

Nickel Compounds and Metallic Nickel

Introduction

Nickel compounds and metallic nickel have many industrial and commercial applications, including use in stainless steel and other nickel alloys, catalysts, batteries, pigments, and ceramics. Nickel and Certain Nickel Compounds were listed in the *First Annual Report on Carcinogens* (1980) as *reasonably anticipated to be human carcinogens*. Nickel compounds as a class were first listed as *known to be human carcinogens* in the *Tenth Report on Carcinogens* (2002); this listing supersedes the listing of "certain nickel compounds" and applies to all members of the class. Metallic nickel was reevaluated in 2000 and remains listed as *reasonably anticipated to be a human carcinogen*. Nickel alloys were reviewed in 2000 but were not recommended for listing in the Report on Carcinogens (see Appendix C).

The profiles for nickel compounds and metallic nickel follow this introduction. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for nickel compounds and metallic nickel. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to both nickel compounds and metallic nickel and therefore is combined into one section following the discussions of cancer studies.

Nickel Compounds

No separate CAS No. assigned for nickel compounds as a class

Known to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Nickel compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. The combined results of epidemiological studies, mechanistic studies, and cancer studies in rodents support the concept that nickel compounds generate nickel ions in target cells at sites critical for carcinogenesis, thus allowing consideration and evaluation of these compounds as a single group.

Cancer Studies in Humans

Several epidemiological cohort studies of workers exposed to various nickel compounds showed an elevated risk of death from lung cancer and nasal cancer. Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel-refining industry cause cancer in humans. The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of nickel compounds encountered in the nickel-refining industry in humans (IARC 1990). In an additional study, nickel-refinery workers exposed primarily to soluble nickel compounds had a significant excess risk of lung cancer, and smoking and nickel exposure had a synergistic effect on cancer risk (Anderson *et al.* 1996). These workers also had an excess risk of nasal cancer.

Cancer Studies in Experimental Animals

In rats and in some studies with mice, inhalation or intratracheal instillation of nickel subsulfide or nickel oxide led to dose-related induction of benign and malignant lung tumors, including carcinoma (IARC 1990, NTP 1996a,b). Inhalation of nickel compounds also

caused tumors at tissue sites other than the lung; in particular, benign or malignant adrenal-gland tumors (pheochromocytoma) were observed in rats (NTP 1996a,b). Injection of rodents with various nickel compounds was repeatedly shown to cause dose-dependent increases in tumors in several species and at several different sites. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral, intrarenal, intratesticular, and intraocular injections of nickel compounds all caused cancer (usually sarcoma) at the injection site. Injection of nickel also produced distant tumors of the liver in some strains of mice. IARC concluded that there was sufficient evidence of the carcinogenicity of several nickel compounds (monoxides, hydroxides, and crystalline sulfides) in experimental animals (IARC 1990).

Soluble nickel acetate is a complete transplacental carcinogen in rats. Brief exposure of pregnant rats to nickel acetate by intraperitoneal injection during pregnancy caused pituitary cancer in the offspring. Transplacental exposure to nickel acetate followed by exposure of the offspring to barbital (a known tumor promoter) caused kidney tumors (renal cortical and pelvic tumors) (Diwan *et al.* 1992). In adult rats, injection of soluble nickel salts followed by barbital exposure caused kidney cancer (renal cortical adenocarcinoma) that frequently metastasized to the lung, liver, and spleen (Kasprzak *et al.* 1990).

Metallic Nickel

CAS No. 7440-02-0

Reasonably anticipated to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as Ni

Carcinogenicity

Metallic nickel is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Metallic nickel caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. In both rats and hamsters, metallic nickel powder caused tumors when administered by intratracheal instillation or by subcutaneous, intramuscular, or intraperitoneal injection. Intratracheal instillation of metallic nickel powder primarily caused adenocarcinoma, whereas injection most frequently caused sarcoma, demonstrating that metallic nickel can induce both epithelial and connective-tissue tumors (IARC 1973, 1976, 1990).

