NICKEL COMPOUNDS
First listed in the *Tenth Report on Carcinogens*

METALLIC NICKEL
First listed in the *First Annual Report on Carcinogens*

INTRODUCTION

Nickel and "certain nickel compounds" were listed in the First Annual Report on Carcinogens as *reasonably anticipated to be human carcinogens*. The specific compounds included in this listing were (metallic) nickel, nickel acetate, nickel carbonate, nickel carbonyl, nickel hydroxide, nickelocene, nickel oxide, and nickel subsulfide. "Nickel compounds" as a class were reviewed for possible listing in the Ninth Edition of the Report on Carcinogens and were recommended to be listed as known human carcinogens. However, this listing was postponed until metallic nickel and nickel alloys could be specifically reviewed for possible listing in the Report on Carcinogens. These substances were reviewed for possible listing in the Tenth Edition of the Report on Carcinogens, and it was recommended that metallic nickel remain listed as *reasonably anticipated to be a human carcinogen*, whereas nickel alloys were not recommended for listing (see Appendix C).

The listing is based on a large body of scientific evidence supporting the concept that the nickel ion is carcinogenic. The hazard associated with a particular nickel compound or alloy largely relates to the propensity for the compound to release ionic nickel in the body. The evidence suggests that the relatively insoluble metallic nickel and nickel alloys are 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 the International Agency for Research on Cancer (IARC) (IARC 1990), which based its overall evaluation of the carcinogenicity of nickel compounds as a group on the combined results of human epidemiological studies, carcinogenicity 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 group correctly pointed out 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 experimental animals indicating that nickel compounds of moderate solubility can, under certain exposure conditions, be more carcinogenic than compounds that are more soluble. Thus, 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.

The evidence for the carcinogenicity of nickel compounds and metallic nickel is discussed separately; however, information on properties, use, production, exposure, and regulation is common to both and is combined. The listings for nickel and nickel compounds are as follows:

- Nickel compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information, which indicates a causal relationship between exposure to nickel compounds and human cancer.

- Metallic nickel is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals.

CARCINOGENICITY

Nickel Compounds

Nickel compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information, which indicates a causal relationship between exposure to nickel compounds and human cancer. The findings of increased risk of cancer in exposed workers are supported by evidence from experimental animals that shows that exposure to an assortment of nickel compounds by multiple routes causes malignant tumors to form at various sites in multiple species of experimental animals. The combined results of epidemiological studies, mechanistic studies and carcinogenesis 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. The IARC (1990) evaluation of nickel and nickel compounds concluded that nickel compounds are carcinogenic to humans based on sufficient evidence for the carcinogenicity of nickel compounds in the nickel refining industry and very strong evidence of carcinogenicity of a variety of nickel compounds in experimental studies in rodents.

Several cohort studies of workers exposed to various nickel compounds showed an elevated risk of death from lung cancer and nasal cancer (IARC 1990). 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 industries cause cancer in humans. IARC (1990) made the overall evaluation of nickel compounds as a group based on indications from mechanistic and animal studies that the event responsible for inducing cancer is generation of ionic nickel at the target site. An additional study has shown that exposure of nickel refinery workers to soluble nickel compounds alone or in combination with other forms of nickel results in significant excess risks for lung and nasal cancer and that smoking and nickel exposure have a multiplicative effect (Andersen *et al*. 1996). Nickel exposure in mild-steel welders is associated with cancer (carcinoma) of the trachea, bronchus, and lung in some cases (Simonato 1991), although subjects in these studies also were exposed to the known carcinogen chromium, which complicates the results.

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 1996 a,b). Inhalation of nickel compounds also causes tumors to form in organs other than the lung, in particular, malignant and benign pheochromocytoma in rats (NTP 1996 a,b). Injection of various nickel compounds has repeatedly been shown to produce dose-dependent increases in tumors at a variety of sites in several species of experimental animals. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral,

intrarenal, intratesticular, and intraocular injections of nickel compounds all have caused malignant tumors to form at the site of injection. These tumors are usually sarcomas, but other types also develop. Injection of nickel produces distant tumors of the liver in some strains of mice (IARC 1990). Soluble nickel acetate is an effective, complete transplacental carcinogen in rats, and brief exposure during pregnancy to this soluble nickel salt induces malignant pituitary tumors in the offspring. Additionally, exposure to nickel acetate through the placenta followed by exposure of the offspring to barbital (a known tumor promoter) produces tumors of the kidney (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 adenocarcinomas) that frequently metastasized to the lung, liver, and spleen (Kasprzak *et al*. 1990).

