



Nickel

Toxicological Overview

Key Points

Kinetics and metabolism

- Nickel is absorbed by inhalation and ingestion
- The absorption of nickel is related to the solubility of the nickel compound
- Absorbed nickel is primarily excreted via the urine

Health effects of acute exposure

- Nickel carbonyl is the most toxic nickel compound following acute inhalation exposure
- The immediate effects of nickel carbonyl exposure are respiratory tract irritation and neurological effects
- Delayed effects of nickel carbonyl exposure include pulmonary oedema, pneumonitis and in severe cases death
- Acute ingestion of nickel compounds can cause nausea, vomiting, diarrhoea and headache
- Dermal contact with nickel or nickel compounds can lead to sensitisation and the development of contact dermatitis

Health effects of chronic exposure

- Chronic inhalation of nickel or nickel compounds can cause rhinitis, sinusitis, anosmia and in extreme cases perforation of the nasal septum
- The International Agency for Research on Cancer (IARC) classified nickel compounds as carcinogenic to humans (Group 1)
- The IARC classified elemental nickel as possibly carcinogenic to humans (Group 2B)
- Nickel carbonyl and soluble nickel salts are considered to be reproductive toxicants

Toxicological Overview

Summary of Health Effects

Nickel carbonyl is the most toxic nickel compound following acute inhalation exposure in humans. The effects of nickel carbonyl inhalation occur in two phases, immediate and delayed. The immediate effects include respiratory tract irritation and neurological effects such as dizziness and headache, following which there is often an asymptomatic period before the onset of the delayed pulmonary symptoms, including chest pain, cough and dyspnoea. In severe cases pulmonary oedema, pneumonitis and death may occur. Patients who survive a severe exposure to nickel carbonyl may develop weakness and neurasthenic syndrome.

Data from occupationally exposed groups indicate that inhalation of nickel compounds may produce rhinitis, sinusitis and anosmia, and after a prolonged exposure, perforation of the nasal septum.

Acute ingestion of nickel compounds may cause nausea, vomiting, diarrhoea, headache, cough and shortness of breath. In severe cases, ingestion of large amounts of a nickel compound may cause death. Chronic oral exposure to nickel or nickel compounds has not been characterised in humans.

Dermal exposure to nickel salts can cause skin irritation. Nickel and its water soluble salts are potent skin sensitisers. Once sensitisation has occurred dermal exposure to even small amounts of nickel or nickel compounds can lead to an outbreak of contact dermatitis. In the past, prolonged dermal exposure of the public to nickel occurred widely from certain jewellery, earrings, watch straps etc. This was a major cause of skin sensitisation. Widespread exposure has now been largely eliminated by the Nickel Directive which places an upper limit ($0.5 \mu\text{g cm}^{-2} \text{ week}^{-1}$) on the amount of nickel released from such products. This was implemented in the UK in 2000.

The International Agency for the Research on Cancer (IARC) concluded that nickel compounds are human carcinogens (Group 1). IARC also concluded that elemental nickel is a possible human carcinogen (Group 2B). No classification was given for nickel alloys.

Nickel carbonyl is classified in the EU as a reproductive toxicant (Risk Phrase R61 – ‘may cause harm to the unborn child’). Several animal studies have reported malformations in the offspring of animals exposed to nickel carbonyl. Soluble salts such as the sulphate and the chloride are also similarly classified.

Kinetics and Metabolism

Nickel can be absorbed via inhalation, ingestion and to a very limited extent following dermal exposure. The absorption of nickel is related to the solubility of the compound, the general order of absorption being: nickel carbonyl > soluble nickel compounds > insoluble nickel compounds.

The extent of absorption following inhalation depends on particle size and the solubility of the compound. Smaller particles penetrate deeper into the respiratory tract than larger ones and therefore the relative absorption is greater. Smaller compounds are absorbed more quickly making them less available for mucociliary clearance and then being swallowed [1].

The presence of food in the stomach reduces the bioavailability of nickel. In an absorption study 27% of nickel sulphate given to humans in drinking water was systemically absorbed compared with 1% when it was given in food [1, 2].