Cancer Studies in Humans

The available epidemiological studies of workers exposed to metallic nickel are limited by inadequate exposure information, low exposure levels, short follow-up periods, and small numbers of cases.

Nickel Compounds and Metallic Nickel

Studies on Mechanisms of Carcinogenesis

The available evidence suggests that metallic nickel has carcinogenic properties because it can slowly dissolve in the body and release ionic nickel, an active genotoxic and carcinogenic form of nickel. There is no evidence to suggest that the mechanisms by which nickel causes tumors in experimental animals would not also operate in humans.

Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, caused genetic damage, including DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair. Chromosomal aberrations have been observed in humans occupationally exposed to nickel. Nickel can bind ionically to cellular components, including DNA. The reduction-oxidation activity of the nickel ion may produce reactive oxygen species that attack DNA, and exposure to nickel ion *in vitro* or *in vivo* can result in production of 8-hydroxy-2'-deoxyguanosine in target tissues for cancer caused by nickel (IARC 1990, Kasprzak *et al.* 1990).

The carcinogenic potency of various nickel compounds varies widely, based on solubility properties and speciation. Studies indicate that soluble nickel salts can be complete carcinogens (Diwan *et al.* 1992) or initiators of carcinogenesis (Kasprzak *et al.* 1990) at tissue sites distant from the site of administration, which confirms that ionic nickel is the carcinogenic species. Differences in the potency of nickel compounds may relate to the specific properties of the compounds that affect the availability of ionic nickel at target sites. The listings of nickel compounds and metallic nickel are based on a large body of scientific evidence supporting the concept that nickel ion is carcinogenic. The hazard associated with a particular nickel compound is related largely to the compound's propensity to release ionic nickel in the body. The evidence suggests that the relatively insoluble metallic nickel is less likely to present a carcinogenic hazard than are the nickel compounds that tend to release proportionately more nickel ion. This view agrees with that expressed by IARC (1990), which based its evaluation of the carcinogenicity of nickel compounds as a group on the combined results of human epidemiological studies, cancer studies in experimental animals, and other data supporting the "underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells." The IARC review noted that the carcinogenicity of nickel compounds depends not solely on their capacity to release ionic nickel, but also on factors that promote localization of high concentrations of nickel ions at critical tissue sites. This conclusion is consistent with evidence from studies in experimental animals indicating that nickel compounds of moderate solubility can, under certain exposure conditions, be more carcinogenic than more soluble compounds. Therefore, it is difficult to predict with any certainty the relative carcinogenic hazard posed by a particular nickel compound without a full understanding of its ability to release ionic nickel under specific exposure conditions.

Properties

Metallic nickel is a group 10 metallic element. It is a lustrous, silvery, hard ferromagnetic metal or a gray powder. It has a vapor pressure of 1 mm Hg at 1,810°C. Metallic nickel is insoluble in water and ammonia, slightly soluble in hydrochloric acid and sulfuric acid, and soluble in dilute nitric acid. It is resistant to attack by air and water at standard temperatures. However, powdered nickel is reactive in air and may ignite spontaneously (IARC 1990, ATSDR 1997, HSDB 2009).

Nickel oxides and hydroxides are practically insoluble in water and soluble in acids and ammonium hydroxide. Nickel monoxide (also known as nickel oxide) is a green to black powder that becomes yellow when heated. The temperature at which the crystal is formed determines the color of the crystal. It is soluble in acids and ammonium hydroxide. Nickel monoxide reacts with acids to form nickel salts and soaps, and mixtures of nickel monoxide and barium oxide react violently with iodine and hydrogen sulfide in air. Nickel hydroxide occurs either as green crystals or as a black powder. It does not burn, but it may produce toxic gases when heated to decomposition. It is available at 97% purity (IARC 1990, HSDB 2009).