Metallic Nickel

Metallic nickel is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals. A variety of carcinogenicity studies in rodents indicate that metallic nickel can produce tumors when given by intratracheal instillation or subcutaneous, intramuscular, or intraperitoneal injection. Intratracheal instillation of metallic nickel induces primarily adenocarcinoma, whereas injection most frequently induces sarcoma, demonstrating that metallic nickel can induce both epithelial and connective-tissue tumors. Tumors have been produced by metallic nickel exposure in both rats and hamsters (IARC 1990).

The available studies of the carcinogenicity of metallic nickel in humans are inadequate for an evaluation.

OTHER INFORMATION RELATING TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, damage genetic material. DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair have been observed in cell-culture studies. 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 8-hydroxy-2'-deoxyguanosine can be produced *in vitro* and *in vivo* in target tissues for cancers caused by nickel (IARC 1990, Kasprzak *et al*. 1990). Nickel can induce chromosomal aberrations in exposed humans.

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) and/or initiators of carcinogenesis (Kasprzak *et al*. 1990) at sites distant from the application site, which confirms that ionic nickel is the carcinogenic species. Differences in potency of nickel compounds may relate to the specific properties of the compounds that affect the availability of ionic nickel at target sites.

Metallic nickel is probably a carcinogen because it can slowly dissolve in the body and release ionic nickel, an active genotoxic and carcinogenic form of nickel. No

available data suggest that mechanisms by which nickel induces cancer in experimental animals would not also operate in humans.

PROPERTIES

Metallic nickel is a lustrous silvery hard ferromagnetic metal or a gray powder. It is soluble in dilute nitric acid, slightly soluble in hydrochloric acid and sulfuric acid, and insoluble in cold and hot water and ammonia. It is available at 99.9% purity and in grades that include electrolytic, ingot, pellets, shot, sponge, powder, high-purity strip, and single crystals. Nickel powder reacts violently with fluorine (F2), ammonium nitrate, hydrazine, ammonia, performic acid, phosphorus, selenium, sulfur, potassium, titanium, and potassium chlorate. When certain nickel compounds are heated to decomposition, toxic gases and vapors (e.g., nickel carbonyl) may be released (IARC 1990, HSDB 2001, NTP 2001).

Nickel oxides and hydroxides are practically insoluble in water. Nickel monoxide 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. The melting point is above 1,950°C. 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 is soluble in acid and ammonium hydroxide. Nickel hydroxide does not burn, but it may produce toxic gases when heated to decomposition (>230°C). It is available at 97% purity (IARC 1990, HSDB 2001).

Nickel sulfides are insoluble in water, and some occur in different forms. Nickel subsulfide exists in both a low-temperature form (α-nickel subsulfide) and a high-temperature form (β-nickel subsulfide). It occurs as lustrous pale yellowish or bronze crystals that are soluble in nitric acid. When heated to decomposition, nickel subsulfide emits toxic fumes of sulfur oxides. Nickel sulfide occurs in three forms (α, β, and amorphous) as dark green to black crystals or powder. The amorphous form is slowly converted to nickel hydroxysulfide on contact with air. Nickel disulfide occurs as black crystals or powder and decomposes at temperatures above 400°C (IARC 1990, NTP 2001).

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 in a grade at greater than 97.0% purity. Nickel chloride occurs as yellow (anhydrous) or green (hexahydrate) deliquescent crystals. The hexahydrate form is available as a laboratory reagent at greater than 99% purity or as industrial products containing approximately 24.7% nickel. Nickel sulfates occur as yellow, green, or blue crystals and are available in anhydrous, hexahydrate, or heptahydrate forms. The hexahydrate and heptahydrate forms melt at 53.3°C and 99°C, respectively, and are available at greater than 99% purity. The anhydrous form decomposes at 848°C. Nickel carbonate occurs as light green rhombic crystals. It is soluble in dilute acids and ammonia, but practically insoluble in water. Laboratory reagent grades contain 45% or 47.5% nickel, and industrial grades contain approximately 45% nickel. Nickel carbonate decomposes before reaching a melting point (IARC 1990, HSDB 2001).

