ducts and follicles is small; hence, penetration through the skin is primarily determined by the rate at which nickel is able to diffuse through the horny layer of the epidermis [31]. Nickel

penetration of skin is modulated by many factors including sweat, solvents, detergents, and occlusion, such as wearing gloves [52-54]. Skin injury or increased water content of the stratum corneum may increase absorption through the skin as well as some solvents and detergents also may increase percutaneous absorption.

Occupational dermal exposure to nickel substances depends on the speciation of the nickel substance. A human in vivo study with nickel metal powder by Hostýnek et al. [55] found that a large part of the administered dose remained on the surface of the skin after 96 hrs with a minor part (around 0.2%) being absorbed in the stratum corneum. A similar study with nickel sulfate examining the skin after 24 hrs gave similar results [56]. An in vitro study of soluble nickel compounds (nickel sulfate, nickel chloride, nickel nitrate, and nickel acetate) using human skin [57] showed about 98% of the dose remained in the donor solution, whereas 1% or less was found in the receptor fluid and less than 1% was retained in the stratum corneum. In vitro studies also indicate that absorption following dermal contact may have a significant lag time.

3.2.3 Gastrointestinal absorption

Gastrointestinal absorption of nickel is relevant to workplace safety and health insofar as the consumption of food or the smoking of cigarettes in the workplace or without adequate hand washing can result in the ingestion of appreciable amounts of nickel compounds.

Intestinal absorption of ingested nickel varies with the type of food being ingested and the type and amount of food present in the stomach at the time of ingestion [58, 59]. A human absorption study showed that 40 times more nickel was absorbed from the gastrointestinal tract when nickel sulfate was given in the drinking water (27±17%) than when it was given mixed with food (0.7±0.4%) [60]. The rate constants for absorption, transfer, and elimination did not differ significantly between nickel ingested in drinking water or with food. The bioavailability of nickel as measured by serum nickel levels, was elevated in fasted subjects given nickel sulfate in drinking water (peak level of 80 µg/L after 3 hrs), but not when nickel was given with food [58].

In another human study where a stable nickel isotope (63Ni) was administered to volunteers, it was estimated that 29-40% of the ingested label was absorbed (based on fecal excretion data) [61]. Serum nickel levels peaked 1.5 and 3 hrs after ingestion of nickel [60-63]. In workers who accidentally ingested water contaminated with nickel sulfate and nickel chloride, the mean serum half-time of nickel was 60 hrs [64]. This half-time decreased substantially (27 hrs) when the workers were treated intravenously with fluids.

Studies in rats and dogs indicate that 1–10% of nickel, given as nickel, nickel sulfate, or nickel chloride in the diet or by gavage, is rapidly absorbed by the gastrointestinal tract [65-68]. In a study in which rats were treated with a single gavage dose of a nickel substance (10 nickel substances) in a 5% starch saline solution, the absorption can be directly correlated with the solubility of the substance [69]. The percentages of the dose absorbed were 0.01% for green nickel oxide, 0.09% for metallic nickel, 0.04% for black nickel oxide, 0.47% for nickel subsulfide, 11.12% for nickel sulfate, 9.8% for nickel chloride, and 33.8% for nickel nitrate. Absorption was higher for the more soluble nickel compounds.

While oral route is not the predominant route of exposure for workers, good industrial hygiene practices should include the banning of food consumption and cigarette smoking in areas where nickel compounds are used and should include requirements for hand washing upon leaving these areas.

3.3 DISTRIBUTION

The kinetic processes that govern transport and distribution of nickel in the body are dependent on the site of absorption, rate and concentration of nickel exposure, solubility of the nickel compound, and physiological status of the body. Nickel is mainly transported in the blood through binding with serum albumin and, to a lesser degree, histidine. The nickel ion may also bind with body proteins to form a nickel-rich metalloprotein [70].

Postmortem analysis of tissues from ten individuals who, with one exception, had no known occupational exposure to nickel, showed that the highest nickel concentrations were in the lungs, thyroid gland, and adrenal gland, followed by lesser concentrations in the kidneys, heart, liver, brain, spleen and pancreas [10]. These values are in general agreement with other autopsy studies that have shown highest concentrations of nickel in lung, followed by lower concentrations in kidneys, liver, heart, and spleen [71, 72].

The distribution of various nickel compounds to tissues has been studied in animals. Such studies reveal that the route of exposure can alter the relative amounts of nickel deposited in various tissues. Animal studies indicate that inhaled nickel is deposited primarily in the lung and that lung levels of nickel are greatest following inhalation of relatively insoluble NiO, followed by moderately soluble Ni_3S_2 and soluble $NiSO_4$ (as $NiSO_4 \bullet 6H_2O$) [44]. Following intratracheal administration of Ni_3S_2 and $NiSO_4$, concentrations of nickel were found to be highest in the lung, followed by the trachea, larynx, kidney, and urinary bladder [73, 74]. Kidney nickel concentrations have been shown to increase in proportion to exposure to $NiSO_4$ via inhalation, indicating that a significant portion of soluble nickel leaving the respiratory tract is distributed to the kidneys [75]. There is also some evidence that the saturation of nickel binding sites in the lung or saturation or disruption of kidney reabsorption mechanisms in rats administered $NiSO_4$ results in more rapid clearance [74]. No distribution studies using dermal exposure have been found, which is not surprising given the very low amount of dermal absorption and negligible contribution to systemic dose.

Not surprisingly, predictions of body burden have varied depending upon the analytical methods used and the assumptions made by investigators to calculate burden. Bennett [38] estimates the average human nickel body burden to be about 0.5 mg (0.0074 mg/kg x 70 kg). In contrast, values of 5.7 mg have been estimated by Sumino et al.[76] on the basis of tissue analyses from autopsy cases.

3.4 EXCRETION

Once absorbed into the blood, nickel is predominantly excreted by the kidneys in urine. Urinary excretion of nickel is thought to follow a first-order kinetic reaction [62].

Urinary half-times in workers exposed to nickel via inhalation have been reported to vary from 17 to 39 hrs in nickel platers who were largely exposed to soluble nickel [77]. Relatively short urinary half-times of 30 to 53 hrs have also been reported in glass workers and welders exposed to relatively insoluble nickel [78]. It should be noted, however, that in these cases the insoluble nickel that workers were exposed to – probably NiO or complex oxides – was likely in the form of welding fumes or fine particles. Such particles may be absorbed more readily than large particles. Difference in particle size may account for why other researchers have estimated much longer biological half-times of months to years for exposures to presumably relatively insoluble nickel compounds of larger particle size [46, 79, 80]. The precise role that particle size or dose may play in the absorption and excretion of insoluble nickel compounds in humans is still uncertain [70].

Reported urinary excretion half-times following oral exposures are similar to those reported for inhalation [60, 62]. Christensen and Lagesson [62] reported that maximal excretion of nickel in urine occurred within the first 8 hrs of ingesting soluble nickel compounds. The highest daily maximum renal excretion reported by the authors was 0.5 mg Ni/day.

Excretion via other routes is somewhat dependent on the form of the nickel compound absorbed and the route of exposure. Unabsorbed dietary nickel is lost in feces. Insoluble particles cleared from the lung via mucociliary action and swallowed into the gastrointestinal tract are also mainly excreted in the feces.

Sweat constitutes another elimination route of nickel from the body; nickel concentrations in sweat have been reported to be 10 to 20 times higher than concentrations in urine [81, 82]. Sunderman et al.[70] state that profuse sweating may account for the elimination of a significant amount of nickel.

Bile has been shown to be an elimination route in laboratory animals, but its importance as an excretory route in humans is unknown.

Hair is also an excretory tissue of nickel. However, use of hair as an internal exposure index has not gained wide acceptance due to problems associated with external surface contamination and non-standardised cleaning methods [37].

Nickel may also be excreted in human breast milk leading to dietary exposure of breast-fed infants. On a body weight basis, such exposures are believed to be similar to average adult dietary nickel intake [39].

3.5 FACTORS AFFECTING METABOLISM

Some disease states and physiological stresses have been shown to either increase or decrease serum nickel concentrations. As reviewed by Sunderman et al.[70] and

the U. S. Environmental Protection Agency [83], serum nickel concentrations have been found to be elevated in patients after myocardial infarction, severe myocardial ischemia, or acute stroke. Serum nickel concentrations are often decreased in patients with hepatic cirrhosis, possibly due to hypoalbuminemia [84]. Physiological stresses such as acute burn injury have been shown to correspond with increased nickel serum levels in rats.

4. TOXICITY OF METALLIC NICKEL AND NICKEL COMPOUNDS

The major routes of nickel exposure that have toxicological relevance to the workplace are inhalation and dermal exposures. Oral exposures can also occur (e.g., hand-to-mouth contact), but the institution of good industrial hygiene practices (e.g., washing hands before eating) can greatly help to minimise such exposures. Therefore, this chapter mainly focuses on the target systems affected by the former routes (i.e., the respiratory system and the skin). To the extent that other routes (such as oral exposures) may play a role in the overall toxicity of nickel and its compounds, these routes are also briefly mentioned. Focus is on the individual nickel species most relevant to the workplace, namely, metallic nickel and nickel alloys, oxidic, sulfidic and soluble nickel compounds, and nickel carbonyl.

4.1 METALLIC NICKEL

Occupational exposure to metallic nickel can occur through a variety of sources. Most notable of these sources are metallurgical operations, including stainless steel manufacturing, nickel alloy production, and related powder metallurgy operations. Other sources of potential occupational exposure to metallic nickel include nickel-cadmium battery manufacturing, chemical and catalyst production, plating, and miscellaneous applications such as coin production. In nearly all cases, metallic nickel exposures include concomitant exposures to other nickel compounds (most notably oxidic nickel, but other nickel compounds as well), and can be confounded with exposure to other non-nickel substances specific to the particular activity or process executed in the workplace. Therefore, it is important to summarise those health effects which can most reasonably and reliably be considered relevant to metallic nickel in occupational settings, even though other nickel and non-nickel compounds may be present.

4.1.1 Inhalation exposure: metallic nickel

With respect to inhalation, the only significant health effects seen in workers occupationally exposed to metallic nickel occur in the respiratory system. Based on the toxicological information available from nickel compounds, the two potential effects of greatest concern with respect to metallic nickel exposures would be non-malignant respiratory effects (including asthma and fibrosis) and respiratory cancer. Factors that can influence these effects include: the presence of particles on the bronchio-alveolar surface of lung tissue, mechanisms of lung clearance (dependent on solubility), mechanisms of cellular uptake (dependent on particle size, particle surface area, particle charge) and the release of Ni (II) ion to the target tissue (of importance to both carcinogenicity and Type I immune reactions leading to asthma).

In the case of respiratory cancer, studies of past exposures and cancer mortality reveal that respiratory tumours have not been consistently associated with all chemical species of nickel. Metallic nickel is one of the species for which this is true. Indeed, epidemiological data generally indicate that metallic nickel is not carcinogenic to humans. Over 40,000 workers from various nickel-using industry sectors (nickel alloy manufacturing, stainless steel manufacturing, and the manufacturing of barrier material for use in uranium enrichment) have been examined for evidence of carcinogenic risk due to exposure to metallic nickel and, in most instances, accompanying oxidic nickel compounds and nickel alloys [14, 15, 85-88]. No nickel-related excess respiratory cancer risks have been found in any of these workers.

Of particular importance are the studies of Cragle et al. [88] and Arena et al. [14]. The former study of 813 barrier manufacturing workers is important because of what it reveals specifically about metallic nickel. There was no evidence of excess respiratory cancer risks in this group of workers exposed predominantly to metallic nickel. The latter study is important because of its size (>31,000 nickel alloy workers) and, hence, its power to detect increased respiratory cancer risks. Exposures in these workers were mainly to oxidic and metallic nickel. Only a very modest relative risk of lung cancer (RR, 1.13; 95% CI 1.05-1.21) was seen in these workers

when compared to the overall U.S. population (smoking not accounted for) and the risks decreased and became statistically nonsignificant (RR, 1.02; 95% CI 0.96-1.10) in comparison to local populations. The lack of a significant excess risk of lung cancer relative to local populations, combined with a lack of an observed dose response with duration of employment regardless of the comparison population used, suggests that other non-occupational factors associated with geographic residence or cigarette smoking may explain the modest elevation of lung cancer risk observed in this cohort [14].

While occupational exposures to metallic nickel in the nickel-using industry have historically been low (< 0.5 mg Ni/m^3), certain subgroups of workers, such as in powder metallurgy, have been exposed to higher concentrations of metallic nickel (around 1.5 mg Ni/m^3) [14]. Such subgroups, albeit small in size, have shown no nickel-related excess cancer risks.

In studies of nickel-producing workers (over 6,000 workers) where exposures to metallic nickel have, in certain instances, greatly exceeded those found in the nickel-using industry, evidence of a consistent association between metallic nickel and respiratory cancer is lacking. For one of these cohorts, the International Committee on Nickel Carcinogenesis in Man [24] did not find an association between excess mortality risk for respiratory cancers and metallic nickel workers, whereas another group of researchers [89] found a significant association using a multivariate regression model. However, the Easton et al.[89] model substantially overpredicted cancer risks in long-term workers (>10 years) who were employed between the years 1930-1939. This led the researchers to conclude that they may have"overestimated the risks for metallic (and possibly soluble) nickel and underestimated those for sulfides and/or oxides"[89]. A 2001 update of hydrometallurgical workers with relatively high metallic nickel exposures confirms the lack of excess respiratory cancer risk associated with exposures to elemental nickel during refining [90]. Review articles published in 2005 [91] and more recently in 2020 [92] have confirmed the earlier findings and not found associations between metallic nickel exposure and increased lung cancer risks.

Animal data on carcinogenicity are largely in agreement with the human data. Early studies on the inhalation of metallic nickel powder, although somewhat limited with respect to experimental design, are essentially negative for carcinogenicity [93, 94]. While intratracheal instillation of nickel metal powder has been shown to produce tumours in the lungs or mediastinum of animals [95, 96], the relevance of such studies in the etiology of lung cancer in humans is questionable. This is because normal defense systems and clearance mechanisms operative via inhalation are by-passed in intratracheal studies. Moreover, high mortality in one of the studies [96] suggests that toxicity could have confounded the carcinogenic finding in this study. Driscoll et al.[97] have cautioned that, in the case of intratracheal instillation studies, care must be taken to avoid doses that are excessive and may result in immediate toxic effects to the lung due to a large bolus delivery.

A definitive animal carcinogenicity study with inhalable nickel metal powder (~1.8 µm MMAD, 2.4 µm GSD) by inhalation in male and female Wistar rats was conducted using a 2-year regimen of exposure at 0, 0.1, 0.4, and 1 mg/m^3. Toxicity and lethality required the termination of the 1 mg/m^3. Nevertheless, the 0.4 mg/m^3 group established the required Maximum Tolerated Dose (MTD) for inhalation of nickel metal powder and hence, was valid for the determination of carcinogenicity. This study, conducted according to OECD guidelines and GLP, did not show an association between nickel metal powder exposure and respiratory tumours [11], at workplace equivalent exposures up to 1.5-4.6 mg Ni/m^3 inhalable Ni (Nickel CSR 2019, Appendix C2).

These data, in concert with the most recent epidemiological findings and a separate negative oral carcinogenicity study with a water-soluble nickel salt (most bioavailable form of nickel), strongly indicate that nickel metal powder is not likely to be a human carcinogen by any relevant route of exposure. Indeed, a recent systematic review of the epidemiological, animal and mechanistic evidence concluded that "the evidence does not support a causal relationship between metallic nickel exposure and respiratory cancer in humans"[92].

With respect to non-malignant respiratory disease, no convincing reports of asthma or fibrosis have been reported in workers with metallic nickel exposures. In the case of asthma, exposure to fine dust containing nickel has only

infrequently been reported in anecdotal publications as a possible cause of occupational asthma [98-100]. Such dust exposures, however, have almost certainly included other confounding agents. Furthermore, no quantitative relationship has been readily established between the concentration of nickel cations in aqueous solution in bronchial challenge tests and equipotent metallic nickel in the occupational environment. In a U.S. study of welders (exposed to fumes containing complex spinels and other metals, with minute amounts of metallic nickel) at a nuclear facility in Oak Ridge, Tennessee, no increased mortality due to asthma was found among the workers studied [86]. Collectively, therefore, the overall data for metallic nickel being a respiratory sensitiser are not compelling, although a definitive study is lacking.

In addition to the unconvincing and very small number of anecdotal case-reports regarding asthma, a few other respiratory effects due to metallic nickel exposures have also been reported. Data relating to respiratory effects associated with short-term exposure to metallic nickel are very limited. One report exists of a fatality involving a man spraying nickel using a thermal arc process [12]. This man was exposed to very fine particles or fumes, likely consisting of metallic nickel or oxidic nickel. He died 13 days after exposure, having developed pneumonia, with postmortem showing shock lung. However, the relevance of this case to normal daily occupational exposures is questionable given the reported extremely high exposure (382 mg Ni/m^3) to relatively fine nickel particles.

