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NICKEL HAZARDS TO FISH, WILDLIFE, AND INVERTEBRATES: A SYNOPTIC REVIEW

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Abstract

Abstract. This account is a selective review and synthesis of the technical literature on nickel and nickel salts in the environment and their effects on terrestrial plants and invertebrates, aquatic plants and animals, avian and mammalian wildlife, and other natural resources. The subtopics include nickel sources and uses; physical, chemical, and metabolic properties of nickel; nickel concentrations in field collections of abiotic materials and living organisms; nickel deficiency effects; lethal and sublethal effects, including effects on survival, growth, reproduction, metabolism, mutagenicity, teratogenicity, and carcinogenicity; currently proposed nickel criteria for the protection of human health and sensitive natural resources; and recommendations for additional research.

Key words: Nickel, nickel compounds, toxicity, deficiency, cancer, residues, criteria, fishes, invertebrates, amphibians, birds, wildlife, livestock.

Introduction

In Europe, nickel (Ni) is listed on European Commission List II (Dangerous Substances Directive) and regulated through the Council of European Communities because of its toxicity, persistence, and affinity for bioaccumulation (Bubb and Lester 1996). In Canada, nickel and its compounds are included in the Priority Substances List under the Canadian Environmental Protection Act (Hughes et al. 1994). The World Health Organization (WHO) classifies nickel compounds in Group 1 (human carcinogens) and metallic nickel in group 2B (possible human carcinogen; U. S. Public Health Service [USPHS] 1993). The U.S. Environmental Protection Agency (USEPA) classifies nickel refinery dust and nickel subsulfide as Group A human carcinogens (USPHS 1993) and nickel oxides and nickel halides as Class W compounds, that is, compounds having moderate retention in the lungs and a clearance rate from the lungs of several weeks (USEPA 1980). Nickel and its compounds are regulated by USEPA's Clean Water Effluent Guideline for many industrial point sources, including the processing of iron, steel, nonferrous metals, and batteries; timber products processing; electroplating; metal finishing; ore and mineral mining; paving and roofing; paint and ink formulating; porcelain enameling; and industries that use, process, or manufacture chemicals, gum and wood, or carbon black (USPHS 1993).

Nickel is ubiquitous in the biosphere. Nickel introduced into the environment from natural or human sources is circulated through the system by chemical and physical processes and through biological transport mechanisms of living organisms (National Academy of Sciences [NAS] 1975; Sevin 1980; WHO 1991). Nickel is essential for the normal growth of many species of microorganisms and plants and several species of vertebrates, including chickens, cows, goats, pigs, rats, and sheep (NAS 1975; USEPA 1980; WHO 1991; USPHS 1993).

Human activities that contribute to nickel loadings in aquatic and terrestrial ecosystems include mining, smelting, refining, alloy processing, scrap metal reprocessing, fossil fuel combustion, and waste incineration (NAS 1975; WHO 1991; Chau and Kulikovsky-Cordeiro 1995). Nickel mining and smelting in the Sudbury, Ontario, region of Canada is associated with denudation of terrestrial vegetation and subsequent soil erosion (Adamo et al. 1996) and gradual ecological changes, including a decrease in the number and diversity of species and a reduction in community biomass of crustacean zooplankton (WHO 1991). At nickel-contaminated sites, plants accumulate nickel and growth is retarded in some species at high nickel concentrations (WHO 1991). But nickel accumulation rates in terrestrial and avian wildlife near nickel refineries are highly variable; Chau and Kulikovsky-Cordeiro (1995) claim similar variability for plants, soils, and interstitial sediment waters.

The chemical and physical forms of nickel and its salts strongly influence bioavailability and toxicity (WHO 1991). In general, nickel compounds have low hazard when administered orally (NAS 1975; USEPA 1980). In humans and other mammals, however, nickel-inhalable dust, nickel subsulfide, nickel oxide, and especially nickel carbonyl induce acute pneumonitis, central nervous system disorders, skin disorders such as dermatitis, and cancer of the lungs and nasal cavity (Graham et al. 1975; NAS 1975; USPHS 1977; Sevin 1980; Smialowicz et al. 1984; WHO 1991; Benson et al. 1995; Table 1). Nickel carbonyl is acutely lethal to humans and animals within 3-13 days of exposure; recovery is prolonged in survivors (Sevin 1980). An excess number of deaths from lung cancer and nasal cancer occurs in nickel refinery workers, usually from exposure to airborne nickel compounds (USPHS 1977). At one nickel refinery, workers had a fivefold increase in lung cancer and a 150-fold increase in nasal sinus cancer when compared to the general population (Lin and Chou 1990). Pregnant female workers at a Russian nickel hydrometallurgy refining plant, when compared to a reference group, showed a marked increase in frequency of spontaneous and threatening abortions and in structural malformations of the heart and musculoskeletal system in live-born infants with nickel-exposed mothers (Chashschin et al. 1994). Nickel is also a common cause of chronic dermatitis in humans as a result of industrial and other exposures, including the use of nickel-containing jewelry, coins, utensils, and various prostheses (NAS 1975; Chashschin et al. 1994). Additional information on ecological and toxicological aspects of nickel in the environment is presented in reviews and annotated bibliographies by Sunderman (1970), Eisler (1973), Eisler and Wapner (1975), NAS (1975), USEPA (1975, 1980, 1985, 1986), International Agency for Research on Cancer (IARC; 1976), Nielsen (1977), USPHS (1977, 1993), Eisler et al. (1978b, 1979), Norseth and Piscator (1979), Brown and Sunderman (1980), Nriagu (1980a), Sevin (1980), National Research Council of Canada (NRCC; 1981), Norseth (1986), Kasprzak (1987), Sigel and Sigel (1988), WHO (1991), Hausinger (1993), Outridge and Scheuhammer (1993), and Chau and Kulikovsky-Cordeiro (1995).

Table 1. Nickel chronology.

Table 1. Date	Event	Reference[a]
220 BCE	Nickel alloys made by the Chinese	1
1500's	Toxicity observed in miners of nickel	2
1751	Nickel isolated and identified. The name nickel was derived from "Old Nick," a gremlin to whom miners ascribed their problems	3
early 1800's	Purified nickel obtained	1
1826	Nickel toxicity in rabbits and dogs demonstrated experimentally. High doses of nickel sulfate given by stomach gavage caused gastritis, convulsions, and death; sublethal doses produced emaciation and conjunctivitis	1, 2, 4
1840's	Commercial nickel electroplating initiated	1
1850's	Commercial exploitation of nickel begins after development of technology to remove copper and other impurities	3
1850-1900	Nickel used therapeutically in human medicine to relieve rheumatism (nickel sulfate) and epilepsy (nickel bromide)	2, 5
1880's	Excess nickel found lethal to animals under controlled conditions	2
1889	Skin dermatitis in humans caused by chemicals used in nickel plating	5
1890	Extraordinary toxicity of nickel carbonyl ($Ni(CO)_4$) established	1
1893	Excess nickel found lethal to plants	2
1912	Nickel dermatitis documented	1
1915-1960	Nickel applied as fungicide found to enhance plant growth and increase yield	2

Table 1. Date	Event	Reference[a]
1926	Nickel dust caused skin dermatitis, especially in hot, industrial environments	5
1932	Increased frequency of lung and nasal cancers reported among English nickel refinery workers exposed to high concentrations of nickel carbonyl	1, 5, 6
1939-1958	Certain forms of nickel found to be carcinogenic to humans	2
1943	Certain forms of nickel found to be carcinogenic to animals	2
1965-1967	Nickel found beneficial to plants	2
1970's	Nickel deficiency leads to adverse effects in microorganisms and plants	2
1980's	Nickel found to be constituent of various essential plant enzymes	2

[a]1, Nriagu 1980b; 2, Hausinger 1993; 3, Sevin 1980; 4, Nielsen 1977; 5, U.S. Public Health Service 1977; 6, Benson et al. 1995.

This report summarizes available ecological and toxicological data on nickel, with emphasis on fishery and wildlife resources. It is part of a continuing series of brief reviews on chemical contaminants and natural resources that are prepared in response to informational requests from environmental specialists of the U.S. Fish and Wildlife Service.

Sources and Uses

General

About 250,000 people in the United States are exposed annually to inorganic nickel in the workplace. This group includes workers in the mining, refining, smelting, electroplating, and petroleum industries and workers involved in the manufacture of stainless steel, nickel alloys, jewelry, paint, spark plugs, catalysts, ceramics, disinfectants, varnish, magnets, batteries, ink, dyes, and vacuum tubes (USPHS 1977). Non-occupational exposure to nickel and its compounds occurs mainly by ingestion of foods and liquids and by contact with nickel-containing products, especially jewelry and coins (Sunderman et al. 1984; WHO 1991). Food processing adds to nickel already present in the diet through leaching from nickel-containing alloys in food-processing equipment made from stainless steel, milling of flour, use of nickel catalysts to hydrogenate fats and oils, and use of nickel-containing fungicides in growing crops (NAS 1975; USEPA 1980). Nickel contamination of the environment occurs locally from emissions of metal mining, smelting, and refining operations; from combustion of fossil fuels; from industrial activities, such as nickel plating and alloy manufacturing; from land disposal of sludges, solids, and slags; and from disposal as effluents (Cain and Pafford 1981; Chau and Kulikovsky-Cordeiro 1995). In Canada in 1988, the mining industry released a total of 11,664 tons of nickel into the air (9.4%), water (0.5%), and on land as sludges or solids (15.4%) and slags (74.7%). The global nickel cycle is unknown, but recent estimates suggest that 26,300 to 28,100 tons are introduced each year into the atmosphere from natural sources and 47,200 to 99,800 tons from human activities; airborne nickel is annually deposited on land at 50,800 tons and in the ocean at 21,800 tons (Chau and Kulikovsky-Cordeiro 1995).

Sources

More than 90% of the world's nickel is obtained from pentlandite ($(FeNi)_9S_8$), a nickel-sulfitic mineral mined underground in Canada and the former Soviet Union (Sevin 1980; IARC 1976; WHO 1991). One of the largest sulfitic nickel deposits is in Sudbury, Ontario (USPHS 1993). Nickeliferous sulfide deposits are also found in Manitoba, South Africa, the former Soviet Union, Finland, western Australia, and Minnesota (Norseth and Piscator 1979; USPHS 1993). Most of the rest of the nickel obtained is from nickel minerals such as laterite, a nickel oxide ore mined by open pit techniques in Australia, Cuba, Indonesia, New Caledonia, and the former Soviet Union (Sevin 1980). Lateritic ores are less well defined than sulfitic ores, although the nickel content (1-3%) of both ores is similar (USPHS 1993). Important deposits of laterite are located in New Caledonia, Indonesia, Guatemala, the Dominican Republic, the Philippines, Brazil, and especially Cuba, which holds 35%

of the known reserves (USPHS 1993). Nickel-rich nodules are found on the ocean floor, and nickel is also present in fossil fuels (Sevin 1980).

Total world mine production of nickel is projected to increase steadily from 7,500 metric tons in 1900 to 2 million tons by 2000 (Table 2). In 1980, nickel mine production in the United States was 14,500 tons, or about 1.8% of the world total (Kasprzak 1987). In 1986, primary nickel production ceased in the United States; secondary nickel production from scrap became a major source of nickel for industrial applications (USPHS 1993). In 1988, the United States imported 186,000 tons of primary nickel; Canada supplied 58% of the total and Norway 14% (USPHS 1993). In 1990, Canada produced 196,606 metric tons of nickel. About 63% of the total production was exported, mostly (56%) to the United States (Chau and Kulikovsky-Cordeiro 1995).

Table 2. World mine production of nickel (National Academy of Sciences 1975; International Agency for Research on Cancer 1976; Duke 1980; Kasprzak 1987; World Health Organization 1991).

Year	Metric tons
1900	7,500
1925	42,700
1950	141,000
1970	694,100
1975	753,000[a]
1980	784,100
1985	821,000[b]
2000 (projected)	>2,000,000

[a]About 32% from Canada, 18% from New Caledonia, 17% from the former Soviet Union, 10% from Australia, 5% from Cuba, 4% from the Dominican Republic, 3% from the Republic of South Africa, 2% each from Greece, Indonesia, and the United States, and 5% from other countries.

[b]Mostly from Canada, the former Soviet Union, Australia, and Cuba, in that order. The United States produced 6,900 tons in 1985.

Natural sources of airborne nickel include soil dust, sea salt, volcanoes, forest fires, and vegetation exudates and account for about 16% of the atmospheric nickel burden (Kasprzak 1987; WHO 1991; Chau and Kulikovsky-Cordeiro 1995). Human sources of atmospheric nickel—which account for about 84% of all atmospheric nickel—include emissions from nickel ore mining, smelting, and refining activities; combustion of fossil fuels for heating, power, and motor vehicles; incineration of sewage sludges; nickel chemical manufacturing; electroplating; nickel-cadmium battery manufacturing; asbestos mining and milling; and cement manufacturing (NAS 1975; IARC 1976; USEPA 1986; Kasprzak 1987; WHO 1991; USPHS 1993). In Canada in 1975, human activities resulted in the release of about 3,000 tons of nickel into the atmosphere, mostly from metallurgical operations (NRCC 1981). Between 1973 and 1981, atmospheric emissions of nickel from stacks of four smelters in the Sudbury Basin, Canada, averaged a total of 495 tons annually (WHO 1991). Industrial nickel dust emissions from a single Canadian stack 381 meters high averaged 228 tons annually (range 53-342) between 1973 and 1981; this stack accounted for 396 tons annually (range 53-896) between 1982 and 1989 (Chau and Kulikovsky-Cordeiro 1995). Three other emission stacks of Canadian nickel producers emitted an average of 226, 228, and 396 tons of nickel, respectively, each year between 1973 and 1989. Industrial emissions of nickel to the Canadian atmosphere in 1982 were estimated at 846 tons, mostly from nickel production in Ontario (48% of total) and Quebec (14%) and from industrial fuel combustion (17%). Nickel released into the air in Canada from smelting processes is likely in the form of nickel subsulfide (52%), nickel sulfate (20%), and nickel oxide (6%). Fuel combustion is also a major contributor of airborne nickel in Canada, mostly from combustion of petroleum (Chau and Kulikovsky-Cordeiro 1995). In the United States, yearly atmospheric emissions from coal and oil combustion are estimated at 2,611 metric tons (WHO 1991).