Percutaneous absorption is minimal, but is clinically important in the development of contact dermatitis [1].

Human autopsy studies on individuals non-occupationally exposed to nickel found the highest concentrations of nickel in the lungs, thyroid and adrenal glands. Lower levels of nickel have been detected in the kidneys, heart, liver, brain, spleen and pancreas [2, 3]. Nickel crosses the placenta and has been found in breast milk [1].

The elimination of absorbed nickel predominately occurs via the urine, although some may be excreted in saliva, sweat, milk and tears. Nickel that is not absorbed from the gastrointestinal tract is excreted in the faeces [1]. A urinary elimination half life (for absorbed nickel) of 17 – 48 hours has been reported in a human oral exposure study [3].

Sources and Route of Human Exposure

Nickel occurs naturally in the earth's crust and is ubiquitous in air, water, soil and the biosphere. The average concentration of nickel in the earth's crust is 0.008% [1, 2].

Nickel also exists as a number of compounds. Nickel compounds that are soluble in water include nickel chloride and nickel sulphate; insoluble nickel compounds include nickel oxide, nickel sulphide and nickel subsulphide [1]. Nickel carbonyl is a highly toxic, volatile liquid that has specialised industrial uses [4].

Nickel is emitted to the atmosphere from natural sources including windblown dust, volcanoes, vegetation, forest fires and meteoric dust [2]. The principle anthropogenic sources of nickel emissions to the atmosphere include the combustion of coal and oil, municipal incineration, steel and other nickel alloy production and electroplating [1, 2]. In urban areas, nickel levels in the ambient air range from 1-10 ng m⁻³. In industrialised areas and large cities levels in the range of 110-180 ng m⁻³ have been recorded [3]. In polluted air, the main nickel compounds appear to be nickel sulphate, nickel oxides, nickel sulphides, and to a smaller extent, elemental nickel [1].

Food and cigarette smoke are the main sources of nickel exposure in the general public [3, 5]. Approximately 0.04-0.58 µg nickel is released with the mainstream smoke of one cigarette. Smoking 40 cigarettes a day may therefore lead to inhalation of 2-23 µg nickel [1]. The average daily intake of nickel from foodstuffs for an adult has been estimated to be

approximately 152 µg [5]. The general public may also be exposed to low levels of nickel by inhaling ambient air or by drinking water contaminated with nickel [2].

In the past, items such as less expensive jewellery, earrings, wristwatches etc were a common source of exposure to nickel (resulting in a high incidence of nickel sensitization). This exposure route has largely been eliminated by the 'Nickel Directive' which was implemented in the UK in 2000. A requirement of the Directive was that the upper limit for nickel release in articles which have direct or prolonged contact with the skin was $0.5 \mu\text{g cm}^{-2} \text{ week}^{-1}$ [6].

Exposure to nickel in the workplace may occur by dermal contact, by inhalation of aerosols, fumes, dusts or mists containing nickel or by inhalation of gaseous nickel carbonyl [7]. Occupational exposure to nickel is considered to be highest for individuals involved in production, processing and use of nickel [2]. Workplace exposure limits (WELs) for nickel and its inorganic compounds have been derived in the UK. The long-term exposure limit (LTEL) for water soluble nickel compounds is 0.1 mg m^{-3} (8 hour time weighted exposure (TWA) reference period) and the LTEL for nickel and water-insoluble nickel compounds is 0.5 mg m^{-3} . The short-term exposure limit (STEL) for nickel carbonyl is 0.24 mg m^{-3} (15 minute reference period) [8].

Health Effects of Acute / Single Exposure

Human Data

Inhalation

Nickel carbonyl is the most toxic nickel compound following acute exposure. The symptoms of acute exposure to nickel carbonyl occur in two stages, immediate and delayed [1, 9]. The immediate toxic effects of nickel carbonyl exposure are respiratory tract irritation and neurological symptoms. Initial symptoms include dizziness, frontal headache, nausea, vomiting, irritability and upper airway irritation [4, 5]. Following the immediate symptoms there is an asymptomatic period before the onset of the delayed pulmonary symptoms; similar to those of a viral pneumonia [1, 9]. Symptoms include chest pain, cough, dyspnoea, tachycardia, weakness and fever with leukocytosis. Pulmonary haemorrhage, cerebral oedema, toxic myocarditis, pulmonary oedema and pneumonitis may occur in severe cases [1, 4]. Neurasthenic syndrome and weakness may develop following a severe exposure to nickel carbonyl, and may persist for up to 6 months [4].