A few other studies have investigated the effects of nickel exposure on pulmonary function and fibrosis. With respect to pulmonary function, Kilburn et al.[101] examined cross-shift and chronic pulmonary effects in a group of stainless steel welders (with predominant nickel exposures to complex oxides but possibly some minute metallic nickel exposure). No differences in pulmonary function were observed in test subjects versus controls during cross-shift or short-term exposures. Although some reduced vital capacities were observed in long-term workers, the authors noted little evidence of chronic effects on pulmonary function caused by nickel. Conversely, in studies of stainless steel and mild steel welders, short-term, cross-shift effects were noted in stainless steel workers (reduced FEV1:FVC ratio), but no long-term effects in lung function were noted in workers with up to 20 years of welding activity [102, 103]. A generalised decrease in lung function, however, was seen in workers with the longest histories (over 25 years) of stainless steel welding. This was attributed to the high concentrations of mixed pollutants (i.e., dust, metal oxides, and gasses) to which these welders were exposed. A higher prevalence of bronchial irritative symptoms, such as cough, was also reported.

With respect to fibrosis, a study on nickel refinery workers in Norway examined the incidence of x-ray abnormalities (ILO ⩾ 1/0) [20]. The incidence of irregular opacities in x-rays was not significantly different from the hospital incidence in "normal" x-rays (4.5% vs 4.2%, respectively). An increased risk of abnormal x-rays was found with cumulative exposure to sulfidic and soluble, but not for oxidic or metallic nickel [20].

Animal studies on the non-carcinogenic respiratory effects of metallic nickel are few. The early studies by Heuper and Payne [94] suggest that inflammatory changes in the lung can be observed in rats and hamsters administered nickel powder via inhalation. However, lack of details within the studies precluded drawing any conclusions with respect to the significance of the findings. In the 2-year cancer bioassay study [11], chronic inflammation was observed in rats exposed to nickel metal powder at ⩾ 0.1 mg/m^3 (MMAD 1.8 µm, GSD 2.4). Studies on the effects of ultrafine metallic nickel powder (mean diameter of 20 nm) administered intratracheally or via short-term inhalation in rats showed significant inflammation, cytotoxicity, and/or increased epithelial permeability of lung tissue [104, 105].

Collectively, the above findings present a mixed picture with respect to the potential risk of non-malignant respiratory disease from metallic nickel exposures. There is an extensive body of litreature demonstrating that past exposures to metallic nickel have not resulted in excess mortality from such diseases [14, 15, 85-88, 90, 106]. Studies of welders may be less relevant for metallic nickel, as exposures are predominantly to complex Ni-metal oxides (spinels), rather than nickel metal. However, additional studies on such effects, particularly with respect to ultrafine nickel powders, would be useful.

4.1.2 Dermal exposure: metallic nickel

Dermal exposure to metallic nickel is possible wherever nickel powders are handled, such as powder metallurgy, and

in the production of nickel-containing batteries, chemicals, and catalysts. Occasional contact with massive forms of metallic nickel could occur during nickel metal production, alloy production, production of articles made of nickel metal or alloys, and use of nickel-containing articles.

Skin sensitisation to nickel metal can occur wherever there is sufficient leaching of nickel ions from articles containing nickel onto exposed skin [107, 108]. However, cutaneous allergy (allergic contact dermatitis) to nickel occurs mainly as the result of non-occupational exposures. Indeed, the evidence for occupationally-associated nickel allergic reactions is sparse [52, 109-111] due in large part to increased occupational hygiene measures.

Sensitisation and subsequent allergic reactions to nickel require direct and prolonged contact with nickel-containing solutions or nickel-releasing items that are non-resistant to sweat corrosion (see further discussion under Sections 5.2 and 5.4). The nickel ion must be released from a nickel-containing article in intimate contact with skin to elicit a response. Evidence suggests that humid environments are more likely to favour the release of the nickel ion from metallic nickel and nickel alloys, whereas dry, clean operations with moderate or even intense contact to nickel objects will seldom, alone, provoke dermatitis [52]. In some occupations for which nickel dermatitis has been reported in higher proportion than the general populace (e.g., cleaning, hairdressing and hospital wet work), the wet work is, in and of itself, irritating and decreases the barrier function of the skin. Often it is the combination of irritant dermatitis and compromised skin barrier that produces the allergic reaction [52]. The role of nickel in the manifestation of irritant dermatitis in metal manufacturing, cement and construction industries, and coin handling has been debated. It has been suggested by some researchers that nickel probably does not elicit dermatitis in workers from such industries unless the worker is already strongly allergic to nickel [52]. There are some reports that oral ingestion of high nickel levels (above 12 µg/kg/day) can trigger a dermatitis response in susceptible nickel-sensitised individuals (see section 5.3).

4.2 NICKEL ALLOYS

Often there is a misconception that the toxicity of nickel-containing alloys is synonymous with the toxicity of metallic nickel. This is not necessarily true. Each type of nickel-containing alloy is a unique substance with its own special physico-chemical and biological properties that differ from those of its individual metal constituents. Alloy constituents can affect the release of nickel metal, increasing or decreasing it from what would be expected based on nickel metal content, changing the toxicity profile of the alloy. The potential toxicity of a nickel alloy (including carcinogenic effects) must, therefore, be evaluated separately from the potential toxicity of nickel metal itself and other nickel-containing alloys.

While there are hundreds of different nickel-containing alloys in different product categories, the major product categories are stainless steel (containing Fe, Cr and up to 34% Ni) and high nickel content alloys. Occupational exposures to nickel from these and other forms of nickel alloys (e.g., superalloys, cast-irons) can occur wherever alloys are produced (metallurgical operations) or in the processing of alloys (such as welding, grinding, cutting, polishing, and forming). Like metallic nickel, occupational exposures to nickel-containing alloys will mainly be via the skin or through inhalation. However, in the case of certain nickel alloys that are used in prosthetic devices, localised internal exposures can occur. Because such exposures are not of specific concern to occupational settings, they are not discussed in this Guide. However, a comprehensive review of information pertaining to prosthetic devices devices are available elsewhere. [112, 113].

4.2.1 Inhalation exposure: nickel alloys

There are no studies of nickel workers exposed solely to nickel alloys in the absence of metallic or oxidic nickel. Clearly, however, workers in alloy and stainless steel manufacturing and processing will likely have some low level exposure to nickel alloys. In general, most studies on stainless steel and nickel alloy workers have shown no significant occupationally-related excess risks of respiratory cancer [14, 15, 85, 86, 114-118]). As noted above and in the discussion on metallic nickel, some of these studies involved thousands of workers [14]. Hence, these studies suggest an absence of nickel-related excess cancer risks in workers exposed to nickel-containing alloys.

There have been some exceptions, however, in certain groups of stainless steel welders [119, 120] where excess lung tumours

were detected. Further analyses of these and other stainless steel workers as part of a large international study on welders (> 11,000 workers) failed to show any association between increased lung cancer mortality and cumulative exposure to nickel [121]. A later analysis of this same cohort [122] showed no trend for lung cancer risk for three levels of nickel exposure. Likewise, no nickel-related tumours were observed in a group of German arc welders exposed to fumes containing chromium and nickel [123]. In 2017, IARC reviewed the evidence for the carcinogenicity of welding fumes and its components and concluded that welding fumes as a whole are Group 1 carcinogens, but did not distinguish between stainless or mild steel welding [124]. Importantly, the exposures during welding are mainly to complex oxides (spinels) of very small particle size with minor contributions from nickel alloys or metal.

Limited data are available to evaluate respiratory carcinogenicity of nickel alloys in animals. One intratracheal instillation study looked at two types of stainless steel grinding dust. An austenitic stainless steel (6.8% nickel) and a chromium ferritic steel (0.5% nickel) were negative in hamsters after repeated instillations [125]. In another study, grinding dust from an austenitic stainless steel (26.8% nickel) instilled in hamsters was also negative [96]. In this same study, an alloy containing 66.5% nickel, 12.8% chromium, and 6.5% iron showed some evidence of carcinogenic potential at the higher doses tested. A significant shortening in survival time in one of the high dose groups compared to untreated controls, however, raises the question of toxicity and its possible confounding effect on tumour formation. As noted in the discussion of metallic nickel, intratracheal instillation studies must be carefully interpreted in light of their artificial delivery of unusually large and potentially toxic doses of chemical agents to the lung [97].

In total, there is little evidence to suggest that nickel alloys, as such, act as respiratory carcinogens. For many alloys, this may be due to their corrosion resistance which results in reduced release of metal ions to target tissues.

With respect to non-carcinogenic respiratory effects, no animal data are available for determining such effects, and the human studies that have looked at such endpoints have generally shown no increased mortality due to non-malignant respiratory disease [14, 15, 85, 86, 114, 121].

4.2.2 Dermal exposure: nickel alloys

Because alloys are specifically formulated to meet the need for manufactured products that are durable and corrosion resistant, an important property of all alloys and metals is that they are insoluble in aqueous solutions. They can, however, react (corrode) in the presence of other media, such as air or biological fluids, to form new metal-containing species that may or may not be water soluble. The extent to which alloys react is governed by their corrosion resistance in a particular medium and this resistance is dependent on the nature of the metals, the proportion of the metals present in the alloy, and the process by which the alloy was made.

Of particular importance to dermal exposures are the potential of individual alloys to corrode in sweat. As noted under the discussion of metallic nickel, sensitisation and subsequent allergic reactions to nickel require direct and prolonged contact with nickel-containing solutions or materials that are non-resistant to sweat corrosion. It is the release of the nickel (II) ion, not the nickel content of an alloy, that will determine whether a response is elicited. Occupational dermal exposures to nickel alloys are possible wherever nickel alloy powders are handled, such as in powder metallurgy or catalyst production. While exposures to massive forms of nickel alloys are also possible in occupational settings, these exposures do not tend to be prolonged, and, hence, are not of greatest concern with respect to contact dermatitis. Dermal contact with nickel-copper alloys in coinage production can also occur. The potential for nickel alloys to elicit an allergic reaction in occupational settings, therefore, will depend on both the sweat resistant properties of the alloy and the amount of time that a worker is in direct and prolonged contact with an alloy.

While the EU Nickel Directive (94/27/EC), limiting the Ni release from alloys that come into close contact with the skin, is geared toward protecting the general public from exposures to nickel contained in consumer items, it may also provide some guidance in occupational settings where exposures to nickel alloys are direct and prolonged. It should be noted, however, that alloys that release greater than 0.5 ug/cm^2/ week of nickel may not be harmful in an occupational or commercial setting. They may be used safely when not in direct and prolonged contact with the skin or where ample protective clothing is provided. A comprehensive review of the health

effects associated with the manufacture, processing, and use of stainless steel can be found in Cross et al.[126].

4.3 SOLUBLE NICKEL

Exposure to readily water-soluble nickel salts occurs mainly during the electrolytic refining of nickel (producing industries) and in electroplating (using industries). Depending upon the processes used, exposures are usually to hydrated nickel (II) sulfate or nickel chloride in solution. Like the previously mentioned nickel species, the routes of exposure of toxicological relevance to the workplace are inhalation and dermal exposures. However, unlike other nickel species, soluble nickel (II) ions are present in drinking water; thus, oral exposures are briefly mentioned below.

4.3.1 Inhalation exposure: soluble nickel

Like metallic nickel, the two effects of greatest concern for the inhalation of soluble nickel compounds are respiratory cancer and non-malignant respiratory effects (e.g., fibrosis, asthma). Unlike metallic nickel, however, which has consistently shown lack of evidence of carcinogenicity, the carcinogenic assessment of soluble nickel compounds has been somewhat challenging. The challenge lies both in reconciling what appears to be inconsistent human data and in interpreting the human and animal data in an integrated manner that provides a cohesive picture of the carcinogenicity of soluble nickel compounds.

Human evidence for the carcinogenicity of soluble nickel compounds comes mainly from studies of nickel refinery workers in Wales, Norway, and Finland[d] [24, 89, 127-129]. In these studies, workers involved in electrolysis, electrowinning, and hydrometallurgy have shown excess risks of lung and/or nasal cancer. Exposures to soluble nickel have generally been regarded to be relatively high in most of these workers (in excess of 1 mg Ni/m^3), although some studies have suggested that exposures slightly lower than 1 mg Ni/m^3 may have contributed to some of the cancers observed [128, 130]. In all instances, soluble nickel exposures in these workers have been confounded by concomitant exposures to other nickel compounds (notably, oxidic and sulfidic nickel compounds), other chemical agents (e.g., soluble cobalt compounds, arsenic, acid mists) or cigarette smoking-all known or believed to be potential carcinogens in and of themselves (see Sections 5.4 and 5.5). Therefore, it is unclear whether soluble nickel, alone, caused the excess cancer risks seen in these workers.

In contrast to these workers, electrolysis workers in Canada and plating workers in the U.K. have shown no increased risks of lung cancer [24, 131-133]. In the case of the Canadian electrolysis workers, their soluble nickel exposures were similar to those of the electrolysis workers in Norway. Soluble nickel exposures in the plating workers, although unknown, are presumed to have been lower. On the whole, these workers were believed to lack, or have lower exposures to, some of the confounding agents present in the work environments of the workers mentioned above. While nasal cancers were seen in a few of the Canadian electrolysis workers, these particular workers had also worked in sintering departments where exposures to sulfidic and oxidic nickel were very high (> 10 mg Ni/m^3). It is likely that exposures to the latter forms of nickel (albeit some of them short) may have contributed to the nasal cancers observed (see Sections 4.4 and 4.5).

Besides the epidemiological studies, the animal data also needs to be considered. The most important inhalation animal studies conducted to date are those of the U.S. National Toxicology Program. In these studies, nickel subsulfide, nickel sulfate hexahydrate, and a high-temperature nickel oxide were administered to rats and mice in two-year carcinogenicity bioassays [19, 21, 134]. Results from the nickel sulfate hexahydrate study [19] are particularly pertinent to the assessment of the carcinogenicity of soluble nickel compounds. This 2-year chronic inhalation study failed to produce any carcinogenic effects in either rats or mice at exposures to nickel sulfate hexahydrate up to 0.11 mg Ni/m^3 or 0.22 mg Ni/m^3, respectively [19]. These concentrations correspond to approximately 0.70-2.0 mg Ni/m^3 workplace aerosols after adjusting for particle size and animal to human extrapolation [43, 135, 136]. It is also worth noting that soluble nickel compounds administered via other relevant routes of exposure (oral) in lifetime carcinogenicity studies have also failed to produce tumours [65, 137-139].

In sum, the negative animal data combined with the conflicting human data make for an uncertain picture regarding the carcinogenicity of soluble nickel alone.

As noted by Oller [140], without a unifying mode of action that can both account for the discrepancies seen in the human data and integrate the results from human and animal data into a single model for nickel respiratory carcinogenesis, assessments of soluble nickel will continue to vary widely. Such a MoA has been proposed in models for nickel-mediated induction of respiratory tumours. These models suggest that the main determinant of the respiratory carcinogenicity of a nickel species is likely to be the bioavailability of the nickel (II) ion at nuclear sites of target epithelial cells [141-144]. Only those nickel compounds that result in sufficient amounts of bioavailable nickel (II) ions at such sites (after inhalation) will be respiratory carcinogens. Because soluble nickel compounds are not phagocytised and are rapidly cleared, substantial amounts of nickel (II) ions that would cause tumour induction simply are not present.

However, at workplace equivalent levels above 0.19-0.26 mg Ni/m^3 [43] chronic respiratory toxicity was observed in animal studies [19]. Respiratory toxicity due to soluble nickel exposures may have enhanced the induction of tumours by less soluble nickel compounds or other inhalation carcinogens seen in refinery workers. This may account for the observed respiratory cancers seen in the Norwegian, Finnish, and Welsh refinery workers who had concomitant exposures to smoking and other inhalation carcinogens. Indeed, in its multi-analysis of many of the nickel cohorts discussed above, the International Committee on Nickel Carcinogenesis in Man (ICNCM) postulated that the effects of soluble nickel may be to enhance the carcinogenic process, as opposed to inducing it [24]. Alternatively, it should be considered that none of the workers in the sulfidic ore refinery studies had pure exposures to soluble nickel compounds that did not include sulfidic or complex nickel oxides, and most of them had confounding by smoking and in some cases arsenic or cobalt.

To identify a practical lung cancer threshold for exposure to the main chemical forms of nickel, the dose-response (D-R) for soluble and oxidic compounds were analysed by Oller et al.[18], taking into account differences in response relative to the presence of sulfidic and oxidic Ni exposure levels above and below 0.2 mg Ni/m^3 (as inhalable aerosol fraction). The (measured or estimated) exposures (corrected to inhalable) and risk ratios from Goodman et al.[142] were used. In total, lung cancer data from 22 process areas arising from 13 cohorts of geographically distinct nickel producing and using operations were included, encompassing >100,000 workers. Based on these data, a practical threshold of inhalable aerosol fraction of 0.10 mg Ni/m^3 soluble Ni (with ⩽ 0.2 mg Ni/m^3 of oxidic and sulfidic Ni) can be conservatively applied to all forms of nickel.