Chemical and physical degradation of rocks and soils, atmospheric deposition of nickel-containing particulates, and discharges of industrial and municipal wastes release nickel into ambient waters (USEPA 1986; WHO 1991). Nickel enters natural waterways from waste water because it is poorly removed by treatment processes (Cain and Pafford 1981). The main anthropogenic sources of nickel in water are primary nickel production, metallurgical processes, combustion and incineration of fossil fuels, and chemical and catalyst

production (USEPA 1986). The primary human sources of nickel to soils are emissions from smelting and refining operations and disposal of sewage sludge or application of sludge as a fertilizer. Secondary sources include automobile emissions and emissions from electric power utilities (USEPA 1986). Weathering and erosion of geological materials release nickel into soils (Chau and Kulikovsky-Cordeiro 1995), and acid rain may leach nickel from plants into soils as well (WHO 1991).

Uses

Most metallic nickel produced is used to manufacture stainless steel and other nickel alloys with high corrosion and temperature resistance (Norseth and Piscator 1979; Norseth 1980; WHO 1991). These alloys are used in ship building, jet turbines and heat elements, cryogenic installations, magnets, coins, welding rods, electrodes, kitchenware, electronics, and surgical implants; other nickel compounds are used in electroplating, battery production, inks, varnishes, pigments, catalysts, and ceramics (IARC 1976; Nriagu 1980b; Sevin 1980; Sunderman et al. 1984; USEPA 1986; Kasprzak 1987; USPHS 1993). Some nickel compounds are preferred for use in nickel electroplating (nickel sulfate, nickel ammonium sulfate, nickel chloride, nickel fluoborate, nickel sulfamate), refining (nickel carbonyl), nickel-cadmium batteries (nickel hydroxide, nickel fluoride, nickel nitrate), manufacture of stainless steel and alloy steels (nickel oxide), electronic components (nickel carbonate), mordant in textile industry (nickel acetate), catalysts and laboratory reagents (nickel acetate, nickel hydroxide, nickel nitrate, nickel carbonate, nickel monosulfide, nickelocene), and some—such as nickel subsulfide—are unwanted toxic byproducts (IARC 1976).

In 1973, global consumption of nickel was 660,000 tons and that of the United States 235,000 tons (Sevin 1980). End uses of nickel in the United States in 1973 were transportation (21%), chemicals (15%), electrical goods (13%), fabricated metal products (10%), petroleum (9%), construction (9%), machinery (7%), and household appliances (7%; IARC 1976); a similar pattern was evident for 1985 (Table 3). In 1988, 40% of all nickel intermediate products consumed was in the production of steel; 21% was in alloys, 17% in electroplating, and 12% in super alloys (USPHS 1993). The pattern for 1985 was similar (Table 3). In Canada, nickel is the fourth most important mineral commodity behind copper, zinc, and gold. In 1990, Canada produced 197,000 tons of nickel worth 2.02 billion dollars and was the second largest global producer of that metal (Chau and Kulikovsky-Cordeiro 1995). Most of the nickel used in the United States is imported from Canada, and secondarily from Australia and New Caledonia (USPHS 1977).

Table 3. Nickel consumption in the United States by intermediate product and end-use industry in 1985[a] (Kasprzak 1987; World Health Organization 1991).

Index	Consumption (% of total)
Intermediate product	
Stainless and alloy steels	42
Nonferrous alloys	36
Electroplating	18
Other	4
Total	100
End-use industry	
Transportation	23
Chemicals	15
Electrical equipment	12
Construction	10
Fabricated metal products	9
Petroleum	8
Household appliances	8
Machinery	8
Other	7
Total	100

[a] Nickel consumption in the United States, exclusive of scrap, was 160,000 tons.

Various nickel salts—including the sulfate, chloride, and bromide—were used in human medicine during the mid- to late-1800's to treat headache, diarrhea, and epilepsy and as an antiseptic. Therapeutic use of nickel compounds was abandoned in the early 1900's after animal studies demonstrated acute and chronic toxicity of these salts (NAS 1975; Nriagu 1980b). Some nickel salts have been incorporated into fungicides to combat plant pathogens, although their use has not been approved by regulatory agencies (NAS 1975).

Chemical and Biological Properties

General

Nickel normally occurs in the 0 and +2 oxidation states, although other oxidation states are reported (NAS 1975; Nriagu 1980b; Higgins 1995). In natural waters Ni^{2+} is the dominant chemical species in the form of $(Ni(H_2O)_6)^{2+}$ (WHO 1991; Chau and Kulikovsky-Cordeiro 1995). In alkaline soils, the major components of the soil solution are Ni^{2+} and $Ni(OH)^{+}$; in acidic soils, the main solution species are Ni^{2+}, $NiSO_4$, and $NiHPO_4$ (USPHS 1993). Most atmospheric nickel is suspended onto particulate matter (NRCC 1981).

Nickel interacts with numerous inorganic and organic compounds (Schroeder et al. 1974; Nielsen 1980a; USEPA 1980, 1985; USPHS 1993). Some of these interactions are additive or synergistic in producing adverse effects, and some are antagonistic.

Toxic and carcinogenic effects of nickel compounds are associated with nickel-mediated oxidative damage to DNA and proteins and to inhibition of cellular antioxidant defenses (Rodriguez et al. 1996). Most authorities agree that albumin is the main transport protein for nickel in humans and animals and that nickel is also found in nickeloplasmin—a nickel-containing alpha-macroglobulin—and in an ultrafilterable serum fraction similar to a nickel-histidine complex (Norseth and Piscator 1979; Sarkar 1980; Sevin 1980; USEPA 1980; Norseth 1986; Sigel and Sigel 1988; WHO 1991; USPHS 1993). Normal routes of nickel intake for humans and animals are ingestion, inhalation, and absorption through the skin (Mushak 1980; USEPA 1975, 1980, 1986; Sigel and Sigel 1988; WHO 1991; USPHS 1993). Nickel absorption is governed by the quantities inhaled or ingested and by the chemical and physical forms of the nickel. Following oral intake by mammals, nickel was found mainly in the kidneys after short-term or long-term exposure to various soluble nickel compounds; significant levels of nickel were also found in the liver, heart, lung, and fat. Nickel also crosses the placental barrier, as indicated by increases in the levels of nickel in the fetuses of exposed mothers (USPHS 1993). Inhaled nickel carbonyl results in comparatively elevated nickel concentrations in lung, brain, kidney, liver, and adrenals (USEPA 1980). Parenteral administration of nickel salts usually results in high levels in kidneys and elevated concentrations in endocrine glands, liver, and lung (USEPA 1980, 1986; WHO 1991). Nickel concentrations in whole blood, plasma, serum, and urine provide good indices of nickel exposure (Sigel and Sigel 1988).

Physical and Chemical Properties

Nickel was first isolated in 1751, and a relatively pure metal was prepared in 1804. In nature, nickel is found primarily as oxide and sulfide ores (USPHS 1977). Nickel has high electrical and thermal conductivities and is resistant to corrosion at environmental temperatures between -20 C and +30 C (Chau and Kulikovsky-Cordeiro 1995). Nickel, also known as carbonyl nickel powder or C.I. No. 77775, has a CAS number of 7440-02-0. Metallic nickel is a hard, lustrous, silvery white metal with a specific gravity of 8.9, a melting point of about 1,455 C, and a boiling point of about 2,732 C. It is insoluble in water and ammonium hydroxide, soluble in dilute nitric acid or aqua regia, and slightly soluble in hydrochloric and sulfuric acid. Nickel has an atomic weight of 58.71. Nickel is a composite of five stable isotopes: Ni-58 (68.3%), -60 (26.1%), -61 (1.1%), -62 (3.6%), and -64 (0.9%). Seven unstable isotopes have been identified: ^{56}Ni (half-life of 6 days), ^{57}Ni (36 h), ^{59}Ni (80,000 years), ^{63}Ni (92 years), ^{65}Ni (2.5 h), ^{66}Ni (55 h), and ^{67}Ni (50 sec). Radionickel-59 (^{59}Ni) and ^{63}Ni are available commercially. In addition to the 0 and +2 oxidation states, nickel can also exist as -1, +1, +3, and +4 (NAS 1975; IARC 1976; Kasprzak 1987; Nriagu 1980b; WHO 1991; Hausinger 1993; USPHS 1993; Foulds 1995; Higgins 1995).

Nickel enters surface waters from three natural sources: as particulate matter in rainwater, through the dissolution of primary bedrock materials, and from secondary soil phases. In aquatic systems, nickel occurs as soluble salts adsorbed onto or associated with clay particles, organic matter, and other substances. The divalent ion is the dominant form in natural waters at pH values between 5 and 9, occurring as the octahedral,

hexahydrate ion $(Ni(H_2O)_6)^{2+}$. Nickel chloride hexahydrate and nickel sulfate hexahydrate are extremely soluble in water at 2,400-2,500 g/L. Less soluble nickel compounds in water include nickel nitrate (45 g/L), nickel hydroxide (0.13 g/L), and nickel carbonate (0.09 g/L). Nickel forms strong, soluble complexes with OH-, SO_4^{2-}, and HCO_3^-; however, these species are minor compared with hydrated Ni^{2+} in surface water and groundwater. The fate of nickel in fresh water and marine water is affected by the pH, pE, ionic strength, type and concentration of ligands, and the availability of solid surfaces for adsorption. Under anaerobic conditions, typical of deep groundwater, precipitation of nickel sulfide keeps nickel concentrations low (IARC 1976; USEPA 1980; WHO 1991; USPHS 1993; Chau and Kulikovsky-Cordeiro 1995).

In alkaline soils, the major components of the soil solution are Ni^{2+} and $Ni(OH)^+$; in acidic soils the main solution species are Ni^{2+}, $NiSO_4$, and $NiHPO_4$ (USPHS 1993). Atmospheric nickel exists mostly in the form of fine respirable particles less than 2 μm in diameter (NRCC 1981), usually suspended onto particulate matter (USEPA 1986).

Nickel carbonyl ($Ni(CO)_4$) is a volatile, colorless liquid readily formed when nickel reacts with carbon monoxide; it boils at 43 C and decomposes at more than 50 C; this compound is unstable in air and is usually not measurable after 30 min (NRCC 1981; Norseth 1986; USPHS 1993). The intact molecule is absorbed by the lung (USEPA 1980) and is insoluble in water but soluble in most organic solvents (WHO 1991).

Analytical methods for detection of nickel in biological materials and water include various spectrometric, photometric, chromatographic, polarographic, and voltametric procedures (Sunderman et al. 1984; WHO 1991). Detection limits for the most sensitive procedures—depending on sample pretreatment and extraction and enrichment procedures—were 0.7-1.0 ng/L in liquids, 0.01-0.2 $\mu g/m^3$ in air, 1-100 ng/kg in most biological materials, and 12 μg/kg in hair (WHO 1991; Chau and Kulikovsky-Cordeiro 1995).

Metabolism

In mammalian blood, absorbed nickel is present as free hydrated Ni^{2+} ions, as small complexes, as protein complexes, and as nickel bound to blood cells. The partition of nickel among these four components varies according to the metal-binding properties of serum albumin, which is highly variable between species (NAS 1975; USEPA 1980, 1986; Kasprzak 1987). A proposed transport model involves the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and L-histidine. The low molecular weight L-histidine nickel complex can then cross biological membranes (Sunderman et al. 1984; Kasprzak 1987; USPHS 1993). Once inside the mammalian cell, nickel accumulates in the nucleus and nucleolus (Sunderman et al. 1984), disrupting DNA metabolism and causing cross links and strand breaks (Kasprzak 1987; USPHS 1993; Hartwig et al. 1994). The observed redox properties of the nickel-histidine complex are crucial for maximizing the toxicity and carcinogenicity of nickel (Datta et al. 1992, 1994).

The acute toxicity and carcinogenicity of Ni_3S_2 and Ni_3S_2-derived soluble nickel (Ni^{2+}) in mice depend, in part, on the antioxidant capacity of target organs, which varies among different strains (Rodriguez et al. 1996). Experimental evidence now support the conclusion that the nickel-dependent formation of an activated oxygen species—including superoxide ion, hydrogen peroxide, and hydroxy radical—is a primary molecular event in acute nickel toxicity and carcinogenicity (WHO 1991; Hausinger 1993; Tkeshelashvili et al. 1993; Novelli et al. 1995; Stohs and Bagchi 1995; Rodriguez et al. 1996). For example, the superoxide radical (O_2^-) is an important intermediate in the toxicity of insoluble nickel compounds such as NiO and NiS (Novelli et al. 1995). One of the keys to the mechanism of nickel-mediated damage is the enhancement of cellular redox processing by nickel. Accumulated nickel in tissues elicits the production of reactive oxygen species, such as the superoxide radical, as the result of phagocytosis of particulate nickel compounds and through the interaction of nickel ions with protein ligands, which promote the activation of the Ni^{2+}/Ni^{3+} redox couple. Thus, NiS and NiO can elicit the formation of O_2^- (Novelli et al. 1995).