There are limited data available on the acute effects of elemental nickel inhalation in humans. Death due to adult respiratory distress syndrome was reported in an individual who was exposed to elemental nickel at a concentration of 382 mg m^{-3} for 90 minutes [2, 5].

Ingestion

Only limited data are available on the effects of acute ingestion of nickel salts in humans.

Thirty-two industrial workers accidentally ingested water contaminated with nickel sulphate and nickel chloride (1.63 g L^{-1}). Twenty of the workers rapidly developed symptoms including nausea, vomiting, diarrhoea, headache, cough and shortness of breath; all were asymptomatic within three days. Temporary elevated levels of blood reticulocytes (7 workers), urine-albumin (3 workers) and serum bilirubin (2 workers) were also reported. The nickel doses in the symptomatic workers were estimated to range from $7\text{-}36 \text{ mg kg}^{-1} \text{ bw}$ [1, 2].

A 2 year old child ingested approximately $570 \text{ mg kg}^{-1} \text{ bw}$ of nickel sulphate crystals and on admission to hospital she was somnolent with wide and unresponsive pupils, high pulse rate and pulmonary rhonchi. Cardiac arrest occurred 4 hours after ingestion. Gastrointestinal distress and muscular pain were also reported [1, 5].

Ingestion of a single dose of nickel salts has been reported to exacerbate vesicular hand eczema in nickel-allergic patients [1, 2, 5].

Dermal/ocular exposure

Primary skin irritation was observed when human skin was patch tested with a solution of nickel salts. A 10% aqueous solution of nickel chloride caused irritation when applied to the back. Irritation was observed when a 20% aqueous solution of nickel sulphate was applied to human forearm skin once a day for 3 days [1].

Animal and In-Vitro Data

General toxicity

The main target organ for nickel induced toxicity in animals is the respiratory tract [3]. The toxicity of nickel compounds appears to be related to the solubility of the compound. Several acute animal studies have reported soluble nickel sulphate as being the most toxic and insoluble nickel oxide the least toxic [2].

Inhalation

The 30 minute LC₅₀ values for nickel carbonyl inhalation in cats, rats and mice were 0.19 mg L⁻¹, 0.24 mg L⁻¹ and 0.067 mg L⁻¹, respectively. The pulmonary effects and lesions are comparable to those seen in cases of human nickel carbonyl poisoning. Pulmonary effects include oedema, intra-alveolar haemorrhage and fibrosis. Other lesions including congestion, oedema, focal haemorrhage, vacuolisation and mild inflammation in the brain, liver, kidney, adrenals, spleen and pancreas have been reported in laboratory animals acutely exposed to nickel carbonyl [1].

In an acute inhalation study, chronic inflammation was observed in rats exposed to nickel sulphate (0.7 mg m⁻³) or nickel subsulphide (0.44 mg m⁻³) 6 hours day⁻¹ for 12 days in a 16 day period. Alveolitis was reported in rats exposed to 0.22 mg m⁻³ as nickel subsulphide 6 hours day⁻¹ for 7 days. Acute lung inflammation was observed in rats exposed to nickel oxide at 7.9 mg m⁻³. In mice, the lowest observed adverse effect levels (LOAELs) of 0.7, 1.83 and > 23.6 mg m⁻³ as nickel sulphate, nickel subsulphide and nickel oxide, respectively, were identified for chronic inflammation. These results suggest that mice are less sensitive than rats to the acute toxicity of nickel [2].

Atrophy of the nasal olfactory epithelium has been reported in rats exposed to nickel sulphate or nickel subsulphide [2]. Inhalation exposure to nickel chloride has resulted in immunological effects including alveolar macrophage alterations in laboratory animals [2].