Animal inhalation studies have shown various non-malignant respiratory effects on the lung following relatively short periods of exposure to relatively high levels of soluble nickel compounds [44, 75, 145-148]). Effects have included marked hyperplasia, inflammation and degeneration of bronchial epithelium, increased mucus secretion, and other indicators of toxic damage to lung tissue. In a study where nickel sulfate was administered via a single intratracheal instillation in rats, the nickel sulfate was shown to transiently affect pulmonary antitumoural immune defenses [149]. Chronic exposures to nickel sulfate hexahydrate result in cell toxicity and inflammation [19]. Moreover, a subchronic study demonstrated that nickel sulfate hexahydrate has a steep dose-response for toxicity and mortality [150]. Hence, although exposure to soluble nickel compounds, alone, may not provide the conditions necessary to cause cancer (i.e., the nickel (II) ion is not delivered to the target tissue in sufficient quantities in vivo), due to their toxicity, soluble nickel compounds may enhance the carcinogenic effect of other nickel compounds or cancer-causing agents by increasing cell proliferation. Cell proliferation, in turn, is required to convert DNA lesions into mutations and expand the mutated cell population, resulting in carcinogenesis.

With respect to non-malignant respiratory effects in humans, the evidence for soluble nickel salts being a causative factor for occupational asthma, while not overwhelming, is more suggestive than it is for other chemical forms of nickel. Such evidence arises mainly from a small number of case reports in the electroplating industry and nickel catalyst manufacturing [151-156]. Exposure to nickel sulfate can only be inferred in some of the cases where exposures have not been explicitly stated. Many of the plating solutions and, hence, aerosols to which some of the workers were exposed may have had a low pH. This latter factor may contribute to irritant effects which are not necessarily specific to nickel. In addition, potential for exposure to other sensitising metals, notably chromium and cobalt, may have occurred. On the basis of

the studies reported, the frequency of occupational asthma cannot be assessed, let alone the dose response determined. Despite these shortcomings, however, the role of soluble nickel as a possible cause of asthma should be considered.

Aside from asthma, the only other non-carcinogenic respiratory effect reported in nickel workers is that of fibrosis. Evidence that soluble nickel may act to induce pulmonary fibrosis at the radiological level comes from a study of nickel refinery workers that showed modest abnormalities in the chest x-rays of workers [20]. Berge and Skyberg identified a dose-response trend for 4 categories of cumulative exposure to soluble Ni. However, there was also evidence that other factors (e.g., age and tobacco consumption) were more reliable predictors of the cohort's incidence of radiographically-identified fibrosis. Thus, the odds ratio for the group with the highest cumulative exposure to soluble Ni lost statistical significance when it was adjusted for age, smoking, asbestos and sulphidic Ni exposure (OR = 2.24, 95% CI 0.82-6.16). The significance of these results for the clinical diagnosis of fibrosis remains to be determined as x-ray findings have been reported to not correlate well with functional diagnosis of lung fibrosis [157].

4.3.2 Dermal exposure: soluble nickel

Historically, risks for allergic contact nickel dermatitis have been elevated in workplaces where exposures to soluble nickel have been high. For example, nickel dermatitis was common in the past among nickel platers. However, due to improved industrial and personal hygiene practices, more recent reports of nickel sensitivity in workplaces such as the electroplating industry have been sparse. Schubert et al., [158] found only two nickel sensitive platers among 176 nickel sensitive individuals studied. A number of studies have shown nickel sulfate to be a skin sensitiser in animals, particularly in guinea pigs [159-162]. Dermal studies in animals suggest that sensitisation to soluble nickel (nickel sulfate) may result in cross sensitisation to cobalt [163] and that oral supplementation with zinc may lessen the sensitivity reaction of $NiSO_4$-induced allergic dermatitis [164]. Soluble nickel compounds should be considered skin sensitisers in humans and care should be taken to avoid prolonged contact with nickel solutions in the workplace.

Allergic contact dermatitis is the most prevalent effect of nickel in the general population. Epidemiological investigations have shown that prevalence of nickel allergy is approximately 14.5% of the general population in several European countries [165]. Significantly decreased prevalence of nickel allergy has been observed in the younger European population, born since the institution of regulation of nickel release from consumer articles used for piercing and intended for direct and prolonged skin contact in the late 1990s (the EU nickel directive), with this Directive being included in the European REACH regulation as entry 27 in Annex XVII in 2009 [166].

4.3.3 Other exposures: soluble nickel

The evidence for the lack of oral carcinogenicity of nickel substances is conclusive. In a study by Heim et al.[137], nickel sulfate hexahydrate was administered daily to rats by oral gavage for 2 years (104 weeks) at exposure levels of 10, 30 and 50 mg $NiSO_4 \bullet 6H_2O$/kg. This treatment produced a statistically significant reduction in body weight of male and female rats, compared to controls, in an exposure-related fashion at 30 and 50 mg/kg/day. An exposure-dependent increase in mortality was observed in female rats. However, daily oral administration of nickel sulfate hexahydrate did not produce an exposure-related increase in any common tumour type or an increase in any rare tumours. This study achieved sufficient toxicity to reach the Maximum Tolerated Dose (MTD) while maintaining a sufficiently high survival rate to allow evaluation for carcinogenicity. The study by Heim et al.[137] demonstrates that nickel sulfate hexahydrate does not have the potential to cause carcinogenicity by the oral route of exposure. Data from this and other studies demonstrate that inhalation is the only route of exposure that may cause concern for cancer in association with nickel compound exposures.

Unlike other species of nickel, oral exposure to soluble nickel (II) ions occurs from drinking water (and from bioavailable nickel present in food). Data from both human and animal studies show that absorption of nickel from food and water is generally low (1-30%), depending on the fasting state of the subject, with most of the nickel excreted in feces [167]. In humans, effects of greatest concern for ingested nickel are those produced in the kidney, possible reproductive effects, and the potential for soluble nickel to exacerbate nickel dermatitis following oral provocation.

Several researchers have examined the evidence of nephrotoxicity related to long-term exposures to soluble nickel in electroplating, electrorefining and chemical workers [168-171]. These workers not only would have been exposed to soluble nickel in their food and water, but also in the workplace air which they breathed. Wall and Calnan [170] found no evidence of renal dysfunction among 17 workers in an electroplating plant. Likewise, Sanford and Nieboer [169], in a study of 26 workers in electrolytic refining plants, concluded that nickel, at best, might be classified as a mild nephrotoxin. In the Sunderman and Horak study [168] and the Vyskočil et al., study [171], elevated markers of renal toxicity (e.g., ß2 microglobulin) were observed, but only spot urinary nickel samples were taken. The chronic significance of these effects is uncertain. In addition, nickel exposures were quite high in these workers (up to 13 mg Ni/m^3 in one instance), and certainly not typical of most current occupational exposures to soluble nickel. Severe proteinuria and other markers of significant renal disease that have been associated with other nephrotoxicants (e.g., cadmium) have not been reported in nickel workers, despite years of biological monitoring and observation. However, a 2020 case-control study suggested an association, albeit tenuous, between chronic, low dose environmental exposure to nickel and acute mesoamerican nephropathy [172]. In animals, kidney toxicity was observed 28 days after gavage treatment of mice with 30 mg/kg nickel chloride [173] and in rats, kidney damage was observed 20 days after intraperitoneal injection of 20 mg/kg bw/day nickel [174].

In regard to reproductive effects, there is some evidence in humans to indicate that absorbed nickel may be able to move across the placenta into fetal tissue [175-177]. An early study of Russian nickel refinery workers purported to show evidence of spontaneous abortions, stillbirths, and structural malformations in babies born to female workers at that refinery [178]. Concerns about the reliability of this study prompted a more thorough and well-conducted epidemiology investigation of the reproductive health of the Russian cohort that was also important for another reason. Specifically, the nickel refineries in this region are the only places worldwide where enough female nickel refinery workers exist to perform an epidemiological survey of reproductive performance at relatively high nickel exposures. In order to accomplish this task, the researchers constructed a birth registry for all births occurring in the region during the period of the study. They also reconstructed an exposure matrix for the workers at the refinery so as to be able to link specific pregnancy outcomes with occupational exposures. The study culminated in a series of manuscripts by A. Vaktskjold et al. [179-184] describing the results of the investigation. The study demonstrated that nickel exposure was not correlated with adverse pregnancy outcome for 1) male newborns with genital malformations, 2) spontaneous abortions, 3) small-for-gestational-age newborns, or 4) musculosketal effects in newborns of female refinery workers exposed to nickel. The lack of a "small-for-gestational-age" and "male genital malformation" findings are considered "sentinel" effects (i.e., sensitive endpoints) for reproductive toxicity in humans. These manuscripts showed no correlation between nickel exposure and observed reproductive impairment. These are important results as spontaneous abortion in humans would most closely approximate the observation of perinatal lethality associated with nickel exposure in rodents.

While the work by Vaktskjold et al. [181-184] is important in demonstrating that any risk of reproductive impairment from nickel exposure is exceedingly small, it should be noted that it is not possible to find women whose occupational nickel exposure persisted throughout their pregnancies until birth. Generally, fetal protection policies require removal of pregnant women from jobs with exposures to possible reproductive toxicants. Therefore, it cannot be concluded that occupational exposure to nickel compounds during pregnancy present no risk, only that any risk is exceedingly small.

With respect to animal studies, a variety of developmental, reproductive, and teratogenic effects have been reported in animals exposed mainly to soluble nickel via oral and parenteral administration [177]. However, factors such as high doses, relevance of routes of exposure, avoidance of food and water, lack of statistical significance, and parental mortality have confounded the interpretation of many of the results [177, 185]. No malformations (i.e., teratogenesis) were identified in a rat prenatal developmental toxicity study with nickel chloride at the maximum tolerated dose of 42 mg Ni/kg bw/day [186, 187], but nickel chloride was shown to cause malformations (e.g., microphthalmia) in a prenatal developmental toxicity study in mice at 46 mg/kg bw/day and other teratogenic effects were evident at higher doses [188].

In the most recent and reliable reproductive study conducted to date, rats were exposed to various concentrations of nickel sulfate hexahydrate by gavage [189, 190]. In the 1-generation range finding study, evaluation of post-implantation/perinatal lethality among the offspring of the treated parental rats (i.e., number of pups conceived minus the number of live pups at birth) showed statistically significant increases at the 6.6 mg Ni/kg/day exposure level and questionable increases at the 2.2 and 4.4 mg Ni/kg/day levels. The definitive 2-generation study demonstrated that these effects were not evident at concentrations up to 1.1 mg Ni/kg/day soluble nickel. Based on these studies a BMDL10 or BMDL5 of 1.3 or 1.8 mg Ni/kg/day were calculated by EFSA [7] and Haber et al [191], respectively. No nickel effects on fertility, sperm quality, estrous cycle and sexual maturation were found in these studies [189, 190].

Nickel dermatitis via oral exposure only occurs in individuals already sensitised to nickel via dermal contact, and in only a very small portion of nickel-sensitised individuals. Studies suggest that only a minor number of nickel sensitive patients react to oral doses below 1.25 mg of nickel (~20 µg Ni/kg). These doses are in addition to the normal dietary nickel intake (~160 µg Ni/day). Systemically induced flares of dermatitis have been reported after oral challenge of nickel-sensitive women with 0.5-5.6 mg of nickel as nickel sulfate administered in a lactose capsule [192]. At the highest nickel dose (5.6 mg), there was a positive reaction in majority of the subjects; at 0.5 mg, only a few persons responded with flares. Responses to oral doses of 0.4 or 2.5 mg of nickel did not exceed responses in subjects given placebos in double-blind studies [193, 194]. The Lowest Observed Adverse Effects Level (LOAEL) for exacerbation of nickel dermatitis symptoms in nickel-sensitised individuals established by EFSA in their Update of the risk assessment of nickel in food and drinking water [7] was 4.3 µg Ni/kg body weight (assuming a body weight of 70 kg), based on the study by Jensen et al. [195]. For nickel-sensitised individuals who are susceptible to orally-induced nickel dermatitis, a low nickel diet or oral hyposensitisation have been investigated. Various low nickel diets have been developed, providing lists of foods to avoid and to eat based on nickel content [196, 197]. Oral hyposensitisation to nickel using nickel sulphate has also been demonstrated to improve dermatitis symptoms in nickel-sensitised individuals in multiple studies [198-201].

Conversely, oral exposure to nickel in non-nickel-sensitised individuals has been shown to provide tolerance to future dermal nickel sensitisation. Observations first made in animal experiments [202] and correlations obtained from studies of human cohorts [203] led to the hypothesis that nickel hypersensitivity reactions may be prevented by prior oral exposure to nickel if long-term, low-level antigenic contact occurs in the non-sensitised organism. Studies that followed van der Burg's initial observation of induced nickel tolerance in humans have repeatedly confirmed the occurrence of this phenomenon both in humans [204-208] and animals [209, 210]. Suppression of dermal nickel allergic reactions can also be achieved in sensitised individuals [201].

4.4 OXIDIC NICKEL

The term "oxidic nickel" includes nickel (II) oxides, nickel (III) oxides, possibly nickel (IV) oxides and other non-stochiometric entities, complex nickel oxides (including spinels in which other metals such as copper, chromium, or iron are present), silicate oxides (garnierite), hydrated oxides, hydroxides, and, possibly, carbonates or basic carbonates which are subject to various degrees of hydration. Therefore, for the purposes of this document they will be considered together.

Oxidic nickel is used in many industrial applications and will be present in virtually every major nickel industry sector. Nickel oxide sinter is often the end product in the roasting of nickel sulfide concentrates. It is used as charge to produce wrought stainless steel and other alloy materials. It is also used in cast stainless steel and nickel-based alloys. Commercially available nickel oxide powders are used in the electroplating industry, for catalysis preparation, and for other chemical applications. Black nickel oxide and hydroxide are used in the production of electrodes for nickel-cadmium batteries utilised in domestic markets and also in large power units. Complex nickel oxides are used in oil refining and ceramic magnets [211, 212].

Like the previously discussed nickel species, inhalation of oxidic nickel compounds is the route of exposure of greatest toxicological concern in occupational settings. Unlike the former species of nickel, however, dermal exposures to oxidic nickel are believed to be of little consequence to nickel workers. While no data are directly available on the

effects of oxidic nickel compounds on skin, due to their low water solubility, very low absorption of nickel through the skin is expected.

4.4.1 Inhalation exposure: oxidic nickel

The critical health effect of interest in relation to occupational exposure to oxidic nickel is, again, respiratory cancer. Unlike metallic nickel, which does not appear to be carcinogenic, there is evidence for the carcinogenicity of certain oxidic nickel compounds even though there is still some uncertainty regarding the forms of oxidic nickel that induce tumourigenic effects. Although oxidic nickel is present in most major industry sectors, it is of interest to note that epidemiological studies have not consistently implicated all sectors as being associated with respiratory cancer. Indeed, excess respiratory cancers have been observed only in refining operations in which nickel oxides were produced during the refining of sulfidic ores and where exposures to oxidic nickel were relatively high (> 5 mg Ni/m^3) [24]. At various stages in this process, nickel-copper oxides may have been formed. In contrast, no excess respiratory cancer risks have been observed in workers exposed to lower levels (< 2 Ni/m^3) of oxidic nickel free of copper during the refining of lateritic ores or in the nickel-using industry.

Specific operations where oxidic nickel was present and showed evidence of excess respiratory cancer risk include refineries in Kristiansand, Norway, Clydach, Wales, and Copper Cliff and Port Colborne, Ontario, Canada. In all instances, workers were exposed to various combinations of sulfidic, oxidic, and soluble nickel compounds. Nevertheless, conclusions regarding the carcinogenic potential of oxidic nickel compounds have been gleaned by examining those workers predominantly exposed to oxidic nickel.

In the case of Kristiansand, this has been done by examining workers in the roasting, smelting and calcining department [24] and by examining all workers by cumulative exposure to oxidic nickel [24, 127]. In the overall cohort, there was evidence to suggest that long-term exposure (≥15 years) to oxidic nickel (mainly nickel-copper oxides at concentrations of 5 mg Ni/m^3 or higher) was related to an excess of lung cancer. There was also some evidence that exposure to soluble nickel played a role in increasing cancer risks in these workers (see Section 5.3). The effect of cigarette smoking has also been examined in these workers [127, 213], with the Grimsrud [213] study showing a multiplicative effect (i.e., interaction) between cigarette smoking and exposure to nickel. Evidence of excess nasal cancers in this group of workers has been confined to those employed prior to 1955. This evidence suggests that oxidic nickel has been a stronger hazard for nasal cancer than soluble nickel, as 12 cases (0.27 expected) out of 32 occurred among workers exposed mostly to nickel oxides.