Nickel sulfides are insoluble in water, and some occur in more than one form. Nickel subsulfide (α form) occurs as lustrous pale-yellowish or bronze crystals that are soluble in nitric acid. Nickel sulfide occurs in three forms (α , β , and amorphous) as dark-green to black crystals or powder. Nickel disulfide occurs as black crystals or powder and decomposes at temperatures above 400°C (IARC 1990).

Nickel salts are green to yellow crystals that generally are soluble in water and decompose when heated. Nickel acetate occurs as a dull-green powder that effloresces somewhat in air. It is available as the tetrahydrate at greater than 97% purity. Nickel chloride occurs as yellow (anhydrous) or green (hexahydrate) deliquescent crystals. It is soluble in ethanol and ammonium hydroxide and insoluble in ammonia. The hexahydrate form is available as a laboratory reagent at greater than 99% purity or as industrial products containing approximately 24.7% nickel. Nickel sulfate occurs as yellow, green, or blue crystals and is available in anhydrous, hexahydrate, or heptahydrate forms. The hexahydrate melts at 53.3°C and the heptahydrate at 99°C; both forms are available at greater than 99% purity. Nickel carbonate occurs as light-green rhombic crystals. It is practically insoluble in water but soluble in dilute acids and ammonia. Laboratory reagent grades contain 45% or 47.5% nickel, and industrial grades contain approximately 45% nickel (IARC 1990, HSDB 2009).

Nickel carbonyl occurs as a colorless, volatile, highly flammable liquid with a musty odor. It is practically insoluble in water but soluble in alcohol, benzene, chloroform, acetone, and carbon tetrachloride, and insoluble in dilute acids and dilute alkalis. It is available in a technical grade at greater than 99% purity. Nickel carbonyl decays spontaneously in air and may decompose violently when exposed to heat or flame in the presence of air or oxygen. When heated or on contact with acid or acid fumes, it emits toxic carbon monoxide fumes (HSDB 2009). Nickelocene occurs as dark-green crystals. It is insoluble in water but soluble in common organic solvents. It is highly reactive and decomposes in air, acetone, alcohol, and ether. It is available in solid form at greater than 90% purity or as an 8% to 10% solution in toluene (IARC 1990).

Physical and chemical properties of metallic nickel and selected nickel compounds are listed in the table on the next page, along with their chemical formulas.

Use

Because of its unique properties, nickel has many uses in industry. The majority (about 80%) of all nickel is used in alloys, because it imparts such properties as corrosion resistance, heat resistance, hardness, and strength (ATSDR 1997). The main uses of nickel are in the production of stainless steel, copper-nickel alloys, and other corrosion-resistant alloys. Pure nickel metal is used in electroplating, as a chemical catalyst, and in the manufacture of alkaline batteries, coins, welding products, magnets, electrical contacts and electrodes, spark plugs, machinery parts, and surgical and dental prostheses (IARC 1990, HSDB 2009). In 2009, 45% of the nickel used in the United States was used in stainless and alloy steel production, 39% in nonferrous alloys and superalloys, 11% in electroplating, and 5% in other uses. The end uses in 2009 were 32% in transportation, 14% in the chemical industry, 10% in electrical equipment, 8% in construction, 8% in fabricated metal products, 8% in the petroleum industry, 6% in household appliances, 6% in machinery, and 8% for other uses (Kuck 2010).

Nickel oxide sinters (a coarse form of nickel monoxide) are used in steel and alloy manufacturing. Green nickel monoxide is used in electronics, in fuel-cell electrodes, as a colorant in ceramics and glass, and to make nickel catalysts. Black nickel monoxide is used in the ceramics industry, to manufacture nickel catalysts, and to manufacture nickel salts. Nickel hydroxide is used in nickel-cadmium batter-