Ingestion

Acute oral lethality studies suggest that soluble nickel compounds are more toxic than the less-soluble nickel compounds. Acute oral LD₅₀ values of 46 and 39 mg kg⁻¹ nickel sulphate were reported in male and female rats, respectively. In rats the oral LD₅₀ values for the less soluble nickel compounds nickel oxide and subsulphide were >3,930 and >3,665 mg kg⁻¹, respectively [2].

The oral LD₅₀ for nickel acetate has been reported as 350 mg kg⁻¹ in the rat and 410 mg kg⁻¹ in the mouse. Diarrhoea, distress and lethargy were noted 2 – 3 hours after exposure in animals which died [1].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

The respiratory tract is the primary site of toxicity following inhalation of nickel and its compounds. Rhinitis, sinusitis, asthma, chronic bronchitis, emphysema and nasal septal perforations have frequently been reported in individuals occupationally exposed to nickel or nickel compounds. Hyposmia or anosmia was also noted in many of the workers with sinusitis. Pulmonary changes with fibrosis were also observed in workers exposed to nickel dust or fumes [1, 5].

Ingestion

There are currently no data available on the effects of chronic ingestion to nickel or nickel compounds in humans.

Dermal / ocular exposure

Nickel and water soluble nickel salts are powerful skin sensitisers. Following sensitisation, dermal exposure to even small amounts of nickel or water soluble nickel salts can cause outbreaks of dermatitis [1].

Contact dermatitis is the predominant effect of nickel in the general population due, in the past, to prolonged dermal exposure from products such as jewellery, buttons and zips. The incidence of nickel sensitivity is higher in females (around 10% of the population) compared with males and has been associated particularly with ear piercing. Occupational induced contact dermatitis occurs in individuals who work in refining and electroplating industries [10].

Genotoxicity

Cytogenetic studies in workers involved in nickel crushing/roasting/smelting processes (mainly exposed to nickel oxide and nickel sulphide) and electrolysis (mainly exposed to nickel chloride and nickel sulphate) reported elevated levels of chromosome aberrations, mainly gaps). Chromosome aberrations, including elevated levels of gaps and breaks, were also seen in retired nickel workers from the same plant who had plasma nickel levels of $2 \mu\text{g L}^{-1}$ [1, 7].

Elevated levels of sister chromatid exchange and chromosome aberrations were reported in electroplating workers. No exposure or chemical data were provided [1]. In contrast, no effects were observed in workers in a nickel carbonyl production plant, although authors proposed this was due to low exposure due to adequate protective measures [1, 7].

Carcinogenicity

Increased risks of cancer of the lungs and nasal passages have been reported in workers exposed to nickel compounds (oxidic and sulphidic nickel) during roasting, sintering and calcining processes, in refineries in the UK, Norway and Canada. These processes have involved substantial exposure to insoluble nickel compounds such as nickel subsulphide and oxide, and also possibly to soluble salts such as nickel sulphate.

Soluble nickel is also associated with an increased risk of cancer to the lungs and nasal passages in, for example, electrolysis workers with estimated exposures of 1-2 mg m⁻³. There is evidence to suggest it may enhance risks associated with exposure to less soluble nickel compounds [1, 7, 11].

The IARC concluded that there is sufficient evidence in humans for the carcinogenicity of nickel sulphate, and of the combinations of nickel sulphides and oxides encountered in the nickel refining industry. Nickel compounds are classified as carcinogenic to humans (Group 1) [7].

No significant increase in respiratory tract cancer was reported in users of elemental nickel powder or in workers involved in high-nickel alloy manufacture. IARC concluded that there is inadequate evidence in humans for the carcinogenicity of elemental nickel and nickel alloys. There was sufficient evidence in experimental animals for the carcinogenicity of elemental nickel hence it was classified as possibly carcinogenic to humans (Group 2B). There was limited evidence for carcinogenicity of nickel alloys in animals. IARC did not give any overall classification for nickel alloys [7].

Reproductive and developmental toxicity

There are no data available on the reproductive and developmental effects of nickel and its compounds in humans.

Animal and In-Vitro Data

Inhalation

A number of studies have investigated the effect of chronic inhalation exposure to nickel or nickel compounds in laboratory animals. The target organ for nickel toxicity is the lung.