In the Welsh and Canadian refineries, workers exposed to some of the highest levels (10 mg Ni/m^3 or higher) of oxidic nickel included those working in the linear calciners and copper and nickel plants (Wales) and those involved in sintering operations in Canada. In Wales, oxidic nickel exposures were mainly to nickel-copper oxides or impure nickel oxide; in Canada, exposures were mainly to high-temperature nickel oxide with lesser exposure to nickel-copper oxides. Unfortunately, in the latter case, oxidic exposures were completely confounded by sulfidic nickel exposures, making it difficult to distinguish between the effects caused by these two species of nickel. Both excess lung and nasal cancer risks were seen in the Welsh and Canadian workers [24, 129, 132].

In contrast to the above refinery studies, studies of workers mining and smelting lateritic ores (where oxidic nickel exposures would have been primarily to silicate oxides and complex nickel oxides free of copper) have shown no evidence of nickel-related respiratory cancer risks. Studies by Goldberg et al. [214, 215] of smelter workers in New Caledonia showed no evidence of increased risk of lung or nasal cancer at estimated exposures of 2 mg Ni/m^3 or less. Likewise, in another study of smelter workers in Oregon, there was no evidence of excess nasal cancers [24]. While there were excess lung cancers, these occurred only in short-term workers, not long-term workers. Hence, there was no evidence to suggest that the lung cancers observed were related to the low concentrations (≤ 1 mg Ni/m^3) of oxidic nickel to which the men were exposed [24].

In nickel-using industries, the evidence for respiratory cancers has also largely been negative. As noted in previous sections (Sections 4.1 and 4.2), most studies on stainless steel and nickel alloy workers that would have experienced some level of exposure to oxidic nickel have shown no significant

nickel-related excess risks of respiratory cancer [14, 15, 85, 86, 114-118, 121, 122]. In Swedish nickel-cadmium battery workers, there is some evidence of an increased incidence of nasal cancers, but it is not clear whether this is due to exposure to nickel hydroxide, cadmium oxide, or a combination of both [216]. In addition, little is known about the previous employment histories of these workers. It is, therefore, not clear whether past exposures to other potential nasal carcinogens may have contributed to the nasal cancers observed in these workers. In contrast, no nickel-related increased risk for lung cancer has been found in these or other nickel-cadmium battery workers [216-220].

From the overall epidemiological evidence, it is possible to speculate that the composition of oxidic nickel associated with an increase of lung or nasal cancer may primarily be nickel-copper oxides produced during the roasting and electrorefining of sulfidic nickel-copper mattes. However, careful scrutiny of the human data also reveals that high respiratory cancer risks occurred in sintering operations-where exposures to nickel-copper oxides would have been relatively low-and, possibly, in nickel-cadmium battery workers, where oxidic exposures would predominantly have been to nickel hydroxide. In addition to the type of oxidic nickel, the level to which nickel workers were exposed must also be taken into consideration. Concentrations of oxidic nickel in the high-risk cohorts (those in Wales, Norway, and Port Colborne and Copper Cliff, Canada) were considerably higher than those found in New Caledonia, Oregon, and most nickel-using industries. In the case of the nickel-cadmium battery workers, the early exposures that would have been critical to the induction of nasal cancers of long latency were believed to have been relatively high (> 2 mg Ni/m^3). Hence, it may be that there are two variables—the physicochemical nature of the oxide and the exposure level—that contribute to the differences seen among the various cohorts studied.

Animal data shed some light on the matter. In the previously mentioned NTP studies, nickel oxide was administered to rats and mice in a two-year carcinogenicity bioassay [21]. The nickel oxide used was a green, high-temperature nickel oxide calcined at 1,350 °C; it was administered to both rats and mice for 6 hrs/day, 5 days/week for 2 years. Rats were exposed to concentrations of 0, 0.5, 1.0, or 2.0 mg Ni/m^3. These concentrations are equivalent to 0.2 to 3.2 mg Ni/m^3 inhalable workplace aerosol after adjusting for particle size differences and animal to human extrapolation [43, 135, 136]. After two years, no increased incidence of tumours was observed at the lowest exposure level in rats (equivalent to 0.23-0.81 mg Ni/m^3 inhalable). At the intermediate and high concentrations, 12 out of 106 rats and 9 out of 106 rats, respectively, presented with either adenomas or carcinomas. On the basis of these results, the NTP concluded that there was some evidence of carcinogenic activity in rats. In contrast, there was no evidence of treatment-related tumours in male mice at any of the doses administered (1.0, 2.0 and 4.0 mg Ni/m^3) and only equivocal evidence in female mice exposed to 1.0 but not 2.0 or 4.0 mg Ni/m^3.

Carcinogenic evidence for other oxidic nickel compounds comes from animal studies using routes of exposure that are not necessarily relevant to man (i.e. intratracheal instillation, injection). In these studies, nickel-copper oxides appear to be as potent as nickel subsulfide in inducing tumours at injection sites [22]. There is, however, no strong evidence to indicate that black (low temperature) and green (high temperature) nickel oxides differ substantially with regard to tumour-producing potency. Some forms of both green and black nickel oxide produce carcinogenic responses, while other forms have tested negative in injection and intratracheal studies [22, 95, 221-226].

On the whole, comparisons between human and animal data suggest that certain oxidic nickel compounds at high concentrations may increase respiratory cancer risks and that these risks are not necessarily confined to nickel-copper oxides. However, there is no single unifying physical characteristic that differentiates oxidic nickel compounds with respect to biological reactivity or carcinogenic potential. Some general physical characteristics which may be related to carcinogenicity include: particle size ⩽ 5 µm, a relatively large particle surface area, presence of metallic or other impurities and/or amount of Ni (II). Phagocytosis appears to be a necessary, but not sufficient condition for carcinogenesis. Solubility in biological fluids will also affect how much nickel ion is delivered to target sites (i.e., cell nucleus) [144].

The ability of particles to generate oxygen radicals may also contribute to their carcinogenic potentia[l [227].

With respect to non-malignant respiratory effects, oxidic nickel compounds do not appear to be respiratory sensitisers. Based upon numerous epidemiological studies of nickel-producing workers, nickel alloy workers, and stainless steel workers, there is little indication that exposure to oxidic nickel results in excess mortality from chronic respiratory disease [14, 15, 85-87, 114, 121, 133]. In the few instances where excess risks of non-malignant respiratory disease did appear- for example, in refining workers in Wales- the excesses were seen only in workers with high nickel exposures (> 10 mg Ni/ m^3), in areas that were reported to be very dusty. With the elimination of these dusty conditions, the risk that existed in these areas seems largely to have disappeared by the 1930s [129].

In a study using radiographs of nickel sinter plant workers exposed to very high levels of oxidic and sulfidic nickel compounds (up to 100 mg Ni/m^3), no evidence that oxidic or sulfidic nickel dusts caused a significant fibrotic response in workers was reported [228]. In a study of Norwegian nickel refinery workers, an increased risk of pulmonary fibrosis was found in workers with cumulative exposure to sulfidic and soluble, but not oxidic nickel [20]. The previously mentioned Kilburn et al.[101] and Sobaszek et al.[102] studies (see Section 5.1.1) showed mixed evidence of chronic effects on pulmonary function in stainless steel welders. Broder et al. [229] showed no differences in pulmonary function of nickel smelter workers versus controls in workers examined for short periods of time (1 week); however, there were some indicators of a healthy worker effect in this cohort which may have resulted in the negative findings. Anosmia (loss of smell) has been reported in nickel-cadmium battery workers, but most researchers attribute this to cadmium toxicity [230].

Animal studies have shown various effects on the lung following relatively short periods of exposure to high levels of nickel oxide aerosols [44, 45, 145, 147, 148]. Effects have included increases in lung weights, increases in alveolar macrophages, fibrosis, and enzymatic changes in alveolar macrophages and lavage fluid. Studies of repeated inhalation exposures to nickel oxide (ranging from two to six months) have shown that exposure to nickel oxide may impair particle lung clearance [51]. Chronic exposures to a high-temperature nickel oxide resulted in statistically significant inflammatory changes in lungs of rats and mice at 0.5 mg Ni/m^3 and 1.0 mg Ni/m^3, respectively [21]. These values correspond to workplace exposures up to 1.6 mg Ni/m^3 [43]. At present, the significance of impaired clearance seen in nickel oxide-exposed rats and its relationship to carcinogenicity is unclear [144].

4.5 SULFIDIC NICKEL

Data relevant to characterising the adverse health effects of nickel "sulfides" in humans arises almost exclusively from processes in the refining of nickel. Exposures in the refining sector should not be confused with those in mining, where the predominant mineral from sulfidic ores is pentlandite [(Ni, Fe)9S8]. Pentlandite is very different from the nickel subsulfides and sulfides found in refining. Although a modest lung cancer excess has been found in some miners [24], this excess has been consistent with that observed for other hard-rock miners of non-nickel ores [231]. This, coupled with the fact that millers have not presented with statistically significant excess respiratory cancer risks, suggests that the lung cancer seen in miners is not pentlandite-related [24]. Pentlandite has not been shown to be carcinogenic in hamsters intratracheally instilled with the mineral over their lifetimes [125], although this study was not conclusive. Therefore, for purposes of this document, any critical health effects discussed relative to "sulfidic nickel" pertains mainly to nickel sulfides (NiS) and subsulfide (Ni_3S_2).

Like oxidic nickel, inhalation of sulfidic nickel compounds is the route of exposure of greatest toxicological concern in occupational settings. No relevant studies of dermal exposure have been conducted on workers exposed to sulfidic nickel. Because exposures to sulfidic and oxidic nickel compounds have often overlapped in refinery studies, it has sometimes been difficult to separate the effects of these two nickel species from each other. Overwhelming evidence of carcinogenicity from animal studies, however, has resulted in the consistent classification of sulfidic nickel as a "known carcinogen" by many scientific bodies [78, 232-234]; refer to section 5.0 on Hazard Classification below. The evidence is discussed below.

4.5.1 Inhalation exposure: sulfidic nickel

The evidence for the carcinogenicity of sulfidic compounds lies mainly in sinter workers from Canada. These workers were believed to have been exposed to some of the highest concentrations of nickel subsulfide (15-35 mg Ni/m^3) found in the producing industry. They exhibited both excess lung and nasal cancers [24, 132]. Unfortunately, as noted in Section 4.4, these workers were also concomitantly exposed to high levels of oxidic nickel, making it difficult to distinguish between the effects caused by these two species of nickel.

Further evidence for the respiratory effects of sulfidic nickel can be gleaned from nickel refinery workers in Clydach, Wales. Specifically, workers involved in cleaning a nickel plant were exposed to some of the highest concentrations of sulfidic nickel at the refinery (18 mg Ni/m^3) and demonstrated a high incidence of lung cancer after 15 years or more since their first exposure. Analysis by cumulative exposure showed that Clydach workers with high cumulative exposures to sulfidic nickel and low level exposures to oxidic and soluble nickel exhibited higher lung cancer risks than workers who had low cumulative exposures to all three nickel species combined [24]. Somewhat perplexing, however, was that the risk of developing lung or nasal cancer in this cohort was found primarily in those employed prior to 1930, although estimated levels of exposure to sulfidic nickel were not significantly reduced until 1937. This suggested that other factors (e.g., possible presence of arsenic in sulfuric acid that resulted in contaminated mattes) could have contributed to the cancer risk seen in these early workers [235]. In another cohort of refinery workers in Norway, increased cumulative exposures to sulfidic nickel did not appear to be related to lung cancer risk, although workers in this latter cohort were not believed to be exposed to concentrations of sulfidic nickel greater than about 2 mg Ni/m^3 [24].

Because of the difficulty in separating the effects of sulfidic versus oxidic nickel in human studies, researchers have often turned to animal data for further guidance. Here, the data unequivocally point to nickel subsulfide as being carcinogenic. In the chronic inhalation bioassay conducted by the NTP [134], rats and mice were exposed for two years to nickel subsulfide at concentrations as low as 0.11 and 0.44 mg Ni/m^3, respectively. These concentrations correspond to approximately 0.5-6.6 mg Ni/m^3 workplace aerosol after accounting for particle size differences and animal to human extrapolation [43, 135, 136]. After two years exposure, there was clear evidence of carcinogenic activity in male and female rats, with a dose-dependent increase in lung tumour response. No evidence of carcinogenic activity was detected in male or female mice. No nasal tumours were detected in rats or mice, but various nonmalignant lung effects were seen. This study was in agreement with an earlier inhalation study which also showed evidence of carcinogenic activity in rats administered nickel subsulfide [236]. These studies, in conjunction with numerous other studies on nickel subsulfide -although, not all conducted by relevant routes of exposure show nickel subsulfide to be a potent inducer of tumours in animals [134].

With respect to non-carcinogenic respiratory effects, a number of animal studies have reported on the inflammatory effects of nickel subsulfide on the lung [44, 45, 134, 145, 237, 238]. These have been to both short- and long-term exposures and have included effects such as increased enzymes in lavage fluid, chronic active inflammation, focal alveolar epithelial hyperplasia, macrophage hyperplasia and fibrosis. For sulfidic nickel, the levels at which inflammatory effects in rats are seen are lower than for oxidic nickel, and similar to those required to see effects with nickel sulfate hexahydrate.

The evidence for non-malignant respiratory effects in workers exposed to sulfidic nickel has been mixed. Mortality due to non-malignant respiratory disease has not been observed in Canadian sinter workers [133]. This is in agreement with the radiographic study by Muir et al. [228] that showed that sinter plant workers exposed to very high levels of oxidic and sulfidic nickel compounds did not exhibit significant fibrotic responses in their lungs. In contrast (as noted in section 4.4), excess risks of non-malignant respiratory disease did appear in refining workers in Wales with high exposures to insoluble nickel (> 10 mg Ni/m^3). With the elimination of the very dusty conditions that likely brought about such effects, the risk of respiratory disease disappeared by the 1930s in this cohort [129]. In a 2003 study of Norwegian nickel refinery workers, a trend in increased risk of pulmonary fibrosis at the radiological level with cumulative exposure to sulfidic nickel was found [20]. Increased odds ratios were seen at lower cumulative exposures of sulfidic than of soluble nickel compounds. As previously noted, the significance of these results for the clinical diagnosis of fibrosis is not certain.

The mechanism for the carcinogenicity of sulfidic nickel (as well as other nickel compounds) has been discussed by a number of researchers [141-144]. Relative to other nickel compounds, nickel subsulfide may be the most efficient at inducing the heritable changes needed for the cancer process. In vitro, sulfidic nickel compounds have shown a relatively high efficiency at inducing genotoxic effects such as chromosomal aberrations and cell transformation as well as epigenetic effects such as increases in DNA methylation [2]. In vivo, nickel subsulfide is likely to be readily endocytised and dissolved by the target cells resulting in efficient delivery of nickel (II) to the target site within the cell nucleus [239, 240]. In addition, nickel subsulfide has relatively high solubility in biological fluids which could result in the release of the nickel (II) ion resulting in cell toxicity and inflammation. Chronic cell toxicity and inflammation may lead to a proliferation of target cells. Since nickel subsulfide is the nickel compound most likely to induce heritable changes in target cells, proliferation of cells that have been altered by nickel subsulfide may be one of the mechanisms behind the observed carcinogenic effects [144].

Because of these effects, sulfidic nickel compounds appear to present the highest respiratory carcinogenic potential relative to other nickel compounds. The clear evidence of respiratory carcinogenicity in animals administered nickel subsulfide by inhalation, together with mechanistic considerations, indicate that the association of exposures to sulfidic nickel and lung and nasal cancer in humans is likely to be causal [142].

4.6 NICKEL CARBONYL

Unlike other nickel species, nickel tetracarbonyl (commonly referred to as nickel carbonyl) can be found as a gas or as a volatile liquid. It is mainly found as an intermediate in the carbonyl process of refining. By virtue of its toxicokinetics, it is the one nickel compound for which short-term inhalation exposures are the most critical. With respect to dermal exposures, although biologically possible, absorption through the skin has not been demonstrated in humans, nor have any dermal studies on animals been conducted. The discussion, below, therefore, focuses on inhalation exposures.

4.6.1 Inhalation exposure: nickel carbonyl

Nickel carbonyl delivers nickel atoms to the target organ (lung) in a manner that is probably different from that of other nickel species. After nickel carbonyl inhalation, removal of nickel from the lungs occurs by extensive absorption and clearance. The alveolar cells are covered by a phospholipid layer, and it is the lipid solubility of nickel carbonyl vapor that is of importance in its penetration of the alveolar membrane. Extensive absorption of nickel carbonyl after respiratory exposure has been demonstrated. Highest nickel tissue concentrations after inhalation of nickel carbonyl have been found in the lungs, with lower concentrations in the kidneys, liver, and brain. Urinary excretion of nickel increases in direct relationship to exposure to nickel carbonyl [241].