Substance	Formula	Atomic or molec. wt.	Specific gravity	Melting point	Boiling point
Metallic nickel	Ni	58.7	8.91	1,455°C	2,730°C
Nickel monoxide	NiO	74.7	6.72	1,955°C	NR
Nickel hydroxide	Ni(OH) ₂	92.7	4.1	230°C (dec)	N/A
Nickel acetate	Ni(C ₂ H ₃ O ₂) ₂	176.8	1.80	NR	16.6°C
Nickel chloride	NiCl ₂	129.6	3.51	1,001°C	973°C (sub)
Nickel sulfate	NiSO ₄	154.8	4.01	848°C (dec)	N/A
Nickel carbonate	NiCO ₃	118.7	4.39	dec	N/A
Nickel carbonyl	Ni(CO) ₄	170.7	1.32	-19°C	43°C

Source: HSDB 2009. NR = not reported; dec = decomposes; N/A = not applicable; sub = sublimes.

ies and as a catalyst intermediate. Nickel sulfides are used as catalysts in the petrochemical industry when high concentrations of sulfur are present in the distillates and as intermediates in hydrometallurgical processing of silicate-oxide nickel ores (IARC 1990). Nickel subsulfide is used in lithium batteries (HSDB 2009).

Nickel salts are widely used in industry. Nickel acetate is used as a catalyst intermediate, as a dye fixative in the textile industry, in electroplating, and as a sealer for anodized aluminum. Nickel chloride is used in nickel catalysts, to absorb ammonia in industrial gas masks, and in electroplating. Nickel sulfates are used in electroplating and electrodeless nickel plating, as chemical intermediates to produce other nickel compounds, and in nickel flashings on steel to prepare it to be porcelain-enameled. Nickel carbonate is used to prepare nickel monoxide, nickel powder, nickel catalysts, colored glass, and certain nickel pigments. It also is used in electroplating and as a catalyst to remove organic contaminants from water (IARC 1990, HSDB 2009).

Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and for continuous nickel coatings on steel and other metals. It also has many small-scale applications, such as vapor plating of nickel and deposition of nickel in semiconductor manufacturing. Nickelocene is used as a catalyst and complexing agent (IARC 1990).

Production

Nickel is refined from either sulfide or silicate-oxide ores, which generally contain no more than 3% nickel. Magmatic sulfide ores are mined underground or by open-pit methods. Pentlandite ([NiFe]₉S₈) is the principal sulfide ore; the largest known deposit is in Ontario, Canada, and substantial deposits are found in Minnesota, South Africa, Russia, Finland, and western Australia. Silicate-oxide ores, or garnierites, originate in (current or former) humid tropical regions and are surface mined by open-pit methods (IARC 1990, ATSDR 1997). Primary nickel production from mines in the United States was steady from the late 1950s to 1980, ranging from 10,000 to 14,000 metric tons (22 million to 31 million pounds) per year (USGS 2010). After 1980, primary production of nickel in the United States started declining, and no primary production has occurred since 1998, when 4,290 metric tons (9.5 million pounds) was produced.

Recycled scrap metal accounts for a large part of the nickel supply; in addition, relatively small quantities of nickel are recovered as a by-product at copper and precious-metal refineries or from reclamation of spent catalysts (Kuck 2009). Production from these secondary sources increased steadily from 21,000 metric tons (46 million pounds) in 1970 to a high of 106,000 metric tons (234 million pounds) in 2006, then declined to 63,500 metric tons (140 million pounds) in 2009.

From 1980 to 2008, U.S. consumption of nickel ranged from 163,000 to 250,000 metric tons (359 to 551 million pounds); consumption was highest in 2006 (USGS 2010). In 2009, consumption was 152,000 metric tons (335 million pounds), the lowest level since 1972 (Kuck 2010, USGS 2010). The demand for nickel is expected to

grow because of increased demand for nickel-based batteries and nickel-bearing superalloys used in aircraft engines (Kuck 2009), with the United States being dependent on foreign sources for most nickel supplies.