Lung irritation was observed in rats, mice and guinea pigs exposed to elemental nickel dust at 15 mg m⁻³. In rats, nasal sinus inflammation and ulcers were also observed [1].

Rats and mice exposed to 0.06 mg m⁻³ nickel sulphate, 0.11 mg m⁻³ nickel subsulphide and 0.4 mg m⁻³ nickel oxide six hours per day, five days per week for 16 or 90 days resulted in inflammation of the lungs, fibrosis and increased lung weight. Toxicity was directly related to the compounds solubility [5].

The toxicity of nickel oxide, nickel sulphate and nickel subsulphide was also investigated in a two year inhalation study in rats and mice. Chronic lung inflammation was observed in rats and mice at the lowest administered dose of nickel oxide (0.5 mg m⁻³) and nickel subsulphide (0.11 mg m⁻³) in both species. Nickel sulphate produced lung effects in both species at doses of 0.06 mg m⁻³ and above [5].

Inflammatory changes in the nasal mucous membranes and the trachea, bronchitis and slight fibrosis in the lung were reported in rabbits exposed to 100 mg m⁻³ nickel graphite dust for 3 hours a day, 5 days a week for 6 months [1].

Rats exposed to nickel oxide (53 mg m⁻³ nickel oxide) for the life span developed emphysema and pneumoconiosis. Abscesses and metaplastic changes were observed in rats exposed to nickel subsulphide for 78 weeks [1].

Other effects reported in laboratory animals exposed to nickel or its compounds include atrophy of the nasal epithelium, reduction in body weight gain and immunological and lymphoreticular effects [1, 2].

Ingestion

The main toxic effects observed following long-term oral exposure of laboratory animals to nickel compounds are on the lungs and kidneys.

Mice exposed to $\geq 108 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ as nickel sulphate in drinking water for 180 days developed minor renal tubular damage. Significant decreases in urinary glucose and urine volume were reported in rats exposed to 14.4 or 28.8 $\text{mg kg}^{-1} \text{ day}$ as nickel sulphate in drinking water for 13 days. Increases in blood urea were also observed in rats exposed to 28.8 mg kg^{-1} [2].

In a two year dietary study rats were given 0, 5, 50 or 125 $\text{mg kg}^{-1} \text{ bw day}^{-1}$ nickel sulphate. A significant reduction in body weight gain was noted in rats given $\geq 50 \text{ mg kg}^{-1} \text{ day}^{-1}$. No histopathological changes were observed; therefore the NOAEL was taken to be 5 $\text{mg kg}^{-1} \text{ bw day}^{-1}$ [5].

In a 90 day gavage study in rats administered nickel chloride the NOAEL was found to be 5 $\text{mg kg}^{-1} \text{ bw day}^{-1}$. Effects on body weight, on organ weight and on the nervous system were reported at doses of 35 and 100 $\text{mg kg}^{-1} \text{ bw day}^{-1}$ [5].

Pneumonitis was reported in rats administered 8.6 $\text{mg kg}^{-1} \text{ bw day}^{-1}$ as nickel chloride by gavage for 91 days. Significant increases in absolute and relative lung weights were reported in rats exposed to 28.8 $\text{mg kg}^{-1} \text{ bw day}^{-1}$ in drinking water for 13 weeks. Dogs exposed to 22.5 $\text{mg kg}^{-1} \text{ bw day}^{-1}$ as nickel sulphate in the diet for 2 years developed emphysema, bronchiolectasis and cholesterol granulomas [2].

A reduction in body weight gain has also been reported in laboratory animals following chronic oral exposure to nickel compounds [2].

Dermal/ocular exposure

Skin atrophy, acanthosis, and hyperkeratinisation were observed in rats following repeated skin application of 40 – 100 mg kg^{-1} as nickel sulphate [1].

Experimental sensitisation has been observed in laboratory animals, but only under special conditions rather than using more routine methods [1].

Genotoxicity

Chromosomal aberrations were induced in the bone marrow cells of Chinese hamsters and Swiss mice administered nickel chloride by intraperitoneal injection [1, 7].