Acute toxicity is of paramount importance in controlling risks associated with exposure to nickel carbonyl. The severe toxic effects of exposure to nickel carbonyl by inhalation have been recognised for many years. The clinical course of nickel carbonyl poisoning involves two stages. The initial stages are characterised by headache, chest pain, weakness, dizziness, nausea, irritability, and a metallic taste in the mouth [242-244]. There is then generally a remission lasting 8-24 hrs followed by a second phase characterised by a chemical pneumonitis but with evidence, in severe cases, of cerebral poisoning. Common clinical signs in severe cases include tachypnoea, cyanosis, tachycardia, and hyperemia of the throat [245]. Hematological results include leukocytosis. Chest x-rays in some severe cases are consistent with pulmonary edema or pneumonitis, with elevation of the right hemidiaphragm. Shi [245] reported three patients with ECG changes of toxic myocarditis. The second stage reaches its greatest severity in about four days, but convalescence is often protracted. In ten patients with nickel carbonyl poisoning, there were initial changes in pulmonary function tests consistent with acute interstitial lung disease [244]. However, these results returned to normal after several months.

The mechanism of the toxic action of nickel carbonyl has never been adequately explained, and the litreature on the topic is dated [242]. Some researchers have held the view that nickel carbonyl passes through the pulmonary epithelium unchanged [246]. However, as nickel carbonyl is known to be reactive to a wide variety of nitrogen and phosphorous compounds, as well as oxidising agents, it is not unreasonable to assume that it is probably reactive with biological materials [242]. It is known to inhibit the utilisation of adenosine triphosphate (ATP) in liver cells and brain

capillaries [247, 248]. Following acute exposure to nickel carbonyl, sections of lung and liver tissue have been shown to contain a granular, brownish-black, non iron-staining pigment [249]. It has not been established, however, whether these dark granules represent metallic nickel or the compound itself. Sunderman et al.[249] proposed that nickel carbonyl may dissociate in the lung to yield metallic nickel and carbon monoxide, each of which may act singly, or in combination with each other, to induce toxicity.

Evidence of chronic effects at levels of exposure below those which produce symptomatic acute toxicity is difficult to find. The only epidemio¬logical study specifically investigating the possible carcinogenic effect of nickel carbonyl [243] was limited in power and confounding factors–such as exposures to certain oxidic and sulfidic nickel species–thereby clouding any interpretation regarding the contribution of nickel carbonyl, per se, to the carcinogenic risk.

Like humans, the lung is the primary target organ from exposure to nickel carbonyl in animals, regardless of route of administration, and effects in animals are similar to those observed in cases of human exposure. Experimental nickel carbonyl poisoning in animals has shown that the most severe pathological reactions are in the lungs with effects in brain and adrenal glands as well. Acute toxicity is of greatest concern. The LD50 in rats is 0.20 mg Ni/litre of air for 15 minutes or 0.12 mg/rat. Effects on the lung include severe pulmonary inflammation, alveolar cell hyperplasia and hypertrophy, and foci of adenomatous change.

With respect to carcinogenic effects, studies on the carcinogenicity of nickel carbonyl were performed prior to present day standardised testing protocols, but because of the extreme toxicity of this material, further studies are not likely to be conducted. Studies by Sunderman et al.,[249] and Sunderman and Donnelly [250] have linked nickel carbonyl to respiratory cancer, but high rates of early mortality in these studies preclude any definitive conclusions regarding the carcinogenicity of nickel carbonyl. Possible developmental toxicity effects are also of concern for nickel carbonyl. In a series of studies, Sunderman et al.[251, 252] demonstrated that nickel carbonyl, administered by inhalation (160-300 mg Ni/m^3) or injection (before or a few days after implantation) produced various types of fetal malformations in hamsters and rats.

5. HAZARD CLASSIFICATIONS

The United States Occupational Safety and Health Administration (OSHA) defines hazard classification as "the process of evaluating the full range of available scientific evidence to determine if a chemical is hazardous, as well as to identify the level of severity of the hazardous effect" [253]. The human health hazard classes discussed here are acute toxicity, skin corrosion/irritation, serious eye damage/eye irritation, respiratory or skin sensitisation, germ cell mutagenicity, carcinogenicity, reproductive toxicity, and specific target organ toxicity. Not all nickel substances have the same hazard classification categories. The hazard classifications of the different international agencies, where available, are listed in the various hazard classes. While there is generally correspondence between the UN GHS and EU CLP hazard categories for nickel substances, there are a few hazard categories where the classifications differ in the two regulations. Where differences exist between the EU CLP and UN GHS hazard classifications, they have been highlighted. The classifications in the subsequent sections are provided as examples for the nickel substances registered in the European Union REACH regulation. The Nickel Institute maintains a website of the updated GHS, EU and country-specific hazard classifications of nickel substances at www.ghs.nickelinstitute.org.

5.1 ACUTE TOXICITY

Some nickel compounds are classified for acute toxicity by the oral and/or inhalation exposure routes. In the European Union Classification, Labelling and Packaging (EU CLP) regulation, nickel metal and nickel compounds are not classified as acutely toxic via the dermal route. Additionally, nickel metal and nickel oxide are not classified as acutely toxic via the oral or inhalation routes. Most of the nickel compounds are classified in the EU CLP as Acute Tox. 4 via inhalation, except nickel chloride which is classified as Acute Tox. 3. Nickel hydroxycarbonate is classified in the EU CLP as Acute Tox 4 via inhalation but the Nickel Institute self-classifies it as Acute Tox 2 via inhalation. The table below lists the acute toxicity classifications of selected nickel compounds via the oral and inhalation routes.

5.2 SKIN CORROSION/IRRITATION & SERIOUS EYE DAMAGE/EYE IRRITATION

Acute dermal corrosion/irritation are usually conducted in rabbits using OECD Guideline 404. Based on negative skin corrosion/irritation studies, nickel metal, nickel oxide, nickel sulfide, nickel subsulfide and nickel acetate are not classified in the EU CLP as skin irritants; nickel sulfamate is also not classified in the EU CLP but it is classified as Skin Mild Irrit. 3 by the UN GHS. In the EU CLP, nickel sulfate, nitrate, chloride, dihydroxide, and hydroxycarbonate are classified as Skin Irrit. 2 and nickel bis(dihydrogen phosphate) is classified as Skin Corr 1B . Nickel nitrate and nickel bis(dihydrogen phosphate) are classified as Eye Damage 1 and nickel hydroxycarbonate is classified as Eye Irrit. 2. Nickel metal and the other nickel compounds are not classified for serious damage/eye irritation in the EU CLP.

5.3 RESPIRATORY OR SKIN SENSITISATION

Nickel metal and many nickel compounds are classified as skin sensitisers in the EU CLP. The REACH registered

Table 5-1 Acute toxicity (oral & inhalation) classifications of selected nickel compounds

	EU CLP		UN GHS		Nickel Institute	
Substance	**Acute toxicity (Oral)**	**Acute toxicity (Inhal)**	**Acute toxicity (Oral)**	**Acute toxicity (Inhal)**	**Acute toxicity (Oral)**	**Acute toxicity (Inhal)**
Ni acetate	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4
Ni sulfate	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4
Ni nitrate	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4
Ni chloride	Acute tox 3	Acute tox 3	Acute tox 4	Acute tox 4	Acute tox 3	Acute tox 3
Ni sulfamate	Acute tox 4*	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4	Acute tox 4
Ni dihydroxide	Acute tox 4	Acute tox 4	Acute tox 5	Not classified	Acute tox 4	Acute tox 4
Ni hydroxycarbonate	Acute tox 4	Acute tox 4	Acute tox 5	Acute tox 2	Acute tox 4	Acute tox 2
Ni bis(dihydrogen phosphate)	Not classified	Not classified	Not classified	Not classified	Acute tox 4	Acute tox 4
Ni sulfide	Not classified	Not classified	Not classified	Acute tox 4	Not classified	Acute tox 4
Ni subsulfide	Not classified	Acute tox 4*	Not classified	Acute tox 4	Not classified	Acute tox 4
*No CLP Harmonized classification (self-classification)						

Table 5-3 Respiratory and skin sensitization classifications for selected nickel compounds

	EU CLP		UN GHS		Nickel Institute	
Substance	**Respiratory sensitization**	**Skin sensitization**	**Respiratory sensitization**	**Skin sensitization**	**Respiratory sensitization**	**Skin sensitization**
Ni acetate	Resp sens 1	Skin sens 1	Resp sens 1B	Skin sens 1A	Resp sens 1	Skin sens 1
Ni sulfate	Resp sens 1	Skin sens 1	Resp sens 1B	Skin sens 1A	Resp sens 1	Skin sens 1
Ni nitrate	Resp sens 1	Skin sens 1	Resp sens 1B	Skin sens 1A	Resp sens 1	Skin sens 1
Ni chloride	Resp sens 1	Skin sens 1	Resp sens 1B	Skin sens 1A	Resp sens 1	Skin sens 1
Ni sulfamate	Resp sens 1	Skin sens 1	Resp sens 1B	Skin sens 1A	Resp sens 1	Skin sens 1
Ni dihydroxide	Resp sens 1	Skin sens 1	Not classified	Not classified	Resp sens 1	Skin sens 1
Ni hydroxycarbonate	Resp sens 1	Skin sens 1	Not classified	Not classified	Resp sens 1	Skin sens 1
Ni bis (dihydrogen phosphate)	Resp sens 1	Skin sens 1	Not classified	Not classified	Resp sens 1	Skin sens 1
Ni sulfide	Not classified	Skin sens 1	Not classified	Skin sens 1	Not classified	Skin sens 1
Ni subsulfide	Not classified	Skin sens 1	Not classified	Skin sens 1	Not classified	Skin sens 1
Ni monoxide	Not classified	Not classified	Not classified	Skin sens 1	Not classified	Skin sens 1
Ni metal	Not classified	Skin sens 1	Not classified	Skin sens 1	Not classified	Skin sens 1

soluble nickel compounds, namely, nickel acetate, chloride, dihydroxide, dinitrate, sulfamate, sulfate and bis (dihydrogen phosphate) are classified as respiratory sensitisers but the insoluble nickel compounds, that is, nickel sulfide, subsulfide, oxide, as well as the metal are not classified as respiratory sensitisers. The table below lists the sensitisation classifications by the NI, CLP and GHS for some selected nickel compounds.

5.4 GERM CELL MUTAGENICITY

Nickel compounds are not mutagenic in bacterial mutation assays and are weak mutagens in in vitro mammalian cultured cells. In the 2018 European Chemicals Agency (ECHA) Risk Assessment Committee (RAC) opinion on occupational exposure limits of nickel and nickel compounds, the RAC affirmed that nickel compounds "are not directly mutagenic" but "induce genotoxic effects via different indirect mechanisms" after careful consideration of all the mutagenicity and genotoxicity evidence. In the EU CLP, the selected nickel compounds in Table 5.3, are classified as Muta 2 (suspected of causing genetic defects) with the exception of nickel oxide. Nickel metal is not classified as a mutagen in the EU CLP.

5.5 CARCINOGENICITY

Over the years, a number of organisations and international agencies have evaluated the evidence regarding the carcinogenic effects of various nickel substances, all with the intent of delineating the potential differences in the bioavailability and toxicity of various nickel species.

IARC classified nickel compounds as Group 1 carcinogens *(carcinogenic to humans)* and metallic nickel as Group 2B carcinogens *(possibly carcinogenic to humans)* [233].

The U. S. Environmental Protection Agency (U. S. EPA) classified nickel subsulfide and nickel refinery dust from pyrometallurgical sulfide nickel matte refineries as Group A carcinogens (human carcinogen), indicating that there is sufficient overall evidence that these forms of nickel are carcinogenic to humans [83]. The Agency also classified nickel carbonyl as a Group B2 (probable human carcinogen).

The American Conference of Governmental Industrial Hygienists (ACGIH) (a non-legislative organisation) has, since the late 1990's, classified the carcinogenicity of nickel and nickel compounds [254] as:

- A5 (Not suspected as a human carcinogen) for metallic nickel,
- A4 (Not classifiable as a human carcinogen) for soluble nickel,
- A1 (Confirmed human carcinogen) for insoluble nickel,
- no classification for nickel carbonyl.

In 2008, the Commission of the European Communities concluded an extensive evaluation of the human health and environmental effects of metallic nickel and a group of nickel compounds including nickel sulfate, nickel chloride, nickel nitrate, nickel carbonate, nickel sulfides (Ni_3S_2 and NiS) and nickel oxides (NiO, Ni_2O_3 and NiO_2). As a result of this hazard and risk assessment, a large number of nickel compounds (including all of the above) were classified as human carcinogens. This Category 1 carcinogen classification for nickel compounds was carried over to the current Classification Labelling and Packaging legislation. The nickel compounds carry the risk phrase, "May cause cancer by inhalation" which specifically eliminates the potential for carcinogenicity by other routes of exposure (e.g., oral). Nickel metal is classified as a Category 2 carcinogen under the CLP on the basis of limited evidence in human studies and in animal studies.

5.6 REPRODUCTIVE TOXICITY

Water-soluble and water-insoluble nickel compounds, and nickel metal do not carry harmonised classifications for fertility effects in the EU CLP. In the available epidemiological and animal studies, no fertility effects associated with nickel exposure have been observed. However, developmental toxicity effects have been observed in rodents with the water-soluble nickel sulfate and nickel chloride. Therefore, the water-soluble nickel compounds carry a harmonised Repr 1B classification in the EU CLP, and in the UN GHS, for developmental toxicity (perinatal mortality). Neither nickel metal nor the water-insoluble nickel compounds carry a harmonised classification in the EU CLP for developmental toxicity.

5.7 SPECIFIC TARGET ORGAN TOXICITY

A substance is classified under Specific Target Organ Toxicity (STOT) following acute exposure (Single Exposure, SE) or chronic exposure (Repeat Exposure, RE) if it produces toxic effects not addressed by any of the hazard classifications in the EU CLP or UN GHS. Nickel compounds, both water-soluble and water-insoluble, and nickel metal are classified as STOT RE 1 (due to respiratory tract toxicity following repeat exposures via inhalation) in the CLP. The selected nickel compounds in Table 5-1 and nickel metal are not classified as STOT following single exposure.

6. REFERENCES

1. Statista. *Mining, Metals & Minerals*. Nickel-Statistics & Facts 2021 [cited 2021 06/23/2021]; Available from: https://www.statista.com/topics/1572/nickel/#:~:text=World%20production%20of%20nickel%20in,%2C%20New%20Caledonia%2C%20and%20Russia.

2. Buxton, S., et al., *Concise review of nickel human health toxicology and ecotoxicology.* Inorganics, 2019. **7**(7): p. 89.

3. Seilkop, S.K., et al., *Respiratory cancer mortality and incidence in an updated cohort of Canadian nickel production workers.* Arch Environ Occup Health, 2017. **72**(4): p. 204-219.

4. Sivulka, D.J. and S.K. Seilkop, *Reconstruction of historical exposures in the US nickel alloy industry and the implications for carcinogenic hazard and risk assessments.* Regul Toxicol Pharmacol, 2009. **53**(3): p. 174-85.

5. Hughson, G.W., K.S. Galea, and K.E. Heim, *Characterization and assessment of dermal and inhalable nickel exposures in nickel production and primary user industries.* Ann Occup Hyg, 2010. **54**(1): p. 8-22.

6. CSR, *Nickel Metal Chemical Safety Report*. 2019, Available on ECHA website.

7. EFSA CONTAM, et al., *Update of the risk assessment of nickel in food and drinking water.* EFSA Journal, 2020. **18**(11): p. e06268.

8. ISO, *Air quality – Particle size fraction definitions for health-related sampling*. 1995, Internation Organization for Standardization: Geneva, Switzerland.

9. Fullerton, A., et al., *Permeation of nickel salts through human skin in vitro.* Contact Dermatitis, 1986. **15**(3): p. 173-7.

10. Rezuke, W.N., J.A. Knight, and F.W. Sunderman, Jr., *Reference values for nickel concentrations in human tissues and bile.* Am J Ind Med, 1987. **11**(4): p. 419-26.

11. Oller, A.R., et al., *Inhalation carcinogenicity study with nickel metal powder in Wistar rats.* Toxicology and applied pharmacology, 2008. **233**(2): p. 262-275.

12. Rendall, R.E., J.I. Phillips, and K.A. Renton, *Death following exposure to fine particulate nickel from a metal arc process.* Ann Occup Hyg, 1994. **38**(6): p. 921-30.

13. UN GHS, *Globally Harmonized System of Classification and Labelling of Chemicals (GHS)*, U. Nations, Editor. 2019, United Nations: New York and Geneva. p. 1-570.

14. Arena, V.C., et al., *Using alternative comparison populations to assess occupation-related mortality risk. Results for the high nickel alloys workers cohort.* J Occup Environ Med, 1998. **40**(10): p. 907-16.