The most serious type of nickel toxicity is that caused by the inhalation of nickel carbonyl (Nielsen 1977). The half-time persistence of nickel carbonyl in air is about 30 min (Sevin 1980). Nickel carbonyl can pass across

cell membranes without metabolic alteration because of its solubility in lipids, and this ability of nickel carbonyl to penetrate intracellularly may be responsible for its extreme toxicity (NAS 1975). In tissues, nickel carbonyl decomposes to liberate carbon monoxide and Ni^0, the latter being oxidized to Ni^{2+} by intracellular oxidation systems. The nickel portion is excreted with urine and the carbon monoxide is bound to hemoglobin and eventually excreted through the lungs (USEPA 1980; Kasprzak 1987). Nickel carbonyl inhibits DNA-dependent RNA synthesis activity, probably by binding to chromatin or DNA and thereby preventing the action of RNA polymerase, causing suppression of messenger-RNA-dependent induction of enzyme synthesis (Sunderman 1968; NAS 1975; USEPA 1980). The lung is the target organ in nickel carbonyl poisoning (USEPA 1980). Acute human exposures result in pathological pulmonary lesions, hemorrhage, edema, deranged alveolar cells, degeneration of bronchial epithelium, and pulmonary fibrosis. The response of pulmonary tissue to nickel carbonyl is rapid: interstitial edema may develop within 1 h of exposure and cause death within 5 days. Animals surviving acute exposures show lung histopathology (USEPA 1980).

Gastrointestinal intake of nickel by humans is high compared to some other trace metals because of contributions of nickel from utensils and food processing machinery; average human dietary values range from 300 to 500 μg daily, with absorption from the gastrointestinal tract of 1-10% (USEPA 1980, 1986; Sigel and Sigel 1988). In humans, nearly 40 times more nickel was absorbed from the gastrointestinal tract when nickel sulfate was given in the drinking water (27%) than when it was given in the diet (0.7%). Uptake was more rapid in starved individuals (WHO 1991; USPHS 1993). Dogs and rats given nickel, nickel sulfate hexahydrate, or nickel chloride in the diet or by gavage rapidly absorbed 1-10% of the nickel from the gastrointestinal tract, while unabsorbed nickel was excreted in the feces (USPHS 1993).

During occupational exposure, respiratory absorption of soluble and insoluble nickel compounds is the major route of entry, with gastrointestinal absorption secondary (WHO 1991). Inhalation exposure studies of nickel in humans and test animals show that nickel localizes in the lungs, with much lower levels in liver and kidneys (USPHS 1993). About half the inhaled nickel is deposited on bronchial mucosa and swept upward in mucous to be swallowed; about 25% of the inhaled nickel is deposited in the pulmonary parenchyma (NAS 1975). The relative amount of inhaled nickel absorbed from the pulmonary tract is dependent on the chemical and physical properties of the nickel compound (USEPA 1986). Pulmonary absorption into the blood is greatest for nickel carbonyl vapor; about half the inhaled amount is absorbed (USEPA 1980). Nickel in particulate matter is absorbed from the pulmonary tract to a lesser degree than nickel carbonyl; however, smaller particles are absorbed more readily than larger particles (USEPA 1980). Large nickel particles (>2 μm in diameter) are deposited in the upper respiratory tract; smaller particles tend to enter the lower respiratory tract. In humans, 35% of the inhaled nickel is absorbed into the blood from the respiratory tract; the remainder is either swallowed or expectorated. Soluble nickel compounds were more readily absorbed from the respiratory tract than insoluble compounds (USPHS 1993). In rodents, the half-time persistence of nickel particles was a function of particle diameter: 7.7 months for particles 0.6 μm in diameter, 11.5 months for particles 1.2 μm in diameter, and 21 months for particles 4.0 μm in diameter (USPHS 1993). In rodents, a higher percentage of insoluble nickel compounds was retained in the lungs for a longer time than soluble nickel compounds, and the lung burden of nickel decreased with increasing particle size. Nickel retention was 6-10 times greater in rodents exposed to insoluble nickel subsulfide compared to soluble nickel sulfate. Lung burdens of nickel generally increased with increasing duration of exposure and increasing concentrations of various nickel compounds in the air (USPHS 1993). Animals exposed to nickel carbonyl by inhalation exhale some of the respiratory burden in 2-4 h. The remainder is slowly degraded to divalent nickel, which is oxidized, and carbon monoxide, which initially binds to hemoglobin, with nickel eventually undergoing urinary excretion (NAS 1975; Norseth and Piscator 1979; USEPA 1980; Norseth 1986).

Dermal absorption of nickel occurs in animals and humans and is related to nickel-induced hypersensitivity and skin disorders (Samitz and Katz 1976; USEPA 1986). Absorption of nickel sulfate from the skin is reported for guinea pigs, rabbits, rats, and humans (Norseth and Piscator 1979). Nickel ions in contact with the skin surface diffuse through the epidermis and combine with proteins; the body reacts to this conjugated protein (Samitz and Katz 1976; Nielsen 1977). Nickel penetration of the skin is enhanced by sweat, blood and other body fluids, and detergents (Nielsen 1977; USEPA 1980). Absorption is related to the solubility of the compound, following the general relation of nickel carbonyl, soluble nickel compounds, and insoluble nickel compounds, in that order; nickel carbonyl is the most rapidly and completely absorbed nickel compound in mammals (WHO 1991). Anionic species differ markedly in skin penetration: nickelous ions from a chloride

solution pass through skin about 50 times faster than do nickelous ions from a sulfate solution (USPHS 1993). Radionickel-57 (^{57}Ni) accumulates in keratinous areas and hair sacs of the shaved skin of guinea pigs and rabbits following dermal exposure. After 4 h, ^{57}Ni was found in the stratum corneum and stratum spinosum; after 24 h, ^{57}Ni was detected in blood and kidneys, with minor amounts in liver (USPHS 1993). As much as 77% of nickel sulfate applied to the occluded skin surface of rabbits and guinea pigs was absorbed within 24 h; sensitivity to nickel did not seem to affect absorption rate (USPHS 1993). In humans, some protection against nickel may be given by introducing a physical barrier between the skin and the metal, including fingernail polish, a polyurethane coating, dexamethasone, or disodium EDTA (Nielsen 1977).

Nickel retention in the body of mammals is low. The half-time residence of soluble forms of nickel is several days, with little evidence for tissue accumulation except in the lung (USEPA 1980, 1986). Radionickel-63 (^{63}Ni) injected into rats and rabbits cleared rapidly; most (75%) of the injected dose was excreted within 24-72 h (USEPA 1980). Nickel clears at different rates from various tissues. In mammals, clearance was fastest from serum, followed by kidney, muscle, stomach, and uterus; relatively slow clearance was evident in skin, brain, and especially lung (Kasprzak 1987). The half-time persistence in human lung for insoluble forms of nickel is 330 days (Sevin 1980).

The excretory routes for nickel in mammals depend on the chemical forms of nickel and the mode of nickel intake. Most (>90%) of the nickel that is ingested in food remains unabsorbed within the gastrointestinal tract and is excreted in the feces (NAS 1975; Sevin 1980; USEPA 1986; Kasprzak 1987; Hausinger 1993; USPHS 1993). Urinary excretion is the primary route of clearance for nickel absorbed through the gastrointestinal tract (USEPA 1976, 1986; USPHS 1993). In humans, nickel excretion in feces usually ranges between 300 and 500 μg daily, or about the same as the daily dietary intake; urinary levels are between 2 and 4 μg/L (USEPA 1980, 1986). Dogs fed nickel sulfate in the diet for as long as 2 years excreted most of the nickel in feces and 1-3% in the urine (USPHS 1993). Biliary excretion occurs in rats, calves, and rabbits, but the role of bile in human metabolism of nickel is not clear (USEPA 1980). Absorbed nickel is excreted in the urine regardless of the route of exposure. The excretory route of inhaled nickel depends on the solubility of the nickel compound. Inhalation studies show that rats excrete 70% of the nickel in soluble nickel compounds through the urine within 3 days and 97% in 21 days. Less soluble nickel compounds (nickel oxide, nickel subsulfide) are excreted in urine (50%) and feces (50%); 90% of the initial dose of nickel subsulfide was excreted within 35 days, and 60% of the nickel oxide—which is less soluble and not as rapidly absorbed as nickel subsulfide—was excreted in 90 days (USPHS 1993). The half-time persistence of inhaled nickel oxide is 3 weeks in hamsters (Sevin 1980). In addition to feces, urine, and bile, other body secretions—including sweat, tears, milk, and mucociliary fluids—are potential routes of excretion (WHO 1991). Sweat may constitute a major route of nickel excretion in tropical climates. Nickel concentrations in sweat of healthy humans sauna bathing for brief periods were 52 μg/L in males and 131 μg/L in females (USEPA 1980). Hair deposition of nickel also appears to be an excretory mechanism (as much as 4 mg Ni/kg dry weight [DW] hair in humans), but the relative magnitude of this route, compared to urinary excretion, is unclear (USEPA 1980, 1986). In the case of nickel compounds administered by way of injection, tests with small laboratory animals show that nickel is cleared rapidly from the plasma and excreted mainly in the urine (Norseth and Piscator 1979; USEPA 1980). About 78% of an injected dose of nickel salts was excreted in the urine during the first 3 days after injection in rats and during the first day in rabbits (Norseth 1986). Exhalation via the lungs is the primary route of excretion during the first hours following injection of nickel carbonyl into rats, and afterwards via the urine (Norseth and Piscator 1979).

In microorganisms, nickel binds mainly to the phosphate groups of the cell wall. From this site, an active transport mechanism designed for magnesium transports the nickel (Kasprzak 1987). In microorganisms and higher plants, magnesium is the usual competitor for nickel in the biological ion-exchange reactions. In lichens, fungi, algae, and mosses, the active binding sites are the carboxylic and hydroxycarboxylic groups fixed on the cell walls. Nickel in hyperaccumulating genera of terrestrial plants is complexed with polycarboxylic acids and pectins, although phosphate groups may also participate (Kasprzak 1987). In terrestrial plants, nickel is absorbed through the roots (USEPA 1975).

Interactions

In minerals, nickel competes with iron, cobalt, and magnesium because of similarities in their ionic radius and electronegativity (NRCC 1981). At the cellular level, nickel interferes with enzymatic functions of calcium,

iron, magnesium, manganese, and zinc (Kasprzak 1987). Binding of nickel to DNA is inhibited by salts of calcium, copper, magnesium, manganese, and zinc (WHO 1991). In toads (*Bufo arenarum*), ionic nickel interferes with voltage-sensitive ionic potassium channels in short muscle fibers (Bertran and Kotsias 1997). Among animals, plants, and microorganisms, nickel interacts with at least 13 essential elements: calcium, chromium, cobalt, copper, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, sodium, and zinc (Nielsen 1980a). Nickel interacts noncompetitively with all 13 elements and also interacts competitively with calcium, cobalt, copper, iron, and zinc. Quantification of these relationships would help clarify nickel-essential mineral interactions and the circumstances under which these interactions might lead to states of deficiency or toxicity (Nielsen 1980a). Mixtures of metals (arsenic, cadmium, copper, chromium, mercury, lead, zinc) containing nickel salts are more toxic to daphnids and fishes than are predicted on the basis of individual components (Enserink et al. 1991). Additive joint action of chemicals, including nickel, should be considered in the development of ecotoxicologically relevant water quality criteria (Enserink et al. 1991).

Nickel may be a factor in asbestos carcinogenicity. The presence of chromium and manganese in asbestos fibers may enhance the carcinogenicity of nickel (USEPA 1980), but this relationship needs to be verified. Barium-nickel mixtures inhibit calcium uptake in rats, resulting in reduced growth (WHO 1991). Pretreatment of animals with cadmium enhanced the toxicity of nickel to the kidneys and liver (USPHS 1993). Simultaneous exposure to nickel and cadmium—an industrial situation common in nickel and cadmium battery production—caused a significant increase in beta-2-macroglobulin excretion (Sunderman et al. 1984). Nickel or cadmium alone did not affect calcium kinetics of smooth muscle from bovine mesenteric arteries. However, mixtures of cadmium and nickel at greater than 100 nM inhibited the calcium function and may explain the vascular tension induced by nickel and other cations (Stockand et al. 1993). Smooth muscle of the ventral aorta of the spiny dogfish (*Squalus acanthias*) contracted significantly on exposure to cadmium or nickel but not to other divalent cations. Atropine inhibited vasoconstriction of shark muscle induced by cadmium, but not that induced by nickel (Evans and Walton 1990). Nickel toxicity in soybeans (*Glycine max*) was inhibited by calcium, which limited the binding of nickel to DNA (WHO 1991). Chromium-nickel mixtures were more-than-additive in toxicity to guppies (*Poecilia reticulata*) in 96-h tests (Khangarot and Ray 1990). Rabbits (*Oryctolagus* sp.) exposed by inhalation to both nickel and trivalent chromium had more severe respiratory effects than did rabbits exposed to nickel alone (USPHS 1993). In natural waters, the geochemical behavior of nickel is similar to that of cobalt (USEPA 1980). It is therefore not surprising that nickel-cobalt mixtures in drinking water of rats were additive in toxicity (WHO 1991) and that there is a high correlation between nickel and cobalt concentrations in terrestrial plants (Memon et al. 1980).

Copper-nickel mixtures have a beneficial effect on growth of terrestrial plants but are more-than-additive in toxic action to aquatic plants (NRCC 1981; WHO 1991). Nickel interacts with iron in rat nutrition and metabolism, but the interaction depends on the form and level of the dietary iron (Nielsen 1980b; USEPA 1985). Weanling rats fed diets containing nickel chloride and ferric sulfate had altered hematocrit, hemoglobin level, and alkaline phosphatase activity which did not occur when a mixture of ferric and ferrous sulfates were fed (Nielsen 1980b). In iron-deficient rats, nickel enhanced the absorption of iron administered as ferric sulfate (USPHS 1993), and nickel acted as a biological cofactor in facilitating gastrointestinal absorption of ferric ion when iron was given as ferric sulfate (USPHS 1993). Mice given a lead-nickel mixture in drinking water (57 mg Ni/L-200 mg Pb/L) for 12 days had increased urinary excretion of delta aminolevulinic acid and increased delta aminolevulinic dehydratase activity in erythrocytes when compared to groups given lead alone or nickel alone (Tomokuni and Ichiba 1990).