Nickel carbonyl occurs as a colorless volatile, highly flammable liquid with a musty odor. At temperatures above 43°C, it occurs as a gas. It is soluble in aqua regia,

ethanol, diethyl ether, benzene, and nitric acid, practically insoluble in water, and insoluble in dilute acids and dilute alkalies. It is available in a technical grade at greater than 99% purity. Nickel carbonyl 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, nickel carbonyl emits toxic carbon monoxide fumes. It decays spontaneously in air (HSDB 2001).

Nickelocene occurs as dark green crystals. It is soluble in common organic solvents and insoluble in water. Nickelocene is a highly reactive compound that 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).

USE

Nickel has many uses in industry because of its unique properties. 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 2001).

In 1987, approximately 39% of the primary nickel consumed in the United States went into stainless and alloy steel production, 28% into nonferrous alloys, and 22% into electroplating. At that time, the ultimate end uses for nickel were transportation, 24%; chemical industry, 15%; electrical equipment, 9%; construction, 9%; fabricated metal products, 8%; petroleum, 8%; household appliances, 7%; machinery, 7%; and other, 13% (USDOI 1988). More recent data indicate that 43% is used in stainless and alloy steel production, 34% in nonferrous alloys and superalloys, 13% in electroplating, and 10% in other uses. The current ultimate end uses are transportation, 29%; chemical industry, 13%; electrical equipment, 11%; construction, 8%; fabricated metal products, 7%; petroleum, 7%; household appliances, 6%; machinery, 6%; and other uses, 13% (USGS 2001a).

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 batteries and as a catalyst intermediate (IARC 1990).

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 2001).

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 2001).

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 depositing 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 ore. These ores generally contain no more than 3% nickel. Magmatic sulfide ores are mined underground or by open-pit methods. Pentlandite ($[NiFe]_9S_8$) 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 between the mid 1950s and 1980, ranging from approximately 10,000 to 14,000 metric tons per year. After 1980, primary production of nickel in the United States declined rapidly. Production from secondary ferrous sources (scrap metal recycling) ranged from approximately 25,000 to 37,600 metric tons per year from 1980 to 1990, whereas secondary production from nonferrous sources declined from approximately 16,700 metric tons in 1980 to 6,300 metric tons in 1990. In addition, relatively small quantities of nickel are recovered as a by-product at copper and precious metals refineries or from reclamation of spent catalysts. Between 1970 and 1990, the United States imported approximately 100,000 to 170,000 metric tons of nickel per year and exported between 11,000 and 40,000 metric tons per year (USGS 2001 a,b).

Primary production of nickel in the United States stopped in 1986 after the main facilities, a mine and smelter in Oregon and a refinery in Louisiana, were closed. In 1989, the Glenbrook Nickel Company purchased the Hanna mine and smelter in Riddle, Oregon, and restarted mining and smelting operations. Mining operations were phased out, and ore was imported from New Caledonia until the nickel smelter and the associated port facilities in Coos Bay, Oregon, were closed in early 1998 (ATSDR 1997, USGS 2001a). Since 1996, secondary nickel production in the United States has ranged from approximately 85,000 to 124,000 metric tons per year. Annual U.S. imports (primary and secondary sources combined) totaled approximately 150,000 to 179,000 metric tons between 1996 and 2000, and annual U.S. exports were approximately 38,000 to 56,600 metric tons (USGS 2001a). Nickel demand in the United States is expected to grow because of increased demand for stainless steel, nickel-bearing superalloys, and nickel-based batteries (Kuck 1999).

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. Typical average levels of airborne nickel are 0.00001 to 0.003 $\mu g/m^3$ in remote areas, 0.003 to 0.03 $\mu g/m^3$ in cities

with no metallurgical industry, and 0.07 to 0.77 μg/m^3 in nickel-processing areas. Intake of nickel by inhalation averages approximately 0.4 μg/day in urban areas and approximately 0.2 μg/day in rural areas. The average intake of nickel from drinking water in the United States is 10 μg/day or less. The average daily oral intake of nickel was estimated at 300 to 600 μg (HSDB 2001).