15. Moulin, J.J., et al., *Risk of lung cancer in workers producing stainless steel and metallic alloys.* Int Arch Occup Environ Health, 2000. **73**(3): p. 171-80.

16. Sorahan, T., *Mortality of Workers at a Plant Manufacturing Nickel Alloys, 1958–2000.* Occupational Medicine, 2004. **54**(1): p. 28-34.

17. Stockmann-Juvala, H., et al., *Inhalation toxicity of 316L stainless steel powder in relation to bioaccessibility.* Hum Exp Toxicol, 2013. **32**(11): p. 1137-54.

18. Oller, A.R., G. Oberdörster, and S.K. Seilkop, *Derivation of PM10 size-selected human equivalent concentrations of inhaled nickel based on cancer and non-cancer effects on the respiratory tract.* Inhal Toxicol, 2014. **26**(9): p. 559-78.

19. NTP, *NTP Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate (CAS No. 10101-97-0) in F344 Rats and B6C3F1 Mice (Inhalation Studies).* National Toxicology Program technical report series, 1996a. **454**: p. 1.

20. Berge, S.R. and K. Skyberg, *Radiographic evidence of pulmonary fibrosis and possible etiologic factors at a nickel refinery in Norway.* J Environ Monit, 2003. **5**(4): p. 681-8.

21. NTP, *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313-99-1) in F344/N Rats and B6C3F1 Mice (Inhalation Studies).* National Toxicology Program, Technical Report Series, 1996b(451).

22. Sunderman, F.W., Jr., et al., *Carcinogenesis bioassays of nickel oxides and nickel-copper oxides by intramuscular administration to Fischer-344 rats.* Res Commun Chem Pathol Pharmacol, 1990. **70**(1): p. 103-13.

23. CSR, *Appendix B3: BACKGROUND-BIOACCESSIBILITY-BASED READ-ACROSS ASSESSMENT OF NICKEL COMPOUNDS-DERMAL SENSITIZATION, DERMAL DNEL DERIVATION, AND DERMAL IRRITATION*. 2019, Available on ECHA website.

24. ICNCM, *Report of the international committee on nickel carcinogenesis in man. Final report*. 1990, Program Resources, Inc., Research Triangle Park, NC (USA).

25. WHO, *Nickel in Drinking Water*, in *Background document for development of WHO Guidelines for Drinking-water Quality*. 2007, WHO/SDE/WSH/05.08/55.

26. Institute of Medicine (US) Panel on Micronutrients, in *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. 2001, National Academies Press (US)

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27. O'Rourke, M.K., et al., *Evaluations of primary metals from NHEXAS Arizona: distributions and preliminary exposures. National Human Exposure Assessment Survey.* J Expo Anal Environ Epidemiol, 1999. **9**(5): p. 435-45.

28. Pennington, J.A. and J.W. Jones, *Molybdenum, nickel, cobalt, vanadium, and strontium in total diets.* J Am Diet Assoc, 1987. **87**(12): p. 1644-50.

29. Thomas, K.W., E.D. Pellizzari, and M.R. Berry, *Population-based dietary intakes and tap water concentrations for selected elements in the EPA region V National Human Exposure Assessment Survey (NHEXAS).* J Expo Anal Environ Epidemiol, 1999. **9**(5): p. 402-13.

30. Nielsen, G.D. and M. Flyvholm, *Risks of high nickel intake with diet.* IARC Sci Publ, 1984(53): p. 333-8.

31. Grandjean, P., G.D. Nelson, and O. Anderson, *Human nickel exposure and chemobiokinetics*, in *Nickel and the skin: immunology and toxicology*, H.E. Maibach and T. Menné, Editors. 1989, CRC Press: Boca Raton, Florida. p. 9-34.

32. De Brouwere, K., et al., *Assessment of indirect human exposure to environmental sources of nickel: oral exposure and risk characterization for systemic effects.* Sci Total Environ, 2012. **419**: p. 25-36.

33. ATSDR, *Toxicological profile for nickel*. 2005, US Department of Health and Human Services, Public Health Service Atlanta, GA. p. 1-397.

34. WHO, *Nickel in Drinking Water. Background document for development of WHO Guidelines for Drinking-water Quality*, in *WHO/SDE/WSH/07.08/55*. 2019.

35. Kinney, P.L., et al., *Exposures to multiple air toxics in New York City.* Environ Health Perspect, 2002. **110 Suppl 4** (Suppl 4): p. 539-46.

36. Koutrakis, P., S.L.K. Briggs, and B.P. Leaderer, *Source apportionment of indoor aerosols in Suffolk and Onondaga counties, New York.* Environmental Science & Technology, 1992. **26**(3): p. 521-527.

37. IPCS, *Environmental Health Criteria 108: Nickel*. 1991, World Health Organization: Geneva, Switzerland. p. 1-255.

38. Bennett, B.G., *Environmental nickel pathways to man.* IARC Sci Publ, 1984(53): p. 487-95.

39. Grandjean, P., *Human exposure to nickel.* IARC Sci Publ, 1984(53): p. 469-85.

40. Aitken, R.J., et al., *AEROSOL INHALABILITY IN LOW AIR MOVEMENT ENVIRONMENTS.* Journal of Aerosol Science, 1999. **30**(5): p. 613-626.

41. Cox, A.L., et al., *Development of an Empirical Formula for Describing Human Inhalability of Airborne Particles at Low Wind Speeds and Calm Air.* Ann Work Expo Health, 2019. **63**(9): p. 1046-1060.

42. Vincent, J.H., *Aerosol sampling: science and practice*. Vol. xix. 1989, Chchester: John Wiley & Sons.

43. CSR, *Appendix C2: Background Document in Support of Long-term Inhalable DNELs for Nickel Metal and Nickel Compounds*. 2019, Available on ECHA website.

44. Dunnick, J., et al., *Lung toxicity after 13-week inhalation exposure to nickel oxide, nickel subsulfide, or nickel sulfate hexahydrate in F344N rats and B6C3F1 mice.* Fundamental and Applied Toxicology, 1989. **12**(3): p. 584-594.

45. Benson, J.M., et al., *Biochemical responses of rat and mouse lung to inhaled nickel compounds.* Toxicology, 1989. **57**(3): p. 255-66.

46. Torjussen, W. and I. Andersen, *Nickel concentrations in nasal mucosa, plasma, and urine in active and retired nickel workers.* Ann Clin Lab Sci, 1979. **9**(4): p. 289-98.

47. Andersen, I. and K.B. Svenes, *Determination of nickel in lung specimens of thirty-nine autopsied nickel workers.* Int Arch Occup Environ Health, 1989. **61**(4): p. 289-95.

48. Svenes, K.B. and I. Andersen, *Distribution of nickel in lungs from former nickel workers.* Int Arch Occup Environ Health, 1998. **71**(6): p. 424-8.

49. Kollmeier, H., et al., *Increased chromium and nickel content in lung tissue and bronchial carcinoma.* Am J Ind Med, 1987. **11**(6): p. 659-69.

50. Raithel, H.J., et al., *Analyses of chromium and nickel in human pulmonary tissue. Investigations in lung cancer patients and a control population under special consideration of medical expertise aspects.* Int Arch Occup Environ Health, 1989. **61**(8): p. 507-12.

51. Benson, J.M., et al., *Particle clearance and histopathology in lungs of F344/N rats and B6C3F1 mice inhaling nickel oxide or nickel sulfate.* Fundam Appl Toxicol, 1995. **28**(2): p. 232-44.

52. Fischer, T., *Occupational nickel dermatitis*, in *Nickel and the skin: immunology and toxicology*, H.I. Maibach and T. Menné, Editors. 1989, CRC Press: Boca Raton, Florida. p. 117-132.

53. Malten, K.E., *Thoughts on irritant contact dermatitis.* Contact Dermatitis, 1981. **7**(5): p. 238-47.

54. Wilkinson, T.C. and J.D. Wilkinson, *Nickel allergy and hand eczema*, in *Nickel and the skin: Immunology and toxicology*, H.I. Maibach and T. Menné, Editors. 1989, CRC Press: Boca Raton, Florida. p. 133-164.

55. Hostýnek, J.J., et al., *Human stratum corneum penetration by nickel. In vivo study of depth distribution after occlusive application of the metal as powder.* Acta Derm Venereol Suppl (Stockh), 2001a(212): p. 5-10.

56. Hostýnek, J.J., et al., *Human stratum corneum adsorption of nickel salts. Investigation of depth profiles by tape stripping in vivo.* Acta Derm Venereol Suppl (Stockh), 2001b(212): p. 11-8.

57. Tanojo, H., et al., *In vitro permeation of nickel salts through human stratum corneum.* Acta Derm Venereol Suppl (Stockh), 2001(212): p. 19-23.

58. Solomons, N.W., et al., *Bioavailability of nickel in man: effects of foods and chemically-defined dietary constituents on the absorption of inorganic nickel.* J Nutr, 1982. **112**(1): p. 39-50.

59. Foulkes, E.C. and D.M. McMullen, *On the mechanism of nickel absorption in the rat jejunum.* Toxicology, 1986. **38**(1): p. 35-42.

60. Sunderman Jr, F.W., et al., *Nickel absorption and kinetics in human volunteers.* Proceedings of the Society for Experimental Biology and Medicine, 1989. **191**(1): p. 5-11.

61. Patriarca, M., T.D. Lyon, and G.S. Fell, *Nickel metabolism in humans investigated with an oral stable isotope.* Am J Clin Nutr, 1997. **66**(3): p. 616-21.

62. Christensen, O.B. and V. Lagesson, *Nickel concentration of blood and urine after oral administration.* Ann Clin Lab Sci, 1981. **11**(2): p. 119-25.

63. Nielsen, G.D., et al., *Absorption and retention of nickel from drinking water in relation to food intake and nickel sensitivity.* Toxicology and applied pharmacology, 1999. **154**(1): p. 67-75.

64. Sunderman Jr, F.W., et al., *Acute nickel toxicity in electroplating workers who accidently ingested a solution of nickel sulfate and nickel chloride.* American journal of industrial medicine, 1988. **14**(3): p. 257-266.

65. Ambrose, A., et al., *Long term toxicologic assessment of nickel in rats and dogs.* 1976.

66. Dutton, M.D., et al., *Gastric bioaccessibility is a conservative measure of nickel bioavailability after oral exposure: Evidence from Ni-contaminated soil, pure Ni substances and Ni alloys.* Environmental Pollution, 2021. **268**: p. 115830.

67. Ho, W. and A. Furst. *Nickel excretion by rats following a single treatment.* in *Proceedings of the Western Pharmacology Society*. 1973. WESTERN PHARMACOL SOC INC UCLA SCHOOL MEDICINE DEPT PHARMACOLOGY, LOS ….

68. Tedeschi, R.E. and F.W. Sunderman, *Nickel poisoning. V. The metabolism of nickel under normal conditions and after exposure to nickel carbonyl.* AMA Arch Ind Health, 1957. **16**(6): p. 486-8.

69. Ishimatsu, S., et al., *Distribution of various nickel compounds in rat organs after oral administration.* Biological trace element research, 1995. **49**(1): p. 43-52.

70. Sunderman JR, F.W., et al., *Biological monitoring of nickel.* Toxicology and industrial health, 1986. **2**(1): p. 17-78.

71. Nomoto, S., *Determination and pathophysiological study of nickel in human and animals, 3.* Shinshu Igaku Zasshi, 1974. **22**(1): p. 45-51.

72. Zober, A., et al., *Nickel and chromium content of selected human organs and body fluids.* Zentralbl Bakteriol Mikrobiol Hyg B, 1984. **179**(1): p. 80-95.

73. Valentine, R. and G.L. Fisher, *Pulmonary clearance of intratracheally administered 63Ni3S2 in strain A/J mice.* Environ Res, 1984. **34**(2): p. 328-34.

74. Medinsky, M.A., J.M. Benson, and C.H. Hobbs, *Lung clearance and disposition of 63Ni in F344/N rats after intratracheal instillation of nickel sulfate solutions.* Environ Res, 1987. **43**(1): p. 168-78.

75. Benson, J.M., et al., *Comparative inhalation toxicity of nickel sulfate to F344/N rats and B6C3F1 mice exposed for twelve days.* Toxicological Sciences, 1988. **10**(1): p. 164-178.

76. Sumino, K., et al., *Heavy Metals in Normal Japanese Tissues.* Archives of Environmental Health: An International Journal, 1975. **30**(10): p. 487-494.

77. Tossavainen, A., et al., *Application of mathematical modelling for assessing the biological half-times of chromium and nickel in field studies.* Br J Ind Med, 1980. **37**(3): p. 285-91.

78. IARC, *Chromium, Nickel and Welding*, in *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. 1990, International Agency for Research on Cancer: Lyon, France.

79. Akesson, B. and S. Skerfving, *Exposure in welding of high nickel alloy.* International archives of occupational and environmental health, 1985. **56**(2): p. 111-117.

80. Boysen, M., et al., *Histological Changes, Rhinoscopical Findings and Nickel Concentration in Plasma and Urine in Retired Nickel Workers.* Acta Oto-Laryngologica, 1984. **97**(1-2): p. 105-115.

81. Christensen, O.B., et al., *Nickel concentration of blood, urine and sweat after oral administration.* Contact Dermatitis, 1979. **5**(5): p. 312-6.

82. Cohn, J.R. and E.A. Emmett, *The excretion of trace metals in human sweat.* Ann Clin Lab Sci, 1978. **8**(4): p. 270-5.

83. USEPA, *Health Assessment Document for Nickel and Nickel Compounds*. 1986, United States Environmental Protection Agency, Office of Health and Environmental Assessment: Washington DC.

84. McNeely, M.D., et al., *Abnormal Concentrations of Nickel in Serum in Cases of Myocardial Infarction, Stroke, Burns, Hepatic Cirrhosis, and Uremia.* Clinical Chemistry, 1971. **17**(11): p. 1123-1128.

85. Cox, J.E., et al., *Mortality of Nickel Workers: Experience of Men Working with Metallic Nickel.* British Journal of Industrial Medicine, 1981. **38**(3): p. 235-239.

86. Polednak, A.P., *Mortality among welders, including a group exposed to nickel oxides.* Arch Environ Health, 1981. **36**(5): p. 235-42.

87. Enterline, P.E. and G.M. Marsh, *Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia.* J Natl Cancer Inst, 1982. **68**(6): p. 925-33.

88. Cragle, D.L., et al., *A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge Gaseous Diffusion Plant.* IARC Sci Publ, 1984(53): p. 57-63.

89. Easton, D., et al., *Respiratory cancer mortality in Welsh nickel refiners: which nickel compounds are responsible?* Advances in environmental science and technology, 1992. **25**: p. 603-619.

90. Egedahl, R., M. Carpenter, and D. Lundell, *Mortality experience among employees at a hydrometallurgical nickel refinery and fertiliser complex in Fort Saskatchewan, Alberta (1954-95).* Occupational and environmental medicine, 2001. **58**: p. 711-715.

91. Sivulka, D.J., *Assessment of respiratory carcinogenicity associated with exposure to metallic nickel: a review.* Regulatory Toxicology and Pharmacology, 2005. **43**(2): p. 117-133.

92. Prueitt, R.L., et al., *Systematic review of the potential respiratory carcinogenicity of metallic nickel in humans.* Crit Rev Toxicol, 2020. **50**(7): p. 605-639.

93. Hueper, W., *Experimental studies in metal carcinogenesis. IX. Pulmonary lesions in guinea pigs and rats exposed to prolonged inhalation of powdered metallic nickel.* Arch Pathol, 1958. **65**: p. 600-607.

94. Hueper, W. and W. Payne, *Experimental studies in metal carcinogenesis: Chromium, nickel, iron, arsenic.* Archives of Environmental Health: An International Journal, 1962. **5**(5): p. 445-462.

95. Pott, F., et al., *Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats.* Experimental pathology, 1987. **32**(3): p. 129-152.

96. Ivankovic, S., et al., *Carcinogenesis of nickel alloys in the hamster following intratracheal instillation [English translation].* Dortmund, Germany: Publication of the Bundesanstalt fur Arbeitsschutz, 1988: p. 105.

97. Driscoll, K.E., et al., *Intratracheal instillation as an exposure technique for the evaluation of respiratory tract toxicity: uses and limitations.* Toxicol Sci, 2000. **55**(1): p. 24-35.

98. Block, G.T. and M. Yeung, *Asthma Induced by Nickel.* JAMA, 1982. **247**(11): p. 1600-1602.

99. Estlander, T., et al., *Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis.* Clin Exp Allergy, 1993. **23**(4): p. 306-10.

100. Shirakawa, T., et al., *Hard metal asthma: cross immunological and respiratory reactivity between cobalt and nickel?* Thorax, 1990. **45**(4): p. 267-271.

101. Kilburn, K.H., et al., *Cross-shift and chronic effects of stainless-steel welding related to internal dosimetry of chromium and nickel.* Am J Ind Med, 1990. **17**(5): p. 607-15.