Magnesium competes with nickel in isolated cell studies (WHO 1991). Treatment with magnesium reduces nickel toxicity, presumably through inhibition of nickel binding to DNA (USPHS 1993; Hartwig et al. 1994). Manganese also inhibits the binding of nickel to DNA (WHO 1991), and manganese administration reduces the accumulation of nickel in some organs (Murthy and Chandra 1979). Manganese dust inhibits nickel subsulfide-induced carcinogenesis in rats following simultaneous intramuscular injection of the two compounds (USPHS 1993). Also, nickel-manganese mixtures are less-than-additive in producing cytotoxicity of alveolar macrophages in rats (WHO 1991). Nickel compounds enhance the cytotoxicity and genotoxicity of ultraviolet radiation, x-rays, and cytostatic agents such as *cis*-platinum, *trans*-platinum, and mitomycin C (Hartwig et al. 1994). Nickel is less-than-additive in toxicity to aquatic algae in combination with zinc (WHO 1991). Treatment with zinc lessens nickel toxicity, presumably by competing with nickel in binding to DNA and proteins (USEPA 1985; WHO 1991; USPHS 1993; Hartwig et al. 1994). Zinc binding sites of DNA-binding proteins, known as “finger loop domains,” are likely molecular targets for metal toxicity. Ionic nickel has a similar ionic radius to

Zn^{2+} and substitution is possible. Such substitution may disrupt nickel-induced gene expression by interfering with site-specific free radical reactions, which can result in DNA cleavage, formation of DNA protein cross links, and disturbance of mitosis (WHO 1991).

Nickel also interacts with chelating agents, phosphatases, viruses, vitamins, and polycyclic aromatic hydrocarbons (PAHs). Chelating agents mitigate the toxicity of nickel by stimulating nickel excretion (USPHS 1993). Chelators reduced the toxicity of nickel to aquatic plants, presumably by lowering nickel bioavailability (WHO 1991). Lipophilic chelating agents, such as triethylenetetramine and Cyclam (1,4,8,11-tetraazacyclotetradecane), are more effective in reducing toxicity than hydrophilic chelating agents such as EDTA, cyclohexanediamine tetraacetic acid, diethylenetriamine pentaacetic acid, and hydroxyethylenediamine triacetic acid. The greater efficacy of the lipophilic agents may be due to their ability to bind to nickel both intracellularly and extracellularly, while the hydrophilic agents can only bond extracellularly (USPHS 1993). Nickel irreversibly activates calcineurin, a multifunctional intracellular phosphatase normally activated by calcium and calmodulin (Kasprzak 1987). With nickel present, Newcastle Disease virus suppresses mouse L-cell interferon synthesis, suggesting virus-nickel synergism (USEPA 1980). Nickel interacts with vitamin C (USEPA 1985) and has a synergistic effect on the carcinogenicities of various PAHs (USEPA 1980). Rats given intratracheal doses of nickel oxide and 20-methylcholanthrene develop squamous cell carcinomas more rapidly than with 20-methylcholanthrene alone. Simultaneous exposure of rats to benzopyrene and nickel subsulfide reduced the latency period of sarcomas by 30% and induced lung histopathology at a higher frequency than either agent alone. Also, tissue retention of PAH carcinogens is prolonged with nickel exposure (USEPA 1980).

Carcinogenicity, Mutagenicity, Teratogenicity

General

Some forms of nickel are carcinogenic to humans and animals (IARC 1976; Smialowicz et al. 1984; USEPA 1986; WHO 1991; Hausinger 1993; USPHS 1993; Hartwig et al. 1994). Carcinogenicity of nickel compounds varies significantly with the chemical form of nickel, route of exposure, animal model used (including intraspecies strain differences), dose, and duration of exposure (USEPA 1980). In tests with small laboratory mammals, inducement of carcinomas of the types found in humans has only been accomplished following exposures by the respiratory route (Sunderman 1968). Inhalation studies with nickel subsulfide and nickel oxide show evidence of carcinogenicity in mammals and humans; however, the evidence based on oral or cutaneous exposure to these and other nickel compounds is either negative or inconclusive (NAS 1975; IARC 1976; Norseth 1980; USEPA 1980, 1986; WHO 1991; USPHS 1993). Nickel carbonyl and metallic nickel are carcinogenic in experimental animals, but data regarding their carcinogenicity in humans are inconclusive (USEPA 1975; Norseth 1980; USPHS 1993).

Certain nickel compounds are weakly mutagenic in a variety of test systems, but much of the evidence is inconclusive or negative (USPHS 1977, 1993; USEPA 1986; Kasprzak 1987; WHO 1991; Outridge and Scheuhammer 1993). Mutagenicity—as measured by an increased frequency of sister chromatid exchange, chromosome aberrations, cell transformations, spindle disturbances, and dominant lethal effects—is induced by various nickel compounds at high concentrations in isolated cells of selected mammals, including humans; however, these effects have not been observed in vivo (Sunderman 1981; USEPA 1986; WHO 1991; USPHS 1993). Nickel mutagenesis is thought to occur through inhibition of DNA synthesis and excision repair, resulting in an increased frequency of cross links and strand breaks (USEPA 1986; WHO 1991; USPHS 1993). DNA strand breaks occur in rat cells exposed to 5-40 mg Ni/kg medium as nickel carbonate; similar effects occur in hamster cells at 10-2,000 mg Ni/kg medium as nickel chloride and nickel subsulfide and in human cells with nickel sulfate (WHO 1991). The ability of a particular nickel compound to cause mutations is considered proportional to its cellular uptake; however, data on nickel bioavailability to cells is scarce (Niebuhr et al. 1980; USPHS 1993).

No teratogenic effects of nickel compounds occur in mammals by way of inhalation or ingestion except from nickel carbonyl (USEPA 1986; Outridge and Scheuhammer 1993). However, injection of low nickel doses results in consistent fetal malformations, particularly when nickel is administered during the organogenic stage of gestation of mammals or during the early development of domestic chick embryos (Outridge and Scheuhammer 1993). Injected doses causing teratogenic effects in rodents were as low as 1.0-1.2 mg Ni/kg body weight (BW), although more malformations resulted at higher dosages (2.3-4.0 mg/kg BW), which also increased fetal mortality and toxicity in the dam (Mas et al. 1985; Outridge and Scheuhammer 1993). Possible

causes of nickel-induced malformations include direct toxicity from high transplacental nickel levels, reduced availability of alpha-fetoprotein to fetuses, or an increase in maternal glucose levels, which induces hyperglycemia in fetuses (Mas et al. 1985; Outridge and Scheuhammer 1993).

Carcinogenicity

Epidemiological studies conducted some decades ago in England, Canada, Japan, Norway, Germany, Russia, New Caledonia, and West Virginia indicated that humans working in the nickel processing and refining industries—or living within 1 km of processing or refining sites—had a significantly increased risk of developing fatal cancers of the nose, lungs, larynx, and kidneys, and a higher incidence of deaths from nonmalignant respiratory disease (Sunderman 1968, 1981; NAS 1975; IARC 1976; USPHS 1977, 1993; Norseth and Piscator 1979; Norseth 1980; Sevin 1980; USEPA 1980; Kasprzak 1987; WHO 1991). Nasal cancers in nickel refinery workers were similar to those of the general population; however, lung cancers of nickel refinery workers had a higher frequency of squamous cell carcinomas (USPHS 1993). Smoking of tobacco contributed to the development of lung cancers in the nickel-exposed workers. Smoking about 15 cigarettes daily for 1 year adds about 1,930 μg of nickel, as nickel carbonyl, to the human lung; this amount is equivalent to a carcinogenic dose of nickel for rats (Sunderman 1970, 1981). Symptoms of cancer in humans may occur 5 to 35 years after exposure (Furst and Radding 1980; Kasprzak 1987; USPHS 1993). The incidence of human lung and nasal cancers in occupationally exposed workers are related to nickel concentration and duration of exposure (USEPA 1986). Nickel compounds implicated as carcinogens include insoluble dusts of nickel subsulfide (Ni_3S_2) and nickel oxides (NiO, Ni_2O_3), the vapor of nickel carbonyl ($Ni(CO)_4$), and soluble aerosols of nickel sulfate ($NiSO_4$), nickel nitrate ($NiNO_3$), and nickel chloride ($NiCl_2$; USPHS 1977; USEPA 1980). Soluble nickel compounds, though toxic, have relatively low carcinogenic activities (Ho and Furst 1973). In general, carcinogenicity of nickel compounds is inversely related to its solubility in water, the least soluble being the most active carcinogen (Sunderman 1968; Furst and Radding 1980; USEPA 1980; USPHS 1993). The highest risk to humans of lung and nasal cancers comes from exposure to respirable particles of metallic nickel, nickel sulfides, nickel oxide, and the vapors of nickel carbonyl (NAS 1975; USPHS 1977; Norseth and Piscator 1979; Norseth 1980; Sunderman 1981; Sunderman et al. 1984; USEPA 1986; Kasprzak 1987; WHO 1991; USPHS 1993). Cancers were most frequent when workers were exposed to soluble nickel compounds at concentrations greater than 1.0 mg Ni/m^3 air and to exposure to less soluble compounds at greater than 10.0 mg Ni/m^3 air (USPHS 1993). Nickel subsulfide appears to be the nickel compound most carcinogenic to humans, as judged by animal studies and epidemiological evidence (Furst and Radding 1980; Outridge and Scheuhammer 1993). The death rate of nickel workers from cancer has declined significantly since the mid-1920's because of improved safety and awareness (USPHS 1977, 1993).

The underlying biochemical mechanisms governing the carcinogenicity of various nickel compounds are imperfectly understood. There is general agreement that intra-cellular nickel accumulates in the nucleus, especially the nucleolar fraction (NAS 1975; USEPA 1980). Intracellular binding of nickel to nuclear proteins and nuclear RNA and DNA may cause strand breakage and other chromosomal aberrations, diminished RNA synthesis and mitotic activity, and gene expression (USEPA 1980; Kasprzak 1987). A key mechanism of the transformation of tumorous cells involves DNA damage resulting from mutation (Sigel and Sigel 1988) caused by hydroxy radical or other oxidizing species (Datta et al. 1994). Alterations in cytokine (also known as tumor necrosis factor) production is associated with fibrotic lung injury in rats. Inhaled nickel oxide is known to increase cytokine production in rats (Morimoto et al. 1995).

Nickel entering the digestive tract of mammals is likely to be noncarcinogenic. Chronic ingestion studies of various nickel compounds that lasted as long as 2 years using several species of mammals show no evidence of carcinogenesis (Outridge and Scheuhammer 1993). Inhalation is the dosing route most relevant to human occupational exposure (Sunderman et al. 1984) and probably an important route for wildlife exposure in the case of nickel powder, nickel carbonyl, and nickel subsulfide (IARC 1976).

Inhalation of airborne nickel powder at 15 mg Ni/m^3 air causes an increased frequency of lung anaplastic carcinomas and nasal cancers in rodents and guinea pigs, especially when the particles are less than 4 μm in diameter (USPHS 1977; USEPA 1980). Rats exposed to airborne dusts of metallic nickel at 70 mg Ni/m^3 air for 5 h daily, 5 days weekly over 6 months had a 40% frequency of lung cancers; the latent period for tumor development was 17 months (Sunderman 1981). A similar case is made for nickel sulfide and nickel oxide

(Sunderman 1981). In Canada, however, metallic nickel is considered “unclassifiable with respect to carcinogenicity” due to the limitations of identified studies (Hughes et al. 1994). Inhaled nickel carbonyl is carcinogenic to the lungs of rats, a species generally considered to be peculiarly resistant to pulmonary cancer (Sunderman and Donnelly 1965; NAS 1975; IARC 1976; USEPA 1980; WHO 1991). Pulmonary cancers developed in rats 24-27 months after initial exposure to nickel carbonyl, and growth and survival of rats during chronic exposure were markedly reduced (Sunderman and Donnelly 1965). Rats exposed to air containing 250 μg nickel carbonyl/L for only 30 min had a 4% incidence of lung cancer in 2-year survivors versus 0% in controls; rats exposed to 30-60 μg/L air for 30 min, three times weekly for 1 year had a 21% incidence of lung cancer in 2-year survivors (Sunderman 1970; NAS 1975). Inhaled nickel oxides do not seem to be tumorogenic to hamsters at concentrations of 1.2 mg Ni/m^3 air during exposure for 12 months (Outridge and Scheuhammer 1993). Hamsters did not develop lung tumors during lifespan inhalation exposure to nickel oxide; however, inhaled nickel oxide enhanced nasal carcinogenesis produced by diethylnitrosamine (USPHS 1977). Inhalation of nickel subsulfide produced malignant lung tumors and nasal cancers in rats in a dose-dependent manner (Ottolenghi et al. 1974; IARC 1976; USPHS 1977, 1993; WHO 1991; Benson et al. 1995; Rodriguez et al. 1996). Rats develop benign and malignant lung tumors (14% frequency vs. 0% in controls) after exposure for 78 weeks (6 h daily, 5 days weekly) to air containing 1.0 mg Ni/m^3 (as nickel subsulfide; particles <1.5 μm in diameter) and during a subsequent 30-week observation period (IARC 1976; USPHS 1977; USEPA 1980; NRCC 1981).

Local sarcomas may develop in humans and domestic animals at sites of nickel implants and prostheses made of nickel. Latency of the implant sarcomas varies from 1 to 30 years in humans (mean, 10 years) and from 1 to 11 years in dogs (mean, 5 years). No cases of malignant tumors are reported at sites of dental nickel prostheses (Kasprzak 1987).