From 1980 to 2008, U.S. imports of nickel remained fairly steady, ranging from 117,000 to 190,000 metric tons (258 million to 419 million pounds); 149,000 metric tons (329 million pounds) was imported in 2008. In 2009, imports fell to 114,800 metric tons (253 million pounds). U.S. exports of nickel ranged from 17,700 to 67,300 metric tons (39 to 148 million pounds) between 1980 and 2006, increasing to 116,000 metric tons (256 million pounds) in 2007, and were 99,680 metric tons (220 million pounds) in 2009 (Kuck 2010, USGS 2010).

Exposure

Environmental exposure to nickel occurs through inhalation, ingestion, and dermal contact. The general population is exposed to low levels of nickel because it is widely present in air, water, food, and consumer products. The general population takes in most nickel through food; the average daily intake from food in the United States is estimated at 150 to 168 µg. Typical daily intake from drinking water is 2 µg and from air is 0.1 to 1 µg. The general population is also exposed to nickel in nickel alloys and nickel-plated materials, such as coins, steel, and jewelry, and residual nickel may be found in soaps, fats, and oils (ATSDR 1997).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, releases of nickel to the environment trended downwards from 1988 to 2003 and then increased, while releases of nickel compounds increased until 1998 but have since decreased by half. In 2007, 1,552 facilities released 8.3 million pounds of nickel, and 1,027 facilities released 30.5 million pounds of nickel compounds (TRI 2009).

Occupational exposure to nickel occurs mainly through inhalation of dust particles and fumes or through dermal contact. Nickel workers can also ingest nickel-containing dusts. Occupational exposure is common for workers involved in mining, smelting, welding, casting, spray-painting and grinding, electroplating, production and use of nickel catalysts, polishing of nickel-containing alloys, and other jobs where nickel and nickel compounds are produced or used (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 23,272 workers potentially were exposed to nickel and nickel compounds (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 507,681 workers, including 19,673 women, potentially were exposed to nickel (molecular formula unknown) (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Nickel carbonyl, nickel cyanide, nickel nitrate, and nickel nitrite are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials; nickel picrate is forbidden from transport.

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Nickel carbonyl, nickel cyanide, and nickel tetracarbonyl are considered marine pollutants and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Nickel compounds are listed as mobile-source air toxics for which regulations are to be developed.

National Emission Standards for Hazardous Air Pollutants: Nickel and its compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 1,000 lb for nickel carbonyl.

Urban Air Toxics Strategy: Nickel compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Biosolids Rule: Limits have been established for nickel in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Effluent Guidelines: Nickel and nickel compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 610 µg/L for metallic nickel; based on fish or shellfish consumption only = 4,600 µg/L for metallic nickel.

Numerous nickel compounds are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for nickel, nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate; 10 lb for nickel carbonyl, nickel cyanide, and nickel hydroxide.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Nickel and nickel compounds are listed substances subject to reporting requirements.

Threshold planning quantity (TPQ) = 1 lb for nickel carbonyl.

Reportable quantity (RQ) = 10 lb for nickel carbonyl.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of nickel or nickel compounds = P073, P074, F006.

Nickel and nickel compounds are listed as hazardous constituents of waste.

Food and Drug Administration (FDA)

Maximum permissible level of nickel in bottled water = 0.1 mg/L.

The color additives ferric ammonium ferrocyanide and ferric ferrocyanide, when used in drugs, may contain nickel at levels no greater than 200 ppm.

Menhaden oil may contain nickel at concentrations not to exceed 0.5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 1 mg/m³ for elemental nickel and compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value - time-weighted average (TLV-TWA) = 1.5 mg/m³ for elemental nickel; = 0.1 mg/m³ for soluble inorganic nickel compounds and nickel subsulfide; = 0.2 mg/m³ for insoluble inorganic nickel compounds).

Threshold limit value - ceiling (TLV-C) = 0.05 ppm for nickel carbonyl.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.015 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Immediately dangerous to life and health (IDLH) limit = 10 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 2 ppm (14 mg/m³) for nickel carbonyl.

Metallic nickel and nickel compounds are listed as potential occupational carcinogens.

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