102. Sobaszek, A., et al., *Acute respiratory effects of exposure to stainless steel and mild steel welding fumes.* J Occup Environ Med, 2000. **42**(9): p. 923-31.

103. Sobaszek, A., et al., *Respiratory symptoms and pulmonary function among stainless steel welders.* J Occup Environ Med, 1998. **40**(3): p. 223-9.

104. Serita, F., H. Kyono, and Y. Seki, *Pulmonary clearance and lesions in rats after a single inhalation of ultrafine metallic nickel at dose levels comparable to the threshold limit value.* Ind Health, 1999. **37**(4): p. 353-63.

105. Zhang, Q., et al., *Differences in the extent of inflammation caused by intratracheal exposure to three ultrafine metals: role of free radicals.* J Toxicol Environ Health A, 1998. **53**(6): p. 423-38.

106. Egedahl, R.D., M. Fair, and R. Homik, *Mortality among employees at a hydrometallurgical nickel refinery and fertilizer complex in Fort Saskatchewan, Alberta (1954-1984).* Can J Public Health, 1993. **84**(1): p. 40-4.

107. Emmett, E.A., et al., *Allergic contact dermatitis to nickel: bioavailability from consumer products and provocation threshold.* J Am Acad Dermatol, 1988. **19**(2 Pt 1): p. 314-22.

108. Hemingway, J.D. and M.M. Molokhia, *The dissolution of metallic nickel in artificial sweat.* Contact Dermatitis, 1987. **16**(2): p. 99-105.

109. Mathur, A., *Occupational dermatitis and absorption in a metal plater.* Contact Dermatitis, 1983. **9**: p. 530.

110. Tanko, Z., T.L. Diepgen, and E. Weisshaar, *Is nickel allergy an occupational disease? Discussion of the occupational relevance of a type IV allergy to nickel (II) sulfate using case reports.* J Dtsch Dermatol Ges, 2008. **6**(5): p. 346-9.

111. Thyssen, J.P., T. Menné, and J.D. Johansen, *Nickel release from inexpensive jewelry and hair clasps purchased in an EU country – Are consumers sufficiently protected from nickel exposure?* Sci Total Environ, 2009. **407**(20): p. 5315-8.

112. FDA, *Biological responses to metal implants.* 2019, U.S. Food & Drug Administration, Center for Devices & Radiological Health.

113. McGregor, D.B., et al., *Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies – a report of an IARC Monographs Programme Meeting. International Agency for Research on Cancer.* Eur J Cancer, 2000. **36**(3): p. 307-13.

114. Moulin, J.J., et al., *Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers.* Cancer Causes Control, 1993. **4**(2): p. 75-81.

115. Cornell, R.G., *Mortality patterns among stainless-steel workers.* IARC Sci Publ, 1984(53): p. 65-71.

116. Svensson, B.G., et al., *Deaths and tumours among workers grinding stainless steel.* Am J Ind Med, 1989. **15**(1): p. 51-9.

117. Hansen, K.S., J.M. Lauritsen, and A. Skytthe, *Cancer incidence among mild steel and stainless steel welders and other metal workers.* American Journal of Industrial Medicine, 1996. **30**(4): p. 373-382.

118. Jakobsson, K., Z. Mikoczy, and S. Skerfving, *Deaths and tumours among workers grinding stainless steel: a follow up.* Occup Environ Med, 1997. **54**(11): p. 825-9.

119. Gerin, M., et al., *Nickel and cancer associations from a multicancer occupation exposure case-referent study: preliminary findings.* IARC Sci Publ, 1984(53): p. 105-15.

120. Kjuus, H., et al., *A case-referent study of lung cancer, occupational exposures and smoking. I. Comparison of title-based and exposure-based occupational information.* Scand J Work Environ Health, 1986. **12**(3): p. 193-202.

121. Simonato, L., et al., *A historical prospective study of European stainless steel, mild steel, and shipyard welders.* British journal of industrial medicine, 1991. **48**(3): p. 145-154.

122. Gérin, M., et al., *Development and use of a welding process exposure matrix in a historical prospective study of lung cancer risk in European welders.* Int J Epidemiol, 1993. **22 Suppl 2**: p. S22-8.

123. Becker, N., *Cancer mortality among arc welders exposed to fumes containing chromium and nickel. Results of a third follow-up: 1989-1995.* J Occup Environ Med, 1999. **41**(4): p. 294-303.

124. IARC, *Welding, Molybdenum Trioxide, and Indium Tin Oxide*, in *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. 2017, International Agency for Research on Cancer: Lyon, France.

125. Muhle, H., et al., *Chronic effects of intratracheally instilled nickel-containing particles in hamsters.* Advances in environmental science and technology, 1992. **25**: p. 467-479.

126. Cross, H., et al., *Manufacture, processing and use of stainless steel: a review of the health effects*, I.o.O. Health, Editor. 1999, Commissioned by: European Confederation of Iron and Steel Industries (EUROFER): Birmingham, UK.

127. Andersen, A., et al., *Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers.* Occupational and environmental medicine, 1996. **53**(10): p. 708-713.

128. Anttila, A., et al., *Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery.* International archives of occupational and environmental health, 1998. **71**(4): p. 245-250.

129. Peto, J., et al., *Respiratory cancer mortality of Welsh nickel refinery workers.* IARC Sci Publ, 1984(53): p. 37-46.

130. Grimsrud, T.K., et al., *Lung cancer incidence among Norwegian nickel-refinery workers 1953–2000.* Journal of environmental monitoring, 2003. **5**(2): p. 190-197.

131. Pang, D., D.C. Burges, and T. Sorahan, *Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945-93.* Occup Environ Med, 1996. **53**(10): p. 714-7.

132. Roberts, R.S., et al., *A study of mortality in workers engaged in the mining, smelting, and refining of nickel. II: Mortality from cancer of the respiratory tract and kidney.* Toxicol Ind Health, 1989a. **5**(6): p. 975-93.

133. Roberts, R.S., et al., *A study of mortality in workers engaged in the mining, smelting, and refining of nickel. I: Methodology and mortality by major cause groups.* Toxicol Ind Health, 1989b. **5**(6): p. 957-74.

134. NTP, *NTP Toxicology and Carcinogenesis Studies of Nickel Subsulfide (CAS No. 12035-72-2) in F344 Rats and B6C3F1 Mice (Inhalation Studies).* National Toxicology Program technical report series, 1996c. **453**: p. 1.

135. Hsieh, T.H., C.P. Yu, and G. Oberdorster, *Deposition and Clearance Models of Ni Compounds in the Mouse Lung and Comparisons with the Rat Models.* Aerosol Science and Technology, 1999. **31**(5): p. 358-372.

136. Yu, C.P., et al., *Evaluation of the human nickel retention model with workplace data.* Regul Toxicol Pharmacol, 2001. **33**(2): p. 165-72.

137. Heim, K.E., et al., *Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats.* Toxicology and applied pharmacology, 2007. **224**(2): p. 126-137.

138. Schroeder, H.A., J.J. Balassa, and W.H. Vinton, Jr., *CHROMIUM, LEAD, CADMIUM, NICKEL AND TITANIUM IN MICE: EFFECT ON MORTALITY, TumourS AND TISSUE LEVELS.* J Nutr, 1964. **83**: p. 239-50.

139. Schroeder, H.A., M. Mitchener, and A.P. Nason, *Life-term effects of nickel in rats: survival, tumours, interactions with trace elements and tissue levels.* J Nutr, 1974. **104**(2): p. 239-43.

140. Oller, A.R., *Respiratory carcinogenicity assessment of soluble nickel compounds.* Environmental health perspectives, 2002. **110 Suppl 5**(Suppl 5): p. 841-844.

141. Costa, M., *Molecular mechanisms of nickel carcinogenesis.* Annu Rev Pharmacol Toxicol, 1991. **31**: p. 321-37.

142. Goodman, J.E., et al., *The nickel ion bioavailability model of the carcinogenic potential of nickel-containing substances in the lung.* Critical reviews in toxicology, 2011. **41**(2): p. 142-174.

143. Haber, L.T., et al., *Hazard identification and dose response of inhaled nickel-soluble salts.* Regul Toxicol Pharmacol, 2000a. **31**(2 Pt 1): p. 210-30.

144. Oller, A.R., M. Costa, and G. Oberdorster, *Carcinogenicity assessment of selected nickel compounds.* Toxicol Appl Pharmacol, 1997. **143**(1): p. 152-66.

145. Dunnick, J., et al., *Comparative toxicity of nickel oxide, nickel sulfate hexahydrate, and nickel subsulfide after 12 days of inhalation exposure to F344/N rats and B6C3F1 mice.* Toxicology, 1988. **50**(2): p. 145-156.

146. Berghem, L., et al., *Fibronectin concentrations in lung lavage fluid after inhalation exposure to low levels of metals.* Environ Res, 1987. **43**(1): p. 179-85.

147. Bingham, E., et al., *Responses of alveolar macrophages to metals. I. Inhalation of lead and nickel.* Archives of environmental health, 1972. **25 6**: p. 406-14.

148. Murthy, R., et al., *Enzymatic Changes in Alveolar Macrophages of Rats Exposed to Lead and Nickel by Inhalation.* International Journal of Toxicology, 1983. **2**: p. 193 – 199.

149. Goutet, M., M. Ban, and S. Binet, *Effects of nickel sulfate on pulmonary natural immunity in Wistar rats.* Toxicology, 2000. **145**(1): p. 15-26.

150. Benson, J.M., et al., *Final report for short-term inhalation study with nickel compounds*. 2002, Inhalation Toxicology Laboratory, Lovelace Research Institute. Study carried out for NiPERA: Albuquerque, NM, USA.

151. Bright, P., et al., *Occupational asthma due to chrome and nickel electroplating.* Thorax, 1997. **52**(1): p. 28-32.

152. Davies, J.E., *Occupational asthma caused by nickel salts.* The Journal of the Society of Occupational Medicine, 1986. **36 1**: p. 29-31.

153. Malo, J.L., et al., *Occupational asthma caused by nickel sulfate.* J Allergy Clin Immunol, 1982. **69**(1 Pt 1): p. 55-9.

154. Malo, J.L., et al., *Isolated late asthmatic reaction due to nickel sulphate without antibodies to nickel.* Clin Allergy, 1985. **15**(2): p. 95-9.

155. McConnell, L.H., et al., *Asthma caused by nickel sensitivity.* Ann Intern Med, 1973. **78**(6): p. 888-90.

156. Novey, H.S., M. Habib, and I.D. Wells, *Asthma and IgE antibodies induced by chromium and nickel salts.* J Allergy Clin Immunol, 1983. **72**(4): p. 407-12.

157. Miller, A., R. Warshaw, and J. Nezamis, *Diffusing capacity and forced vital capacity in 5,003 asbestos-exposed workers: relationships to interstitial fibrosis (ILO profusion score) and pleural thickening.* Am J Ind Med, 2013. **56**(12): p. 1383-93.

158. Schubert, H., et al., *Epidemiology of nickel allergy.* Contact Dermatitis, 1987. **16**(3): p. 122-8.

159. Lammintausta, K., K. Kalimo, and C.T. Jansén, *Experimental nickel sensitization in the guinea pig: comparison of different protocols.* Contact Dermatitis, 1985. **12**(5): p. 258-62.

160. Zissu, D., C. Cavelier, and J. De Ceaurriz, *Experimental sensitization of guinea-pigs to nickel and patch testing with metal samples.* Food Chem Toxicol, 1987. **25**(1): p. 83-5.

161. Rohold, A.E., G.D. Nielsen, and K.E. Andersen, *Nickel-sulphate-induced contact dermatitis in the guinea pig maximization test: a dose-response study.* Contact Dermatitis, 1991. **24**(1): p. 35-9.

162. Nielsen, G.D., A.E. Rohold, and K.E. Andersen, *Nickel contact sensitivity in the guinea pig. An efficient open application test method.* Acta Derm Venereol, 1992. **72**(1): p. 45-8.

163. Cavelier, C., et al., *Allergy to nickel or cobalt: tolerance to nickel and cobalt samples in man and in the guinea pig allergic or sensitized to these metals.* Contact Dermatitis, 1989. **21**(2): p. 72-8.

164. Warner, R.D., et al., *Zinc effects on nickel dermatitis in the guinea pig.* Contact Dermatitis, 1988. **19**(2): p. 98-108.

165. Diepgen, T.L., et al., *Prevalence of contact allergy in the general population in different European regions.* Br J Dermatol, 2016. **174**(2): p. 319-29.

166. Heim, K. and D. Basketter, *Metal Exposure Regulations and Their Effect on Allergy Prevention*, in *Metal Allergy: From Dermatitis to Implant and Device Failure*, J.K. Chen and J.P. Thyssen, Editors. 2018, Springer International Publishing: Cham. p. 39-54.

167. Diamond, G.L., et al., *Gastrointestinal absorption of metals*. Drug Chem Toxicol, 1998. **21**(2): p. 223-51.

168. Sunderman JR, F.W. and E. Horak, *Biochemical indices of nephrotoxicity, exemplified by studies of nickel nephrotoxicity*, in *Organ-Directed Toxicity*, S. Brown and D. Davies, Editors. 1981, Pergamon Press: Oxford, UK. p. 55-67.

169. Sanford, W.E. and E. Nieboer, *Renal toxicity of nickel in human*, in *Nickel and Human Health: Current Perspectives*, E. Nieboer and J.O. Nriagu, Editors. 1992, Wiley & Sons Inc.: New York, NY. p. 123-134.

170. Wall, L.M. and C.D. Calnan, *Occupational nickel dermatitis in the electroforming industry.* Contact Dermatitis, 1980. **6**(6): p. 414-420.

171. Vyskočil, A., et al., *Biochemical Renal Changes in Workers Exposed to Soluble Nickel Compounds*. Human & Experimental Toxicology, 1994. **13**(4): p. 257-261.

172. Fischer, R.S.B., et al., *Evidence of nickel and other trace elements and their relationship to clinical findings in acute Mesoamerican Nephropathy: A case-control analysis.* PLoS One, 2020. **15**(11): p. e0240988.

173. Yin, H., et al., *Nickel induces autophagy via PI3K/AKT/mTOR and AMPK pathways in mouse kidney.* Ecotoxicology and Environmental Safety, 2021. **223**: p. 112583.

174. Elangovan, P., et al., *Beneficial Protective Effect of Troxerutin on Nickel-Induced Renal Dysfunction in Wistar Rats*. 2018. **37**(1): p. 1-14.

175. Casey, C.E. and M.F. Robinson, *Copper, manganese, zinc, nickel, cadmium and lead in human foetal tissues.* Br J Nutr, 1978. **39**(3): p. 639-46.

176. Chen, C.Y. and T.H. Lin, *Nickel toxicity to human term placenta: in vitro study on lipid peroxidation.* J Toxicol Environ Health A, 1998. **54**(1): p. 37-47.

177. Haber, L.T., et al., *Hazard identification and dose response of ingested nickel-soluble salts.* Regul Toxicol Pharmacol, 2000b. **31**(2 Pt 1): p. 231-41.

178. Chashschin, V.P., G.P. Artunina, and T. Norseth, *Congenital defects, abortion and other health effects in nickel refinery workers.* Science of the total environment, 1994. **148**(2-3): p. 287-291.

179. Vaktskjold, A., et al., *The prevalence of selected pregnancy outcome risk factors in the life-style and medical history of the delivering population in north-western Russia.* International journal of circumpolar health, 2004. **63**(1): p. 39-60.

180. Vaktskjold, A., et al., *The Kola birth registry and perinatal mortality in Mončegorsk, Russia.* Acta obstetricia et gynecologica Scandinavica, 2004. **83**(1): p. 58-69.

181. Vaktskjold, A., et al., *Genital malformations in newborns of female nickel-refinery workers.* Scand J Work Environ Health, 2006. **32**(1): p. 41-50.

182. Vaktskjold, A., et al., *Small-for-gestational-age newborns of female refinery workers exposed to nickel.* Int J Occup Med Environ Health, 2007. **20**(4): p. 327-38.

183. Vaktskjold, A., et al., *Spontaneous abortions among nickel-exposed female refinery workers.* International journal of environmental health research, 2008. **18**(2): p. 99-115.

184. Vaktskjold, A., et al., *Maternal nickel exposure and congenital musculoskeletal defects*. American journal of industrial medicine, 2008. **51**(11): p. 825-833.

185. Nieboer, E., *Reproductive and developmental health in relation to occupational exposure to nickel in the Kola Peninsula of Russia: A feasibility study*. 1997, Final Report to Nickel Producers Environmental Research Association, Durham, North Carolina, USA. Available through NiPERA Inc.

186. RTI (Research Triangle Institute), *Fertility and Reproductive Performance of the P(0) Generation: Two-Generation Reproduction and Fertility Study of Nickel Chloride Administered to CD Rats in the Drinking Water, Final Report*. 1988a, Research Triangle Institute: Research Triangle Park, NC, USA.