Injection site tumors are induced by many nickel compounds that do not cause cancer in animals by other routes of exposure (USPHS 1977). In fact, most of the published literature on nickel carcinogenesis concerns injected or implanted metallic nickel or nickel compounds. However, these data seem to be of limited value in determining carcinogenic exposure levels for avian and terrestrial wildlife (Outridge and Scheuhammer 1993). The applicability of these studies to a recommendation for human workplace exposure is also questionable (USPHS 1977). Nevertheless, injection or implantation site sarcomas have been induced by many nickel compounds after one or repeated injections or implantations in rats, mice, hamsters, guinea pigs, rabbits, and cats (NAS 1975; IARC 1976; USPHS 1977, 1993; Norseth and Piscator 1979; USEPA 1980; NRCC 1981; Sunderman 1981; WHO 1991). Nickel compounds known to produce sarcomas or malignant tumors by these routes of administration (implantation, intratracheal, intramuscular, intraperitoneal, subcutaneous, intrarenal, intravenous, intratesticular, intraocular, intraosseus, intrapleural, intracerebral, intrahepatic, intraarticular, intrasubmaxillary, intraadipose, intramedullary) include nickel subsulfide, nickel carbonyl, nickel powder or dust, nickel oxide, nickel hydroxide, nickel acetate, nickel fluoride, nickelocene, nickel sulfate, nickel selenide, nickel carbonate, nickel chromate, nickel arsenide, nickel telluride, nickel antimonide, nickel-iron matte, nickel ammonium sulfate, and nickel monosulfide.

Some parenteral routes of administration were less effective than others in producing an increase in the frequency of benign or malignant tumors, including intravenous, submaxillary, and intrahepatic injection routes (Sunderman 1981). Some nickel compounds are more effective at inducing tumors than others, for example, nickel sulfate and nickel acetate induce tumors in the peritoneal cavity of rats after repeated intraperitoneal injections but nickel chloride does not (WHO 1991). Likewise, some species are more sensitive to tumor inducement by injection than others; rats, for example, are more sensitive than hamsters (USPHS 1977). Most nickel compounds administered by way of injection usually produce responses at the site of injection; however, nickel acetate injected intraperitoneally produced pulmonary carcinomas in mice (USEPA 1980). Some carcinogenic nickel compounds produce tumors only when a threshold dose is exceeded (IARC 1976; USPHS 1993), and some strains of animals are more sensitive than others. In one study, three strains of male mice (*Mus* sp.) were given a single intramuscular injection of 0.5, 2.5, 5.0, or 10.0 mg nickel subsulfide per mouse—equivalent to 19, 95, 190, or 380 mg Ni_3S_2/kg BW—and observed for 78 weeks for tumor development (Rodriguez et al. 1996). Nickel subsulfide is a water-insoluble compound suspected to damage cells through oxidative mechanisms. The highest dose injected was lethal (53-93% dead) within 7 days. The final incidence of sarcomas in the 5 mg/mouse groups ranged between 40 and 97%, with decreased survival and growth noted in all test groups. In the most sensitive strain tested, there was a dose-dependent increase in tumor frequency, with a significant increase in tumors at the lowest dose tested (Rodriguez et al. 1996).

Carcinogenic properties of nickel are modified by interactions with other chemicals (NAS 1975; USEPA 1985; WHO 1991). Nickel-cadmium battery workers exposed to high levels of both nickel and cadmium have an increased risk of lung cancer when compared to exposure from cadmium alone (WHO 1991). Some nickel compounds interact synergistically with known carcinogens (WHO 1991). Nickel chloride enhances the renal carcinogenicity of N-ethyl-N-hydroxyethyl nitrosamine in rats. Metallic nickel powder enhances lung carcinogenicity of 20-methylcholanthrene when both are administered intratracheally to rats. Nickel subsulfide in combination with benzo(a)pyrene shortens the latency time to local tumor development and produces a disproportionately higher frequency of malignant tumors. Nickel sulfate enhanced dinitrosopiperazine carcinogenicity in rats (WHO 1991). And nickel potentiated the specific effects of cobalt in rabbits by enhancing the formation of lung nodules (Johansson et al. 1991). Some chemicals inhibit nickel-induced carcinogenicity. Carcinogenicity induced by nickel subsulfide is reduced by manganese dust (Sunderman 1981; Sunderman et al. 1984; WHO 1991). Manganese protects male guinea pigs against tumorogenesis induced by nickel subsulfide, possibly due to the stimulating effect of manganese on macrophage response and by displacing nickel from the injection site (Murthy and Chandra 1979). Sodium diethyldithiocarbamate reduced tumor incidence in rats implanted with nickel subsulfide (WHO 1991). And magnesium acetate and calcium acetate inhibit lung adenoma formation in mice treated intraperitoneally with nickel acetate (WHO 1991). Nickel interactions with other suspected carcinogens, such as chromium, merit additional research (Norseth 1980). Nickel and other trace metals in asbestos fibers are responsible, in part, for the pulmonary carcinogenicity found in asbestos workers (Sunderman 1968). Nickel-sulfur mineral complexes may also have carcinogenic potential; a similar case is made for the corresponding arsenides, selenides, and tellurides (USEPA 1980).

Mutagenicity

Nickel salts gave no evidence of mutagenesis in tests with viruses (USPHS 1977), and bacterial mutagenesis tests of nickel compounds have consistently yielded negative or inconclusive results (USPHS 1977; Sunderman 1981; Sunderman et al. 1984; WHO 1991). However, nickel chloride and nickel sulfate were judged to be mutagenic or weakly mutagenic in certain bacterial eukaryotic test systems (USEPA 1985). Nickel subsulfide was positively mutagenic to the protozoan *Paramecium* sp. at 0.5 mg Ni/L (WHO 1991). Ionic Ni^{2+} was mutagenic to *Escherichia coli*; mutagenesis was enhanced by the addition of both hydrogen peroxide and tripeptide glycyl-L-histidine, suggesting that short-lived oxygen free radicals are generated (Tkeshelashvili et al. 1993). Nickel chloride hexahydrate induced respiratory deficiency in yeast cells, but this may be a cytotoxic effect rather than a gene mutation (USPHS 1977; WHO 1991).

Nickel is weakly mutagenic to plants (USPHS 1977) and insects (WHO 1991). Abnormal cell divisions occur in roots of the broad bean (*Vicia faba*) during exposure to various inorganic nickel salts at nickel concentrations of 0.1-1,000 mg/L (USPHS 1977). All nickel salts tested produced more abnormal cell divisions than did controls. In beans, nickel nitrate was the most effective inorganic nickel compound tested in producing deformed cells, abnormal arrangement of chromatin, extra micronuclei, and evidence of cell nucleus disturbances; however, nickel salts showed only weak mutagenic action on rootlets of peas, *Pisum* sp. (USPHS 1977). Nickel sulfate induced chromosomal abnormalities in root tip cells of onions, *Allium* sp. (Donghua and Wusheng 1997) and caused sex-linked recessive mutations in the fruit fly (*Drosophila melanogaster*) at 200-400 mg Ni/L culture medium (WHO 1991).

Human cells exposed to various nickel compounds have an increased frequency of chromosomal aberrations, although sister chromatid exchange frequency is unaffected. Cells from nickel refinery workers exposed to nickel monosulfide (0.2 mg Ni/m^3) or nickel subsulfide (0.5 mg Ni/m^3) showed a significant increase in the incidence of chromosomal aberrations (Boysen et al. 1980; WHO 1991; USPHS 1993). No correlation was evident between nickel exposure level and the frequency of aberrations (USPHS 1993).

In Chinese hamster ovary cells, nickel chloride increased the frequency of chromosomal aberrations and sister chromatid exchanges. Cells with aberrations increased from 8% at about 6 μg Ni/L to 21% at about 6 mg Ni/L in a dose-dependent manner (Howard et al. 1991). There is a large difference in the mutagenic potential of soluble and insoluble nickel compounds that seems to reflect the carcinogenic potential of these nickel forms (Lee et al. 1993). For example, insoluble particles less than 5 μm in diameter of crystalline nickel subsulfide—a carcinogen—produced a strong, dose-dependent mutagenic response in Chinese hamster ovary cells up to 80 times higher than in untreated cells; however, soluble nickel sulfate produced no significant increase in mutational response over background in Chinese hamster ovary cells (Lee et al. 1993). A similar response is

reported for Syrian hamster embryo cells (USPHS 1993). Interactions of carcinogens and soluble nickel salts need to be considered. Benzo(a)pyrene, for example, showed a comutagenic effect with nickel sulfate in hamster embryo cells (USEPA 1985).

In rats, nickel carbonyl is reported to cause dominant lethal mutations (WHO 1991), but this needs verification. Nickel sulfate, when given subcutaneously at 2.4 mg Ni/kg BW daily for 120 days causes infertility; testicular tissues are adversely affected after the first injection (USEPA 1980). Nickel salts given intraperitoneally to rats at 6 mg Ni/kg BW daily for 14 days did not produce significant chromosomal changes in bone marrow or spermatogonial cells (Mathur et al. 1978).

In mice, nickel chloride produces a dose-dependent increase in abnormal lymphoma cells (WHO 1991). Mice given high concentrations of nickel in drinking water, equivalent to 23 mg Ni/kg BW daily and higher, have an increased incidence of micronuclei in bone marrow (USPHS 1993). However, mice injected once with 50 mg Ni/kg BW as nickel chloride show no evidence of mutagenicity (USPHS 1977).

Teratogenicity

Nickel carbonyl at high doses is a potent animal teratogen (Sunderman et al. 1984). Inhalation exposure to nickel carbonyl caused fetal death and decreased weight gain in rats and hamsters (WHO 1991) and eye malformations in rats (Sevin 1980; Sunderman et al. 1980). Studies on hamsters, rats, mice, birds, frogs, and other species suggest that some individuals are susceptible to reproductive and teratogenic effects when given high doses of nickel by various routes of administration (USPHS 1977; Sunderman et al. 1980; USEPA 1986; WHO 1991; Hausinger 1993). Intravenous injection of nickel sulfate to hamsters at 2-25 mg/kg BW on day 8 of gestation produces developmental abnormalities (USPHS 1977; Norseth and Piscator 1979). Teratogenic malformations—including poor bone ossification, hydronephrosis, and hemorrhaging—occur in rats when nickel is administered during organogenesis, and these malformations are maximal at dose levels toxic for the dam (Mas et al. 1985). A dose of 4 mg/kg BW given intraperitoneally on day 12 or 19 of pregnancy is teratogenic in rats (Mas et al. 1985). Rats exposed continuously for three generations to drinking water containing 5 mg Ni/L produce smaller litters, higher offspring mortality, and fewer males (NAS 1975; USPHS 1977). An increase in the number of runts suggests that transplacental toxicity occurs (USPHS 1977; Norseth and Piscator 1979).

Divalent nickel is a potent teratogen for the South African clawed frog (*Xenopus laevis*). Frog embryos actively absorb Ni^{2+} from the medium and develop ocular, skeletal, craniofacial, cardiac, and intestinal malformations (Sunderman et al. 1990; Hopfer et al. 1991; Hausinger 1993; Luo et al. 1993; Hauptman et al. 1993; Plowman et al. 1994). A Ni^{2+}-binding serpin, *pNiXa*, is abundant in clawed frog oocytes and embryos; binding of Ni^{2+} to *pNiXa* may cause embryotoxicity by enhancing oxidative reactions that produce tissue injury and genotoxicity (Beck et al. 1992; Haspel et al. 1993; Sunderman et al. 1996). Another Ni^{2+}-binding protein, *pNiXc*, isolated from mature oocytes of the clawed frog, was identified as a monomer of fructose-1,6-biphosphate aldolase A and raises the possibility that aldolase A is a target enzyme for nickel toxicity (Antonijczuk et al. 1995).

Nickel is embryolethal and teratogenic to white leghorn strains of the domestic chicken (*Gallus* sp.), possibly due to the mitosis-inhibiting activity of nickel compounds (Gilani and Marano 1980). Fertilized chicken eggs injected with 0.02-0.7 mg Ni/egg as nickel chloride on days 1-4 of incubation show a dose-dependent response. All dose levels of nickel tested were teratogenic to chickens. Malformations include poorly developed or missing brain and eyes, everted viscera, short and twisted neck and limbs, hemorrhaging, and a reduction in body size. Toxicity and teratogenicity are highest in embryos injected on day 2 (Gilani and Marano 1980). Mallard (*Anas platyrhynchos*) ducklings from fertile eggs treated at age 72 h with 0.7 μg Ni as nickel mesotetraphenylporphine show a marked decrease in survival. Among survivors, there is a significant increase in the frequency of developmental abnormalities, a reduction in bill size, and a reduction in weight (Hoffman 1979).

Changes in employment practices in North America and Europe have increased the proportion of women among workers in nickel mines and refineries and in nickel-plating industries; this increase has heightened concern regarding possible fetal toxicity associated with exposures of pregnant women to nickel during gestation (Sunderman et al. 1978). One preliminary report (Chashschin et al. 1994) strongly suggests that exposure to nickel of Russian female hydrometallurgy workers causes significantly increased risks for abortion, total defects, cardiovascular defects, and defects of the musculoskeletal system.

Nonteratogenic reproductive effects of nickel include increased resorption of embryos and fetuses, reduced litter size, testicular damage, altered rates of development and growth, and decreased fertility. Nickel compounds can penetrate the mammalian placental barrier and affect the fetus (USEPA 1980; Sunderman et al. 1984; Mas et al. 1985). Intravenous administration of nickel acetate (0.7-10.0 mg Ni/kg BW) to pregnant hamsters on day 8 of gestation resulted in dose-dependent increases in the number of resorbed embryos (USEPA 1980). Rats injected intramuscularly with nickel chloride on day 8 of gestation with 12 or 16 mg Ni/kg BW produced significantly fewer live fetuses than did controls (USPHS 1977). Three generations of rats given nickel in their diets at 250-1,000 mg Ni/kg ration had increased fetal mortality in the first generation and reduced body weights in all generations at 1,000 mg/kg (USPHS 1977). Litter sizes were reduced in pregnant rats fed nickel in various forms at 1,000 mg Ni/kg ration (USEPA 1980). Rodents exposed to nickel during gestation show a decline in the frequency of implantation of fertilized eggs, enhanced resorption of fertilized eggs and fetuses, an increased frequency of stillbirths, and growth abnormalities in live-born young (Hausinger 1993). Exposure of eggs and sperm of rainbow trout to 1.0 mg Ni/L as nickel sulfate for 30 min did not affect fertilization or hatchability; however, most exposed zygotes hatched earlier than the controls (NAS 1975). Nickel salts produced testicular damage in rats and mice given oral, subcutaneous, or intratesticular doses of 10-25 mg Ni/kg BW; nickel-treated male rats were unable to impregnate females (USPHS 1977). Nickel sulfate at 25 mg Ni/kg BW daily for 120 days via the esophagus selectively damaged the testes of rats (inhibition of spermatogenesis) and resulted in a reduced procreative capacity (USPHS 1977); males were permanently infertile after 120 days on this regimen (NAS 1975).