Occupational exposure to nickel occurs mainly by inhalation of dust particles and fumes or by dermal contact. Nickel workers also can ingest nickel-containing dusts. The National Occupational Exposure Survey conducted by NIOSH between 1981 and 1983 estimated that 507,681 workers potentially were exposed to nickel and nickel compounds (NIOSH 1990). 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 2001).

REGULATIONS

Nickel Compounds:

In 1980, the U.S. Consumer Product Safety Commission (CPSC) preliminarily determined that nickel carbonyl was not present in consumer products under its jurisdiction. Public comment was solicited to verify the accuracy of this information; no comments were received. Pending receipt of new information, CPSC plans no action on this chemical.

The U.S. Environmental Protection Agency (EPA) regulates nickel and nickel compounds under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), and Superfund Amendments and Reauthorization Act (SARA). Reportable quantities (RQs) have been established for nickel, nickel carbonyl, and nickel hydroxide under CERCLA. RCRA regulates nickel and nickel compounds as hazardous wastes. RCRA and SARA subject nickel and nickel compounds to reporting and record keeping requirements. SARA also establishes threshold planning quantities.

The U.S. Food and Drug Administration (FDA) has taken no action on nickel as a carcinogen because the data available are not adequate to assess its carcinogenicity through dietary exposure. Nickel is a compound generally recognized as safe when used as a direct human food ingredient.

The Occupational Safety and Health Administration (OSHA) adopted permissible exposure limits (PELs) of 0.007 mg/m^3 as an 8-hour time-weighted average (TWA) for nickel carbonyl and 1 mg/m^3 as an 8-hour TWA for nickel metal and soluble nickel compounds. OSHA adopted these standards for toxic effects other than cancer. NIOSH recommended to OSHA that exposure to nickel be limited to 0.015 mg/m^3 (as a 10-hour TWA) because of observed carcinogenicity of nickel metal and all inorganic nickel compounds. The American Conference of Governmental Industrial Hygienists has set the threshold limit value at 1.5 mg/m^3 (as inhalable fraction). OSHA regulates nickel and nickel compounds under the Hazard Communication Standard and as chemical hazards in laboratories.

Metallic Nickel:

The U.S. EPA regulates metallic nickel under the Clean Air Act, the Clean Water Act, RCRA, CERCLA, and SARA. The nickel salt of an organo compound containing nitrogen is regulated under the Toxic Substances Control Act. Effective in 1990, liquid hazardous wastes containing nickel compounds at concentrations of 134 mg/L or greater are prohibited from underground injection. Reportable quantities have been established for the release of specific nickel compounds. An RQ of 100 lb has been set for nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate, and an RQ of 10 lb for nickel carbonyl, nickel cyanide, and nickel hydroxide. Under the Federal Water Pollution Control Act, nickel compounds are designated toxic pollutants. Effluent limitations and pretreatment and performance standards have been created for point sources producing nickel sulfate, nickel chloride, nickel nitrate, nickel fluoroborate, and nickel carbonate.

The FDA regulates the amount of nickel oxide in the color additive chromium-cobalt-aluminum oxide to less than 1%. FDA also regulates nickel as a contaminant in bottled water, to no more than 0.1 mg/L.

NIOSH has recommended an exposure limit of 0.007 mg/m^3 as a TWA (time not specified) for nickel carbonyl and 0.015 mg/m^3 for inorganic nickel compounds (as Ni) in the workplace. NIOSH considers nickel and its compounds to be potential occupational carcinogens and recommends that occupational exposures to carcinogens be limited to the lowest feasible concentration. OSHA has set a PEL for nickel carbonyl (as Ni) at 0.007 mg/m^3 as an 8-hour TWA. For other nickel compounds, soluble and insoluble, the PEL is 1 mg/m^3. OSHA also regulates metallic nickel under the Hazard Communication Standard and as a hazardous chemical in laboratories. Regulations are summarized in Volume II, Table 117.

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