Nickel compounds produced negative results in the majority of bacterial mutation assays reported [1, 7].

In one study, elemental nickel did not induce chromosomal aberrations in cultured human peripheral lymphocytes [7].

Nickel subsulphide induced cell transformation and increased the frequency of sister chromatid exchange but did not cause gene mutation in cultured human cells. In animal cells *in-vitro* nickel subsulphide and nickel sulphide induced cell transformation, gene mutation

and DNA damage; nickel sulphide also induced sister chromatid exchange and chromosome aberrations [7].

Soluble nickel compounds have generally given positive results in human and animal *in-vitro* assays. In human cells *in-vitro*, nickel sulphate induced cell transformation and chromosome aberrations, nickel sulphate and nickel chloride increased the frequency of sister chromatid exchange. Nickel sulphate and nickel chloride have been reported to cause cell transformation, chromosome aberrations, sister chromatid exchange and gene mutations in cultured animal cells. Nickel chloride has also been reported to induce DNA damage in animal cells [1, 7].

In summary nickel compounds are generally inactive in bacterial assays but positive results were obtained in mammalian cell assays. There is a lack of information from published *in-vivo* assays.

Carcinogenicity

A number of studies have investigated the carcinogenicity of nickel and its compounds in experimental animals [7].

Several studies reported that tumours were induced at the site of injection or implantation of a nickel compound. In these studies nickel subsulphide was the most potent carcinogen [7].

An inhalation study reported an increased incidence of lung tumours (adenomas, adenocarcinomas, squamous cell carcinomas and fibrosarcoma) in rats exposed to nickel subsulphide [2, 7]. In a 2 year NTP inhalation bioassay in mice and rats exposed to nickel subsulphide, nickel oxide or nickel sulphate no increased incidences of tumours were reported in mice exposed to any of the compounds or rats exposed to nickel sulphate. However, significant increases in lung adenomas and carcinomas were observed in rats exposed to the less-soluble nickel compounds (nickel oxide and nickel subsulphide). Exposure to nickel oxide or subsulphide also caused significant increases in the incidence of adrenal pheochromocytomas in rats [2, 3].

In 1990, IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of elemental nickel, nickel monoxides, nickel hydroxides and crystalline nickel sulphides. IARC also concluded that there is insufficient evidence in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides and nickel telluride. The evidence in experimental animals for the carcinogenicity of nickel trioxide, amorphous nickel sulphide and nickel titanate was considered to be inadequate [7].

Reproductive and developmental toxicity

A number of multigeneration reproductive studies have been carried out in rats, administered soluble nickel salts in water. The main effect noted was increased neonatal mortality at exposures producing maternal toxicity. In some studies there was also some evidence for effects at levels that did not produce maternal toxicity [5].

In a two generation study using nickel chloride in drinking water, reduced numbers of viable pups and increased mortality was seen at doses above $30.8 \text{ mg kg}^{-1} \text{ bw day}^{-1}$, which were also associated with maternal toxicity. There was equivocal evidence at lower dose levels. In another two generation study in rats, however, increased perinatal mortality was seen in the second litter at the lowest dose investigated ($1.3 \text{ mg kg}^{-1} \text{ bw day}^{-1}$), but there was no clear dose response in this study. In a three generation study in rats, increased neonatal mortality was seen at doses estimated to be approximately $0.5 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ [5].

In a more recent gavage study, an increased post-implantation loss and pup mortality were seen in rats given nickel sulphate at $2.2 \text{ mg kg}^{-1} \text{ bw day}^{-1}$ [5].

A series of studies reported malformations in the offspring of rats and hamsters exposed to nickel carbonyl by inhalation or injection before, or a few days after implantation. Malformations reported include anophthalmia, microphthalmia, cystic lungs, fused rib, cleft palate, exencephaly and hydronephrosis [1, 7].

Both nickel carbonyl and a number of soluble nickel salts (sulphate, chloride, nitrate and carbonate) are classified in the EU as toxic to reproduction Category 2 on the basis of their developmental toxicity (and are required to be labelled 'may cause harm to the unborn child') [12].

There are limited data from investigating nickel compounds specifically in developmental toxicant studies.

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