Concentrations in Field Collections

General

Nickel is ubiquitous in the biosphere and is the 24th most abundant element in the earth's crust with a mean concentration of 75 mg/kg (Sevin 1980; Chau and Kulikovsky-Cordeiro 1995). Nickel enters the environment from natural and human sources and is distributed throughout all compartments by means of chemical and physical processes and biological transport by living organisms. Nickel is found in air, soil, water, food, and household objects; ingestion or inhalation of nickel is common, as is dermal exposure (USPHS 1977). In general, nickel concentrations in plants, animals, and abiotic materials are elevated in the vicinity of nickel smelters and refineries, nickel-cadmium battery plants, sewage outfalls, and coal ash disposal basins (NAS 1975; Kasprzak 1987; WHO 1991; USPHS 1993; Chau and Kulikovsky-Cordeiro 1995). A global inventory estimate of nickel shows that living organisms contain about 14 million metric tons of nickel, mostly (98.8%) in terrestrial plants (Table 4). But plants and animals account for only 0.00000031% of the total nickel inventory estimate of 4,500 trillion metric tons, the vast majority of the nickel being present in the lithosphere and other abiotic materials (Table 4).

Table 4. Inventory of nickel in various global environmental compartments (modified from Nriagu 1980b).

Compartment	Mean concentration (mg/kg)	Nickel in compartment (metric tons)
Lithosphere, down to 45 km	75	4,300,000,000,000,000
Sedimentary rocks	48	120,000,000,000,000
Soils, to 100 cm	16	5,300,000,000,000
Oil shale deposits	30	1,400,000,000,000
Dissolved oceanic	0.0006	840,000,000
Nickel ore reserves	>2,000	160,000,000
Coal deposits	15	150,000,000
Terrestrial litter	15	33,000,000
Terrestrial plants	6	14,000,000
Suspended oceanic particulates	95	6,600,000
Crude oil	10	2,300,000
Terrestrial animals	2.5	50,000
Swamps and marshes	7	42,000
Lakes and rivers, total	0.001	34,000
Consumers/reducers (biological)	3.5	11,000
Atmosphere	0.3	1,500
Oceanic plants	2.5	500
Lakes and rivers, plankton	4	230

Table 5. Nickel concentrations in selected abiotic materials.

Table 5. Material and units of concentration	Concentration[a]	Reference[b]
Air, ng/m^3		
Asbestos textile plants, 1961-65	8.8	1
Canada, 1987-90		
Arctic	0.38; Max. 0.68	2
Copper Cliff, Ontario	Max. 6,100	2
Hamilton, Ontario	7; Max. 77	2
Quebec City	5; Max. 15	2
Toronto	3; Max. 11	2
Near nickel alloy plants	Max. 1,200	3
Occupational exposure		
Miners	6-40	24
Mill area	Max. 2,800,000	24
Matte separation area	170,000-15,300,000	24
Converter furnace area	Max. 200,000	24
Particulate materials, United States		
Remote areas	0.0-6.0	4
Rural areas	0.6-78	4
Urban areas	1-328	4
Urban areas, North America		
Canada, 1971		
Sudbury, Ontario	Max. 2,101	5
Toronto	Usually <59	5
United States		
1970-74; various locations	9-15	5
1982; 111 cities	8 (1-86)	4, 7
217 locations; summer vs. winter	17 (Max. 39) vs. 25 (Max. 112)	3, 4, 8, 9
All locales	Usually <20; Max. 328	10
Chicago, 1968-71	18	4
Detroit		
1971-82	21-51 (6-130)	10
1982-92	7-14 (4-32)	10
Houston, 1968-71	15	4
New York, 1968-71	42	4
Texas, 1978-82	1; Max. 49	4
Washington, D.C., 1968-71	23	4
Various locations		
Canadian Arctic	0.1-0.5	4
Continental	1-3	11
Europe	Usually <20; Max. 1,400	10
Marine	<0.1-1	11
Nonurban areas	6 (2-11)	3, 6, 8, 9
Remote areas	<0.1-3	11
Drinking water, μg/L		
Canada		
Ontario except Sudbury	0.2-7	2
Sudbury		
Prior to 1972	200 (141-264)	5
1972-92	26-300	2
Current	Max. 72	4
Europe	1-11	4
United States		
All locations	Usually <10; sometimes 10-20;	4, 8, 9
rarely 75; Max. 200		

Table 5. Material and units of concentration	Concentration[a]	Reference[b]
969 locations, 1964-70	4.8; <1% had >20; Max. 75	3, 4, 6, 12
Ten largest cities	Usually <5.6	6
Hartford, Connecticut	1	4, 5
Philadelphia	13	6
Fossil fuels, mg/kg		
Coal		
Canadian	15 dry weight (DW)	11
Flyash; particle diameter 1.1-2.1 μm vs. >11.3 μm	1,600 DW vs. 460 DW	5
Crude oil		
Western Canadian	0.1-76 fresh weight (FW)	11
Various	10 FW; Max. 20 FW	5, 8
Groundwater, μg/L		
Contaminated with nickel compounds from a nickel-plating factory	Max. 2,500	4
Guelph, Ontario	2.5	2
Newfoundland	<0.2	2
New Jersey, 1977-79	3; Max. 600	4
United States; 1982; upper Mississippi River Basin vs. Ohio River Basin	3 vs. 4,430	7
Meteorites, mg/kg, selected	50,000-500,000	5
Rain, μg/L		
Bermuda	0.2	4
Delaware	0.8	4
Massachusetts	0.8 (0.5-1.5)	4
Ontario, Canada; 1982	0.5-0.6	4
Prince Edward Island, Canada	<0.5; Max. 30	2
Sweden	0.2-0.5	4
Rivers and lakes (freshwater), µg/L		
Lake Huron, 1980	0.5; Max. 3.8	4
Lake Ontario, 1980 vs. 82	4 vs. 6 (<1-17)	4
Most locations	Usually <10; 4.8 (4-71)	4, 5, 12
Near Sudbury, Ontario	131 (8-2,700)	2, 14
Near Sudbury refinery	Max. 183,000	13
New York State, Adirondacks region; summer, 1975		
Six lakes	0.4-1.1	16
Lake Champlain (contaminated)	12-15	16
River basins, United States; 1975; dissolved	0.5-0.6; Max. 56.0	4, 13
Smoking Hills, Northwest Territories of combustion of bituminous shales)	6,300 (from atmospheric releases	2
United Kingdom		
River Ivel (receives municipal wastes) vs. River Yare (reference)	28 (11-84) vs. 3.7 (1.3-11.5)	15
United States; 1982; Great Basin of southern Nevada vs. Ohio River basin	Max. <5 vs. Max. >600	7
Rocks, mg/kg		
Acid	5-20	2
Mafic	130-160	2
Sandstone, limestone	5-20	2
Shales	50-70	2
Ultramific	1,400-2,000	2
Seawater, μg/L		
Dissolved		

Table 5. Material and units of concentration	Concentration[a]	Reference[b]
Atlantic Ocean; offshore; surface vs. 400 m	0.10 vs. 0.16	4
Eastern Arctic Ocean; surface vs. 2,000 m	0.13 vs. 0.22	4
Most locations	0.1-0.7	4, 5, 9, 11
Dissolved plus particulate		
Caribbean Sea	2.1	12
Indian Ocean	5.4	12
Northwest Atlantic	3.1-3.5	12
Southwest Atlantic	4.8-19.2	12
Nearshore vs. open ocean	1.8 vs. 1.2	12
Estuaries, Greece		
Euripos Straits; 1980 vs. 1993		
Dissolved	2.5 vs. 1.8	18
Particulate	0.6 vs. 1.4	18
Louros estuary; summer, 1986		
Dissolved; surface vs. 5 m	0.5-7.4 vs. 3.1-9.2	17
Particulate; surface vs. 5 m	Max. 1 vs. Max. 36	17
Sediments, mg/kg DW		
Canada, lake sediments		
Uncontaminated vs. contaminated	<20 vs. >4,000 (Max. 100,000)	2, 14
Precambrian Shield lakes	20-30	14
34% of all samples	<16	2
About 65% of all samples	16-74	2
0.1% of all samples	>75	2
50% of all samples	27	2
15% of all samples	>31	2
Sudbury, Ontario		
About 180 km from Sudbury smelters	<31	4
Within 10 km of smelters	2,500-4,490	4, 12, 13
Europe		
Ems estuary	21-42	12
Louros estuary, Greece; summer 1986	113-242	17
Europos Straits, Greece; 1980 vs. 1993	59 vs. 64	18
Former West Germany	100-210	12
Rhine-Meuse estuary	19-59	12
United States		
Alaska, off northern coast	25-31	4
Casco Bay, Maine	18	4
Eastern Long Island	8	4
Great Lakes	0.1-500	12
Lake St. Clair	14 (9-31)	4
New England	4-58	4
New York; Adirondacks region; six lakes vs. Lake Champlain	0.1-3 vs. 3-5	16
Penobscot Bay, Maine	8-35	4
Rocky Mountain lakes		
four lakes	(10-18)	4
five lakes	(6-38)	4
Washington; Puget Sound; near sewage treatment plant outfall	35-50	19
Sewage liquids, *µ*g/L		
New York City, 1974		
Industrial	100 (70-240)	13
Municipal	50 (10-150)	13

Table 5. Material and units of concentration	Concentration[a]	Reference[b]
Sewage recipients; harbor waters vs. adjacent marine waters	15 vs. 4	13
Wastewater treatment plants	200	11
Sewage sludge, mg/kg DW		
Missouri; 74 publicly owned treatment works (POTW)	33 (10-13,000)	20
United States; 50 POTW	134	20
United States	Max. 53,000	7
Snow, µg/kg DW		
Montreal, Canada	2-300	4
Snow particulates	100-500	4
Soils, mg/kg DW		
Cultivated soils		
Canada	5-50; Max. 950	2, 4, 14
England and Wales	26 (4-80)	4
Farm soils, all locales	Usually 4-80 (<5-1,000)	4, 9, 11, 20
Farm soils, United States; mean vs. too acidic to support plant growth	30 vs. <3	5
Forest soils; nine northeastern states vs. Idaho	11 vs. 12-23	4
Contaminated soils		
Near metal refineries	Max. 24,000 DW	14
Near nickel smelter	80-5,100; Max. 9,372	4, 14
Near nickel smelter, top 5 cm		
Mineral soils; 3 km from smelter vs. 11-18 km distant	500-1,500 vs. 16	21
Organic soils; 1 km from smelter vs. reference site	600-6,455 vs. 29	21
Near Sudbury smelter vs. site 10 km distant	580 (80-2,149) vs. 210 (23-475)	22
Roadside soils, Germany; near road vs. site 5 m from road	32 vs. 8	23
Earth's crust		
Mean	60-90	14
Glacial till	>1,000	4
Podzol soil	5,000	4
United States	13 (<5-700)	4
Wastewaters, µg/L		
Canada; 1988-90; from nickel mining, smelting, and refinery operations	16-27,200	2

[a]Concentrations are shown as means, range (in parentheses), and maximum (Max.).

[b]1, Sunderman 1968; 2, Chau and Kulikovsky-Cordeiro 1995; 3, Sevin 1980; 4, U.S. Public Health Service (USPHS) 1993; 5, National Academy of Sciences 1975; 6, U.S. Environmental Protection Agency (USEPA) 1980; 7, USEPA 1986; 8, Norseth 1986; 9, Norseth and Piscator 1979; 10, Pirrone et al. 1996; 11, World Health Organization 1991; 12, Snodgrass 1980; 13, Kasprzak 1987; 14, National Research Council of Canada 1981; 15, Bubb and Lester 1996; 16, Williams et al. 1977; 17, Scoullos et al. 1996; 18, Dassenakis et al. 1996; 19, Schell and Nevissi 1977; 20, Beyer 1990; 21, Frank et al. 1982; 22, Adamo et al. 1996; 23, Munch 1993; 24, USPHS 1977.

Abiotic Materials

Nickel concentrations are elevated in air, water, soil, sediment, and other abiotic materials in the vicinity of nickel mining, smelting, and refining activities; in coal flyash; in sewage sludge; and in wastewater outfalls (Table 5). Maximum concentrations of nickel found in abiotic materials were 15,300 ng/L in air under conditions of extreme occupational exposure, 19.2 µg/L in seawater, 30 µg/L in rain, 240 µg/L in sewage liquids, 300 µg/L

in drinking water near a nickel refinery, 500 μg/kg in snow, 183,000 μg/L in fresh water near a nickel refinery, 4,430 μg/L in groundwater, 27,200 μg/L in waste water from nickel refineries, 1,600 mg/kg in coal flyash, 2,000 mg/kg in ultramific rocks, 24,000 mg/kg in soils near metal refineries, 53,000 mg/kg in sewage sludge, more than 100,000 mg/kg in lake sediments near a nickel refinery, and 500,000 mg/kg in some meteorites (Table 5).