187. RTI (Research Triangle Institute), *Fertility and Reproductive Performance of the F(1) Generation: Two-Generation Reproduction and Fertility Study of Nickel Chloride Administered to CD Rats in the Drinking Water, Final Report*. 1988b, Research Triangle Institute: Research Triangle Park, NC, USA.

188. Saini, S., N. Nair, and M.R. Saini, *Embryotoxic and teratogenic effects of nickel in Swiss albino mice during organogenetic period.* Biomed Res Int, 2013. **2013**: p. 701439.

189. SLI, *An Oral (Gavage) 1-Generation Reproduction Study of Nickel Sulfate Hexahydrate in Rats*. 2000a, Springborn Laboratories, Inc.: Spencerville, OH, USA.

190. SLI, *An Oral (Gavage) Two-Generation Reproduction Toxicity Study in Sprague-Dawley Rats with Nickel Sulfate Hexahydrate*. 2000b, Springborn Laboratories Inc.: Spencerville, OH, USA.

191. Haber, L.T., et al., *Derivation of an oral toxicity reference value for nickel.* Regul Toxicol Pharmacol, 2017. **87 Suppl 1**: p. S1-s18.

192. Veien, N.K., et al., *Oral challenge with nickel and cobalt in patients with positive patch tests to nickel and/or cobalt.* Acta Derm Venereol, 1987. **67**(4): p. 321-5.

193. Gawkrodger, D.J., et al., *Contact clinic survey of nickel-sensitive subjects.* Contact Dermatitis, 1986. **14**(3): p. 165-169.

194. Jordan, W.P., Jr. and S.E. King, *Nickel feeding in nickel-sensitive patients with hand eczema.* J Am Acad Dermatol, 1979. **1**(6): p. 506-8.

195. Jensen, C.S., et al., *Experimental systemic contact dermatitis from nickel: a dose-response study.* Contact Dermatitis, 2003. **49**(3): p. 124-32.

196. Mislankar, M. and M.J. Zirwas, *Low-nickel diet scoring system for systemic nickel allergy.* Dermatitis, 2013. **24**(4): p. 190-5.

197. Sharma, A.D., *Low nickel diet in dermatology.* Indian J Dermatol, 2013. **58**(3): p. 240.

198. Panzani, R.C., et al., *Oral hyposensitization to nickel allergy: preliminary clinical results.* Int Arch Allergy Immunol, 1995. **107**(1-3): p. 251-4.

199. Santucci, B., et al., *Nickel sensitivity: effects of prolonged oral intake of the element.* Contact Dermatitis, 1988. **19**(3): p. 202-5.

200. Santucci, B., et al., *Serum and urine concentrations in nickel-sensitive patients after prolonged oral administration.* Contact Dermatitis, 1994. **30**(2): p. 97-101.

201. Sjövall, P., O.B. Christensen, and H. Möller, *Oral hyposensitization in nickel allergy.* J Am Acad Dermatol, 1987. **17**(5 Pt 1): p. 774-8.

202. Vreeburg, K.J., et al., *Induction of immunological tolerance by oral administration of nickel and chromium.* J Dent Res, 1984. **63**(2): p. 124-8.

203. van der Burg, C.K., et al., *Hand eczema in hairdressers and nurses: a prospective study. I. Evaluation of atopy and nickel hypersensitivity at the start of apprenticeship.* Contact Dermatitis, 1986. **14**(5): p. 275-9.

204. Kerosuo, H., et al., *Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears.* American Journal of Orthodontics and Dentofacial Orthopedics, 1996. **109**(2): p. 148-154.

205. Scheper, R.J., et al. *Preliminary Results of a Multicenter Study on the Incidence of Nickel Allergy in Relationship to Previous Oral and Cutaneous Contacts*. in *Current Topics in Contact Dermatitis*. 1989. Berlin, Heidelberg: Springer Berlin Heidelberg.

206. Todd, D.J. and D. Burrows, *Nickel allergy in relationship to previous oral and cutaneous nickel contact.* The Ulster medical journal, 1989. **58**(2): p. 168-171.

207. Van Hoogstraten, I.M., et al., *Reduced frequency of nickel allergy upon oral nickel contact at an early age.* Clin Exp Immunol, 1991a. **85**(3): p. 441-5.

208. van Hoogstraten, I.M., et al., *Effects of oral exposure to nickel or chromium on cutaneous sensitization.* Curr Probl Dermatol, 1991b. **20**: p. 237-41.

209. van Hoogstraten, I.M., et al., *Persistent immune tolerance to nickel and chromium by oral administration prior to cutaneous sensitization.* J Invest Dermatol, 1992. **99**(5): p. 608-16.

210. Van Hoogstraten, I.M., et al., *Oral induction of tolerance to nickel sensitization in mice.* J Invest Dermatol, 1993. **101**(1): p. 26-31.

211. Thornhill, T.C., *Properties of nickel oxide used in toxicological research: the importance of appropriate characterization*. 2000, Final Report to the Nickel Producers Environmental Research Association, Durham NC. Available through NiPERA Inc.: Durham, NC.

212. Van Vlack, L., *The oxides of nickel*. 1980, International NIckel Company Inc., Toronto, Canada: New York, NY.

213. Grimsrud, T.K., *Lung cancer among Norwegian nickel-refinery workers: Reappraisal of a classical study [English translation]*. Nor J Epidemiol, 2001. **11**: p. 171-176.

214. Goldberg, M., et al., *Epidemiology of respiratory cancers related to nickel mining and refining in New Caledonia (1978-1984)*. Int J Cancer, 1987. **40**(3): p. 300-4.

215. Goldberg, M., et al., *A seven year survey of respiratory cancers among nickel workers in New Caledonia (1978-1984)*, in *Nickel and human health: current perspectives*, E. Nieboer and J.O. Nriagu, Editors. 1992, John Wiley & Sons: New York, NY. p. 649-657.

216. Järup, L., et al., *Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel*. Occup Environ Med, 1998. **55**(11): p. 755-9.

217. Kjellström, T., L. Friberg, and B. Rahnster, *Mortality and cancer morbidity among cadmium-exposed workers*. Environmental health perspectives, 1979. **28**: p. 199-204.

218. Sorahan, T., *Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946-84*. Br J Ind Med, 1987. **44**(12): p. 803-9.

219. Sorahan, T. and J.A. Waterhouse, *Mortality study of nickel-cadmium battery workers by the method of regression models in life tables*. Br J Ind Med, 1983. **40**(3): p. 293-300.

220. Andersson, K., et al., *Mortality among cadmium and nickel-exposed workers in a Swedish battery factory*. Toxicological & Environmental Chemistry, 1984. **9**(1): p. 53-62.

221. Kasprzak, K.S., P. Gabryel, and K. Jarczewska, *Carcinogenicity of nickel(II)hydroxides and nickel(II)sulfate in Wistar rats and its relation to the in vitro dissolution rates*. Carcinogenesis, 1983. **4**(3): p. 275-9.

222. Sunderman, F.W., Jr., K.S. McCully, and S.M. Hopfer, *Association between erythrocytosis and renal cancers in rats following intrarenal injection of nickel compounds*. Carcinogenesis, 1984b. **5**(11): p. 1511-7.

223. Sunderman Jr, F.W., *Carcinogenicity of nickel compounds in animals*. IARC scientific publications, 1984a(53): p. 127.

224. Berry, J.P., et al., *In vitro electron microprobe of carcinogenic nickel compound interaction with tumour cells*. Ann Clin Lab Sci, 1985. **15**(2): p. 109-20.

225. Judde, J.G., et al., *Inhibition of Rat Natural Killer Cell Function by Carcinogenic Nickel Compounds: Preventive Action of Manganese2*. JNCI: Journal of the National Cancer Institute, 1987. **78**(6): p. 1185-1190.

226. Pott, F., et al., *Carcinogenicity of nickel compounds and nickel alloys in rats by intraperitoneal injection*. Advances in environmental science and technology, 1992. **25**: p. 491-502.

227. Kawanishi, S., et al., *Oxidative DNA damage in cultured cells and rat lungs by carcinogenic nickel compounds*. Free Radic Biol Med, 2001. **31**(1): p. 108-16.

228. Muir, D., et al., *Prevalence of small opacities in chest radiographs of nickel sinter plant workers*. Occupational and Environmental Medicine, 1993. **50**(5): p. 428-431.

229. Broder, I., et al., *Health status and sulfur dioxide exposure of nickel smelter workers and civic laborers*. J Occup Med, 1989. **31**(4): p. 347-53.

230. Sunderman, F.W., Jr., *Nasal toxicity, carcinogenicity, and olfactory uptake of metals*. Ann Clin Lab Sci, 2001. **31**(1): p. 3-24.

231. Muller, J., et al., *Study of Mortality of Ontario Miners 1955-1977. Part I*. 1983, Ontario Ministry of Labour, Ontario Workers' Compensation Board, Atomic Energy Control Board of Canada.

232. NTP, *Report on Carcinogens*. 2016, National Toxicology Program, U.S. Department of Health and Human Services: Research Triangle Park, NC.

233. IARC, *Nickel and Nickel Compounds*, in *Arsenic, Metals, Fibres and Dusts: A Review of Human Carcinogens*. 2012, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Lyon, France. p. 169-211.

234. ATSDR, *Toxicological Profile for Nickel*. 1998, U.S. Dept. Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

235. Duffus, J.H., *Epidemiology and the identification of metals as human carcinogens*. Sci Prog, 1996. **79 (Pt 4)**: p. 311-26.

236. Ottolenghi, A.D., et al., *Inhalation studies of nickel sulfide in pulmonary carcinogenesis of rats*. J Natl Cancer Inst, 1975. **54**(5): p. 1165-72.

237. Benson, J.M., et al., *Comparative inhalation toxicity of nickel subsulfide to F344/N rats and B6C3F1 mice exposed for 12 days*. Toxicological Sciences, 1987. **9**(2): p. 251-265.

238. Benson, J.M., et al., *Comparative acute toxicity of four nickel compounds to F344 rat lung.* Fundam Appl Toxicol, 1986. **7**(2): p. 340-7.

239. Abbracchio, M.P., J.D. Heck, and M. Costa, *The phagocytosis and transforming activity of crystalline metal sulfide particles are related to their negative surface charge.* Carcinogenesis, 1982. **3**(2): p. 175-80.

240. Costa, M. and H.H. Mollenhauer, *Carcinogenic activity of particulate nickel compounds is proportional to their cellular uptake.* Science, 1980a. **209**(4455): p. 515-7.

241. Sunderman, F.W., Jr., et al., *Rapid analysis of nickel in urine by electrothermal atomic absorption spectrophotometry.* Ann Clin Lab Sci, 1986b. **16**(3): p. 219-30.

242. Sunderman, F.W. and J.F. Kincaid, *NICKEL POISONING: II. STUDIES ON PATIENTS SUFFERING FROM ACUTE EXPOSURE TO VAPORS OF NICKEL CARBONYL*. Journal of the American Medical Association, 1954. **155**(10): p. 889-894.

243. Morgan, L.G., *Problems in the toxicology, diagnosis, and treatment of nickel carbonyl poisoning*, in *Nickel and human health: current perspectives*, E. Nieboer and J.O. Nriagu, Editors. 1992, John Wiley & Sons: New York, NY. p. 261-271.

244. Vuopala, U., et al., *Nickel carbonyl poisoning. Report of 25 cases.* Ann Clin Res, 1970. **2**(3): p. 214-22.

245. Shi, Z.C., *Acute nickel carbonyl poisoning: a report of 179 cases.* British journal of industrial medicine, 1986. **43**(6): p. 422-424.

246. Amor, A.J., *The Toxicology of the Carbonyls*. Journal of Industrial Hygiene, 1932. **14**.

247. Joo, F., *Changes in the molecular organization of the basement membrane after inhibition of adenosine triphosphate activity in the rat brain capillaries.* Cytobios, 1969. **1**: p. 289-301.

248. Sunderman, F.W., Jr., *Effect of nickel carbonyl upon hepatic concentrations of adenosine triphosphate.* Res Commun Chem Pathol Pharmacol, 1971. **2**(4): p. 545-51.

249. Sunderman, F.W., et al., *Nickel poisoning. IX. Carcinogenesis in rats exposed to nickel carbonyl.* AMA Arch Ind Health, 1959. **20**(1): p. 36-41.

250. Sunderman, F.W. and A.J. Donnelly, *STUDIES OF NICKEL CARCINOGENESIS METASTASIZING PULMONARY TumourS IN RATS INDUCED BY THE INHALATION OF NICKEL CARBONYL*. The American journal of pathology, 1965. **46**(6): p. 1027-1041.

251. Sunderman, F.W., et al., *Eye Malformations in Rats: Induction by Prenatal Exposure to Nickel Carbonyl.* Science, 1979. **203**(4380): p. 550-553.

252. Sunderman, F.W., Jr., et al., *Teratogenicity and embryotoxicity of nickel carbonyl in Syrian hamsters.* Teratog Carcinog Mutagen, 1980. **1**(2): p. 223-33.

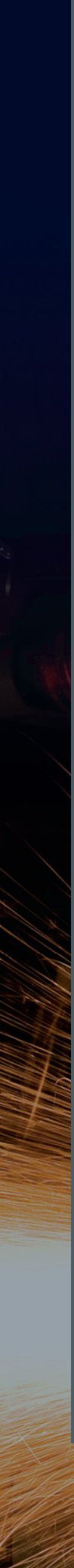
253. OSHA, *Hazard Communication: Hazard Classification Guidance for Manufacturers, Importers, and Employers*. 2016, Occupational Safety and Health Administration, U.S. Department of Labor. p. 1-432.

254. ACGIH, *Documentation for nickel and inorganic compounds (CAS No. 7440-02-0), including nickel subsulfide (CAS No. 12035-72-2)*. 2001, American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the Threshold Limit Values and Biological Exposure Indices.

1. ABBREVIATIONS AND ACRONYMS

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
BEI	Biological Exposure Indices
CFR	Code of Federal Regulations
CHIP	Chemical (Hazard Information and Packaging) Regulations
CLP	Classification, Labelling and Packaging regulation
cm^2	Centimeter squared
COSHH	Control of Substances Hazardous to Health
Disulfiram	Tetraethylthiuram disulfide
Dithiocarb	Diethyldithiocarbamate
DNA	Deoxyribonucleic acid
ECHA	European Chemicals Agency
EEC	European Economic Community
EKAs	Exposure equivalents for carcinogenic materials
EPA	Environmental Protection Agency
EU	European Union
FeSO4	Iron sulfate
FEV1.0	Forced expiratory volume in one second
FVC	Forced vital capacity
g	Gram
GHS	Globally Harmonized System
GSD	Geometric Size Distribution
H2SO4	Sulfuric acid
HEPA	High efficiency particulate air
HSC	Health and Safety Commission
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
ICNCM	International Committee on Nickel Carcinogenesis in Man
ILO	International Labour Organization
IPCS	International Programme on Chemical Safety
ISO	International Organization for Standards
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
L	Litre
LOAEL	Lowest Observed Adverse Effect Level
m^3	Meter cubed
MAK	Maximale Arbeitsplatzkonzentrationen
MEL	Maximum Exposure Limit
mg	Milligram
MMAD	Mass Median Aerodynamic Diameter
MOL	Ministry of Labor
MoA	Mode of Action
MSDS	Material Safety Data Sheets
MTD	Maximum Tolerated Dose
ng	Nanogram
NiO	Nickel oxide
Ni_3S_2	Nickel subsulfide

$NiSO_4$	Nickel sulfate
$NiSO_4 \bullet 6H_2O$	Nickel sulfate hexahydrate
(Fe,Ni)1-xS	Nickelferrous pyrrhotite
(Ni,Fe)9S8	Pentlandite
NiDI	Nickel Development Institute
NIOSH	National Institute for Occupational Safety and Health
NiPERA	Nickel Producers Environmental Research Association
NOAEL	No Observed Adverse Effect Level
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program
NTP RoC	National Toxicology Program Report on Carcinogens
OEL	Occupational Exposure Limit
OES	Occupational Exposure Standard
OSHA	Occupational Safety and Health Administration
OSHAct	Occupational Safety and Health Act
PAHs	Polycyclic aromatic hydrocarbons
PEL	Permissible Exposure Limit
PPE	Personal Protective Equipment
SCBA	Self-Contained Breathing Apparatus
SMR	Standardized Mortality Ratio
STOT RE	Specific Target Organ Toxicity Repeat Exposure
STOT SE	Specific Target Organ Toxicity Single Exposure
TRK	Technische Richtkonzentrationen
TVL	Threshold Limit Value
TWA	Time-Weighted Average
TWAEC	Time-Weighted Average Exposure Concentration
TWAEVs	Time-Weighted Average Exposure Values
µg	Microgram
µm	Micron
µM	Micromolar
U.K.	United Kingdom
U.S.	United States
WHMIS	Workplace Hazardous Materials Information System
WHO	World Health Organization
Wt%	Weight%



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