Nickel in the atmosphere is mainly in the form of particulate aerosols (WHO 1991) resulting from human activities (Sevin 1980). Air concentrations of nickel are elevated near urbanized and industrialized sites and near industries that process or use nickel (USPHS 1993; Chau and Kulikovsky-Cordeiro 1995; Pirrone et al. 1996; Table 5). The greatest contributor to atmospheric nickel loadings is combustion of fossil fuels in which nickel appears mainly as nickel sulfate, nickel oxide, and complex metal oxides containing nickel (USEPA 1986). Nickel concentrations in the atmosphere of the United States are highest in winter and lowest in summer, demonstrating the significance of oil and coal combustion sources (USPHS 1993; Pirrone et al. 1996). Nickel in the atmosphere is removed through rainfall and dry deposition, locating into soils and sediments; atmospheric removal usually occurs in several days. When nickel is attached to small particles, however, removal can take more than a month (USPHS 1993). Cigarette smoke contributes significantly to human intake of nickel by inhalation; heavy smokers can accumulate as much as 15 μg of nickel daily from this source (USEPA 1980).

Most unpolluted Canadian rivers and lakes sampled between 1981 and 1992 contained 0.1-10 μg Ni/L; however, natural waters near industrial sites may contain 50-2,000 μg Ni/L (Chau and Kulikovsky-Cordeiro 1995). Nickel concentrations in snow from Montreal, Canada, are high compared with ambient air (Table 5); nickel burdens in Montreal snow are positively correlated with those of vanadium, strongly suggesting that combustion of fuel oil is a major source of nickel (USPHS 1993). In drinking water, nickel levels may be elevated due to the corrosion of nickel-containing alloys used in the water distribution system and from nickel-plated faucets (USPHS 1993). Nickel concentrations in uncontaminated surface waters are usually lower with increasing salinity or phosphorus loadings (USPHS 1993). Nickel tends to accumulate in the oceans and leaves the ocean as seaspray aerosols which release nickel-containing particles into the atmosphere (USEPA 1986).

Sediment nickel concentrations are grossly elevated near the nickel-copper smelter at Sudbury, Ontario, and downstream from steel manufacturing plants. Sediments from nickel-contaminated sites have between 20 and 5,000 mg Ni/kg DW; these values are at least 100 times lower at comparable uncontaminated sites (Chau and Kulikovsky-Cordeiro 1995). A decrease in the pH of water caused by acid rain may release some of the nickel in sediments to the water column (NRCC 1981). Transfer of nickel from water column to sediments is greatest when sediment particle size is comparatively small and when sediments contain high concentrations of clays or organics (Bubb and Lester 1996).

In soils, nickel exists in several forms, including inorganic crystalline minerals or precipitates, as free ion or chelated metal complexes in soil solution, and in various formulations with inorganic cationic surfaces (USEPA 1986). Soil nickel is preferentially adsorbed onto iron and manganese oxides (USPHS 1993; Chau and Kulikovsky-Cordeiro 1995); however, near Sudbury, Ontario, soil nickel is mostly associated with inorganic sulfides (Adamo et al. 1996). The average residence time of nickel in soils is estimated at 3,500 years, as judged by nickel concentrations in soils and estimates of the loss of nickel from continents (Nriagu 1980b). Natural levels of soil nickel are augmented by contamination from anthropogenic activities including atmospheric fallout near nickel-emitting industries, automobile traffic, and treatment of agricultural lands with nickel-containing phosphate fertilizers or municipal sewage sludge (USEPA 1980; Munch 1993). Soils with less than 3 mg Ni/kg DW are usually too acidic to support normal plant growth (NAS 1975). Nickel availability to plants grown in sludge-amended soils is correlated with soil-solution nickel (USPHS 1993). Sewage-derived fertilizers from industrial areas may contain 1,000 mg Ni/kg DW or more (NRCC 1981). In sewage sludge, a large percentage of the nickel exists in a form that is easily released from the solid matrix (USPHS 1993). Water solubility of nickel in soils and its bioavailability to plants are affected by soil pH, with decreases in pH below 6.5 generally mobilizing nickel (USPHS 1993; Chau and Kulikovsky-Cordeiro 1995).

Terrestrial Plants and Invertebrates

Nickel is found in all terrestrial plants, usually at concentrations of less than 10 mg/kg DW (NRCC 1981; Kasprzak 1987). The majority of terrestrial plants are nickel-intolerant species and are restricted to soils of relatively low nickel content; some plants without specific nickel tolerance can accumulate anomalous levels of nickel, but at a cost of reduced metabolism (Rencz and Shilts 1980). Plants grown on nickel-rich soils can accumulate high concentrations of nickel (Sigel and Sigel 1988). Crops grown in soils amended with sewage

sludge may contain as much as 1,150 mg Ni/kg DW (USEPA 1986). Vegetation near point sources of nickel, such as nickel refineries, have elevated nickel concentrations that decline with increasing distance from the source (WHO 1991; Table 6). Fruits and vegetables grown near nickel smelters contain 3-10 times more nickel in edible portions than those grown in uncontaminated areas (NRCC 1981). Trees, ferns, and grasses near nickel smelters had elevated concentrations of nickel, as much as 174 mg/kg DW in trees and ferns and 902 mg/kg DW in wavy hairgrass (*Deschampsia flexuosa*; Table 6). Nickel concentrations in lichens and other vegetation were elevated when grown on nickeliferous rocks, serpentine soils, near nickel smelters (Jenkins 1980b), near urban and industrial centers (Richardson et al. 1980), and near roadsides treated with superphosphate fertilizers (NAS 1975).

Table 6. Nickel concentrations (milligrams of nickel per kilogram fresh weight [FW] or dry weight [DW]) in field collections of representative plants and animals.

Table 6. Taxonomic group, organism, and other variables	**Concentration (mg/kg)[a]**	**Reference[b]**
Terrestrial Plants		
Red maple, *Acer rubrum*; leaf; various distances from nickel smelter		
2 km	98 DW	1
20 km	57 DW	1
40 km	14 DW	1
Onion, *Allium cepa*; spring vs. fall		
Leaf	9.4 DW vs. 3.8 DW	1
Root	18.4 DW vs. 10.9 DW	1
Celery, *Apium graveolans*; spring vs. fall		
Leaf	36 DW vs. 5 DW	1
Root	32 DW vs. 3 DW	1
Paper birch, *Betula papyrifera*; leaf; various distances from nickel smelter; June vs. August		
1.0 km	158 DW vs. 148 DW	1
4.6 km	82 DW vs. 111 DW	1
12.0 km	66 DW vs. 64 DW	1
Coffee, *Coffea arabacia*; green beans	0.1-0.3 FW	1
Sweet fern, *Comptonia peregrina*; leaf; various distances from nickel smelter; August		
1.0 km	174 DW	1
6.5 km	46 DW	1
31.0 km	15 DW	1
Lichen, *Compylium polyanum*; whole; from serpentine soils	420 DW	1
Wavy hairgrass, *Deschampsia flexuosa*; leaf; various distances from nickel smelter		
1.7 km	902 DW	1
2.1 km	242 DW	1
7.4 km	160 DW	1
20.4 km	43 DW	1
52.7 km	37 DW	1
Tall fescue, *Festuca* sp.; shoot; Maryland; various distances from highway		
8 m	(3.8-5.0) DW	1
16 m	(2.5-3.8) DW	1
32 m	(1.3-2.8) DW	1
Forest species; Nagoya University, Japan; leaves		
57 species	2-8 DW	2

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
3 species	10-16 DW	2
Grasses, various species; near roadside vs. >30 m from roadside	3.8 DW vs. 1.3 DW	3
Hypnum moss, *Hypnum cupressiforme*; whole; United Kingdom; downwind of nickel industrial complex <3 km	All dead; no residues measured	1
8 km	193 DW	1
25 km	420 DW	1
Lettuce, *Lactuca sativa*; spring vs. fall		
Leaf	28 DW vs. 3 DW	1
Root	15 DW vs. 4 DW	1
Lichens		
Industrial sites; 13 species	2-52 DW	4
Near nickel smelters; three species	220-846 DW	4
Rural sites		
Mineralized substrates; 19 species	1-115 DW	4
Nonmineralized substrates; 13 species	1-10 DW	4
Urban sites; two species	33-183 DW	4
Macrophytes, four species; 1.6 km from smelter (soil had 2,679 mg Ni/kg DW)	109-902 DW	5
Mosses, 4 species; isolated areas	0.2-5.0 DW	4
Nickel hyperaccumulator plants		
Allysum spp.; various locations		
Flowers	Max. 5,400 DW	1
Fruits	Max. 5,800 DW	1
Leaves	2,590-9,330 DW; Max. 20,400 DW	1, 6
Roots	Max. 3,100 DW	1
Seeds	Max. 6,100 DW	1
Stems	Max. 13,500 DW	1
Geissosis prainosa; New Caledonia; leaves	6,720 DW	6
Homalium spp; New Caledonia; nine species; leaves		
Three species	3,730-9,580 DW	6
Three species	446-662 DW	6
Three species	15-75 DW	6
Hybanthus spp.; New Caledonia; two species; leaves	6,820-14,900 DW	6
Pearsonia metallifera; Rhodesia; leaves	10,600 DW	6
Planchonella oxyedra; southeast Asia; leaves	1,600 (50-19,600) DW	1
Psychotria douarrei; New Caledonia; leaf	13,400 DW; Max, 47,000 DW	1, 6
Sebertia acuminata; New Caledonia		
Latex	112,000 FW; 167-257,000 DW	1, 6
Leaves	10,200-11,700 DW	1, 6
Rice, *Oryza sativa*; Japan; polished vs. unpolished grain	0.50-0.65 FW vs. 1.8 FW	1
Moss, *Pleurozium schreberi*		
Near nickel smelter	Max. 195 DW	4
Rural sites	1-34 DW	4
Urban sites	Max. 100 DW	4
Red oak, *Quercus rubra*; leaf; 1.6 km vs. 10.6 km from nickel smelter	(79-108) DW vs. (12-57) DW	1
Spinach, *Spinacia oleracea*; leaf		
Alabama	2.3 DW	1

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
New Jersey	2.2 DW	1
World, 44 varieties	4.2 DW	1
United States	0.35 FW	1
Lichen, *Umbilicaria* sp.; whole; 16 km vs. 90 km from nickel smelter	220 DW vs. 37 DW	1
Terrestrial vegetation		
Hyperaccumulator plants	>1,000 DW	5
Most species	0.05-5.0 DW (>50 DW is toxic)	5
Vegetables		
Grown on soils containing 558 mg Ni/kg DW through sewage sludge application		
Beans and peas	42-65 DW	5
Green vegetables, cabbage, onions	11-65 DW	5
Root vegetables	8-27 DW	5
Grown on nickel-contaminated soils (>1,500 mg Ni/kg DW surface soils) vs. reference site		
Heads and tops	15-400 DW vs. Max. 5.0 DW	8
Roots	24-280 DW vs. Max. 5.0 DW	8
Near nickel smelter vs. reference site; edible portions		
Cabbage, *Brassica oleracea capitata*	4.7 DW vs. 1.2 DW	7
Lettuce, *Lactuca sativa*	11.0 DW vs. 3.5 DW	7
Corn, *Zea mays*	2.8 DW vs. 1.1 DW	7
Wheat, *Triticum aestivum*; from sludge-amended soil (19.4 mg Ni/kg DW soil) vs. nonsludge-amended soil	0.98 DW vs. 0.40 DW	9
Lowbush blueberry, *Vaccinium angustifolium*; leaf; various distances from nickel smelter		
1.7 km	92 DW	1
7.4 km	45 DW	1
52.7 km	14 DW	1
Corn, *Zea mays*		
Grain vs. root	(0.1-5.0) DW vs. 28.0 DW	1
Grown on soil containing 745 mg Ni/kg DW		
Kernels	2.3-4.3 DW	5
Leaves	6.7-10.7 DW	5
Stems	4.3-5.5 DW	5
Aquatic Plants		
Algae and macrophytes: nickel-contaminated areas vs. reference sites	About 150 DW vs. usually <15 DW	5
Brown alga, *Ascophyllum nodosum*		
Norway	(1-22) DW	1
Nova Scotia	0.6 DW	1
Former Soviet Union	0.4 DW	1
Scotland	0.9 FW; (1.5-6.3) DW	1
Alga, *Cymodocea* sp.; Puerto Rico	2.1 (1.5-2.6) FW; 24 (19-29) DW	1
Bladder wrack, *Fucus vesiculosus*		
England	(1.2-29.6) DW	1
Greenland	(0.6-2.3) DW	1
Norway	(2-7) DW	1

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Nova Scotia	2 DW	1
Scotland	1.4 FW; 4.9 DW	1
Duckweed, *Lemna minor*; from ponds (27 µg Ni/L) in southern Ontario, Canada	5.4-35.1 DW	5
Marine algae and macrophytes		
England, 14 species	2.7-10.3 DW	10
India, 27 species	3.5-39.1 DW	10
Japan, 60 species	0.2-31.0 DW	10
Texas, Harbour Island, 14 species	0.2-2.6 DW	10
Pond lily, *Nuphar* sp.; Ontario, Canada; nickel-contaminated areas		
Leaf	8-62 FW	1
Peduncle	3-9 FW	1
Petiole	5-35 FW	1
Root	5-14 FW	1
Laver, *Porphyra umbilicalis*; whole	0.2-9.7 DW	1
Sargassum, *Sargassum* spp.; Gulf of Mexico; whole	0.9-15.6 DW	10
Smooth cordgrass, *Spartina alterniflora*; leaves	5.3 DW	1
Terrestrial Invertebrates		
Earthworm, *Allolabophophora* sp.; whole; Maryland	12.9-37.5 DW	1
Beach flies, two species; whole; California	Max. 7.0 DW	1
Gypsy moth, *Porthetria dispar*; near ore smelter at Sudbury, Ontario, Canada vs. reference site		
Adult males; whole	8.8 DW vs. 2.9 DW	11
Larvae		
Feces	28 DW (reflects nickel content	11
of leaf diet) vs. <2 DW		
Whole	20.4 DW vs. 0.4-7.2 DW	11
Pupae	1.5 DW vs. 1.6 DW	11
Termites, *Odontotermes transvaalensis*, *Trinervitermes dispar*; whole		
Queen	20 DW	1
Soldier	100 DW	1
Worker	5,000 DW	1
Aquatic Invertebrates		
Protozoans, marine		
Foraminiferan tests	15.4-23.0 DW	10
Radiolarians, whole	3.7 DW	10
Sponge, *Halichondria* sp.; whole; Sweden	22.0 DW	1
Corals; open ocean species vs. shallow coastal zone species	<2.0-23.0 DW vs. Max. 3.0 DW	10
Mollusks		
Duck mussel, *Anodonta anatina*; Thames River, England; soft parts; near sewage outfall	Max. 46.0 DW	12
Ocean quahog, *Arctica islandica*; soft parts		
Long Island, New York; 1974-75; offshore	1.1-7.0 FW	13
New England; offshore; February vs. March	5-29 DW vs. 4-18 DW	10
Waved whelk, *Buccinum undatum*; soft parts; near sludge dump site vs. reference site	8.5 DW vs. 0.6 DW	1

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Scallop, *Chlamys opercularis*		
Digestive gland	4.3 DW	10
Kidneys	78.2 DW	10
Shell	(0.2-7.6) DW	10
Other tissues	0.2-1.6 DW	10
Pacific oyster, *Crassostrea gigas*; soft parts		
South Africa	Max. 2.0 DW	1
United Kingdom	(1-10) DW	1
United States	Max. 0.2 FW	1
World	0.1-1.6 DW	10
Eastern oyster, *Crassostrea virginica*; shell vs. soft parts	<1.0 DW vs. (0.9-5.4) DW; 0.19 (0.08-1.8) FW	1, 10
Common Atlantic slippersnail, *Crepidula fornicata*; United Kingdom; shell vs. soft parts	1.6 DW vs. 127.0 FW; 850.0 DW	1, 10
Red abalone, *Haliotis rufescens*; California		
Digestive gland	(3-11) DW	1, 10
Foot	(0.2-1.6) DW	1, 10
Gills	(69-112) DW	1, 10
Mantle	(19-57) DW	1, 10
Abalone, *Haliotis tuberculata*; soft parts; England	13.6-15.9 DW	14
Marine mollusks; 21 species; soft parts	Max. 3.4 FW	10
Northern quahog, *Mercenaria mercenaria*; soft parts		
United Kingdom	2.2 FW; (6.5-19.2) DW	1
United States	1.2 (0.1-2.4) FW	1
Common mussel, *Mytilus edulis*; soft parts		
France	0.5 FW; 2.4 DW	1
The Netherlands, 1985-90	0.33-0.52 FW	15
Norway	(6-43) DW	1
United Kingdom	0.4 FW; Max. 53.0 FW; 3.7 (5-12) DW	1
United States	(11-14) DW	1
Mud snail, *Nassarius* sp.; soft parts; Los Angeles, California	36 DW	1
Common limpet, *Patella vulgata*; soft parts		
Israel; near sewage discharge vs. control site	12 DW vs. 5-9 DW	1
Norway	(4-11) DW	1
United Kingdom	7.3 (2.5-24.0) DW	1
Pen shell, *Pinna nobilis*; contaminated area		
Byssus gland	200 DW	10
Gonads	74 DW	10
Nervous system	18 DW	10
Soft parts	21 DW	10
Stomach plus intestines and hepatopancreas	170 DW	10
Sea scallop, *Placopecten magellanicus*		
Long Island, New York; 1974-75; soft parts	(<0.5-3.3) FW	13
North Atlantic coast, 42 stations		
Gonads	0.2-2.5 FW	16
Muscle	<0.3-0.7 FW	16
Viscera	0.3-1.6 FW	16
Vicinity ocean disposal sites; soft parts	4.4 DW	17
Clam, *Scrobicularia plana*		

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Contaminated estuary, soft parts	Max. 11.9 DW	18
United Kingdom; digestive gland		
Camel estuary	10.6 DW	10
Gannel estuary	43.1 DW	10
Tamar estuary	(6.6-25.0) DW	10
Arthropods		
Amphipods; whole; Antarctica	2.2 DW	19
Green crab, *Carcinus maenas*; all tissues	6.2-12.3 FW	1
Sand shrimp, *Crangon allmanni*;	15 DW vs. 92 DW	1
Scotland; soft parts; reference site vs. waste dump site		
Seaskaters (oceanic insects), *Halobates* spp.,	6-18 DW	20
Rheumobates sp.; whole; from mangrove swamps		
American lobster, *Homarus americanus*; serum	0.012 (0.008-0.020) FW	3, 21
Marine crustaceans		
Muscle, 10 species	0.2-0.9 FW	10
Whole, various species	6.5-9.8 FW	10
Aesop shrimp, *Pandalus montagui*;	25 DW vs. 70 DW	1
soft parts; Scotland; reference site vs. waste dump site		
Caribbean spiny lobster, *Panulirus argus*; soft parts;		
Puerto Rico		
Anasco Bay	1.3 (1-2) FW; 4.5 (8-9) DW	1
West coast	4.6 (1.4-5.0) FW; 36 (22-60) DW	1
Brown shrimp, *Penaeus aztecus*; Texas		
Exoskeleton	6.2 DW; Max. 17.9 DW	1
Muscle	1.4 DW; Max. 1.9 DW	1
Viscera	5.7 DW; Max. 5.8 DW	1
Zooplankton; New York Bight vs. Long Island Sound	1.7-4.6 DW vs. 0.9-4.5 DW	22
Annelids, marine		
Sandworm, *Nereis diversicolor*; whole;	2.1-5.2 DW	10
British Columbia; various locations		
Polychaete worms, three species;	(3.8-18.7) DW	1
whole; California		
Echinoderms		
Starfish, *Asterias rubens*		
Gonad	2.4 DW	10
Pyloric caeca	4.1 DW	10
Other tissues	0.7-1.5 DW	10
Rock boring sea urchin, *Echinometra lucunter*; Puerto Rico; skeleton vs. whole	51 (42-78) DW vs. 37 DW	1
Sea urchin, *Tripneustes esculentus*; Puerto Rico		
Ovary	1.4 FW	1
Skeleton	35 (18-54) DW	1
Testes	22 FW	1
Tunicate, *Halocynthia roretzi*; whole	0.1 FW	10
Fishes and Elasmobranchs		
Rock bass, *Ambloplites rupestris*; near smelter; Sudbury, Ontario, Canada		
Gills	31.7 FW	1
Kidneys	17.3 FW	1

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Livers	17.0 FW	1
Muscle	12.5 FW	1
Whitetip shark, *Carcharhinus longimanus*		
Liver	0.05 FW; 0.1 DW	1
Skin	1.9 FW; 7.3 DW	1
Vertebrae	1.6 FW; 4.9 DW	1
White sucker, *Catostomus commersoni*; muscle; near smelter vs. reference site	13.2 FW vs. 0.1 FW	1
Blackfin icefish, *Chaenocephalus aceratus*; Antarctica; muscle vs. liver	0.2 DW vs. 0.3 (0.2-0.5) DW	19
Lake whitefish, *Coregonus clupeaformis*; muscle; northern Quebec; 1989-90	<0.01 FW	23
Lumpfish, *Cyclopterus lumpus*; United Kingdom; all tissues	3.2-5.2 FW	1
Northern pike, *Esox lucius*; muscle		
Canada		
Ontario; near smelter	13.3 FW	1
Northern Quebec, 1989-91	<0.05-0.05 FW	23
Illinois vs. New York	0.15 (0.08-0.19) FW vs. (0.2-3.8) FW	1
Muskellunge, *Esox masquinongy*; muscle; New York	0.2-1.3 FW	1
Chain pickerel, *Esox niger*; muscle; New York	0.1-0.25 FW	1
Pickerel, *Esox* sp.; near smelter; Sudbury, Ontario		
Gills	16.0 FW	1
Kidneys	51.6 FW	1
Livers	14.4 FW	1
Muscle	13.8 FW	1
Skipjack tuna, *Euthynnus pelamis*; muscle		
Peru	2.0 FW; 5.0 DW	1
Puerto Rico	0.5 FW; 2.2 DW	1
Fishes, 10 species; muscle; Bay of Bengal, India	0.7-6.1 DW	24
Atlantic cod, *Gadus morhua*; all tissues	1.6-4.6 FW	1
Brown bullhead, *Ameiurus nebulosus*; near smelter;		
Canada		
Gills	11.1 FW	1
Kidneys	11.8 FW	1
Livers	10.7 FW	1
Muscle	9.5 FW	1
Yellowtail flounder, *Pleuronectes ferruginea*; New York Bight; liver vs. muscle	0.2-1.1 FW vs. <0.2-0.4 FW	1
Marine fishes		
Liver; five species; New York Bight; 1971-73	<0.2-1.7 FW	25
Most species; all tissues	Usually <0.3 FW; rarely >3.0 FW in uncontaminated areas; Max. 16.0 DW	10
Muscle		
New Zealand, nine species	0.02-0.07 FW	1
United Kingdom, eight species	2.1-3.5 DW	1
Atlantic croaker, *Micropogonias*	2.7 DW vs. 3.8 DW	1

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
undulatus; Texas; muscle vs. skin		
Smallmouth bass, *Micropterus dolomieu*; muscle; New York vs. Illinois	(0.16-1.2) FW vs. 0.13 (0.08-0.19) FW	1
Largemouth bass, *Micropterus salmoides*; muscle; New York vs. Illinois	(0.18-1.9) FW vs. 0.11 (0.05-0.23) FW	1
Dover sole, *Microstomus pacificus*; California; muscle vs. liver	0.2 (0.1-0.3) FW vs. 1.4-2.6 FW	1
Hump rock cod, *Notothenia gibberfrons*; muscle; Antarctica	0.22 DW	19
Rainbow trout, *Oncorhynchus mykiss*		
Kidney, liver	Usually <1.5 FW	5
Muscle	Usually <0.5 FW	5
Kelp bass, *Paralabrax clathratus*; California		
Gonad	1.5-2.2 DW	1
Liver	3.9-7.6 DW	1
Muscle	5.0-6.4 DW	1
Skin	9.0-10.2 DW	1
Winter flounder, *Pleuronectes americanus*		
New York Bight; muscle vs. skin	<0.3-0.5 FW vs. <0.3-1.0 FW	1
Texas; muscle vs. skin	3.3 (0.6-7.4) DW vs. 4.4 (2.9-7.4) DW	1
Lake trout, *Salvelinus namaycush*; whole less head and viscera; New York		
Ages 1-4 years	Max. 0.009 FW	1
Ages 5-8 years	Max. 0.022 FW	1
Ages 9-12 years	Max. 0.022 FW	1
Sharks, 10 species; British and Atlantic waters; 1984-88; inshore species vs. offshore species		
Gills	0.3-1.8 FW vs. 1.7-1.9 FW	26
Gonads	<0.02-8.3 FW vs. 1.7 FW	26
Heart	No data vs. 2.8 FW	26
Jaws	5.7 FW vs. 0.3 FW	26
Kidneys	0.07-1.2 FW vs. 1.6 FW	26
Liver	<0.02-0.8 FW vs. 1.9-3.2 FW	26
Muscle	<0.02-1.8 FW vs. 1.4-2.6 FW	26
Pancreas	0.9 FW vs. No data	26
Skin	<0.02-3.4 FW vs. 1.0-2.0 FW	26
Spleen	<0.02-0.8 FW vs. 1.3 FW	26
Vertebrae	0.5-2.4 FW vs. 0.2-10.8 FW	26
South Carolina; gamefish; 1990-93; whole		
Spotted seatrout, *Cynoscion nebulosus*	Max. 12.6 FW	27
Southern flounder, *Paralichthys lethostigma*	Max. 8.2 FW	27
Red drum, *Sciaenops ocellatus*	Max. 2.9 FW	27
Scup, *Stenotomus chrysops*; Texas		
Muscle	1.0 (0.5-2.0) DW	1
Skin	4.9 (2.8-7.4) DW	1
Viscera	3.5 DW	1
Amphibians		
Maryland; 1991; tadpoles		
Northern cricket frog, *Acris crepitans*; whole	2.4-10.0 DW	28
Gray treefrog, *Hyla versicolor*; whole	2.0-7.1 DW	28

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Green frog, *Rana clamitans*; body vs. gut coil	4.7 DW vs. 16.4 DW	28
Birds		
Wood duck, *Aix sponsa*; ducklings; liver; Ontario, Canada; polluted area	0.2 FW	29
Mallard, *Anas platyrhynchos*		
Canada; nickel-contaminated areas vs. reference site		
Liver	0.1-1.4 FW vs. 0.2 FW	29
Muscle (breast)	0.1-0.8 FW vs. 0.6 FW	29
New Jersey; Raritan Bay; contaminated environment; liver vs. salt gland	0.1-2.5 FW vs. 9.7 FW	30, 31
Primary flight feathers; 1975; various distances from nickel smelter		
20-30 km	2.0-12.5 DW; Max. 36.7 DW	32
50-60 km	0.2-3.8 DW	32
85 km	0.2-1.5 DW	32
95-140 km	0.0-4.3 DW	32
Reference site	0.0-0.4 DW	32
Black duck, *Anas rubripes*		
Canada; ducklings; nickel-contaminated vs. reference site		
Kidney	0.3 FW vs. 0.3 FW	29
Liver	0.6 FW vs. 0.4 FW	29
Canada; primary feathers; contaminated vs. noncontaminated areas	2.5-3.7 DW vs. 0.2-1.5 DW	32
Raritan Bay, New Jersey; liver vs. salt gland	0.2-2.7 FW vs. 15.2 FW	30, 31
Gadwall, *Anas strepera*; Canada; muscle; contaminated area	0.3 FW	29
Antarctica; February-March 1989		
Gentoo penguin, *Pygoscelis papua*; muscle vs. liver	<0.03 DW vs. 0.09 DW	19
Adelie penguin, *Pygoscelis adeliae*; muscle vs. liver	<0.03 DW vs. 0.06 DW	19
Chinstrap penguin, *Pygoscelis antarctica*		
Feces	3.5 (3.2-3.7) DW	19
Liver	0.07 DW	19
Muscle	<0.03 DW	19
Blue-eyed cormorant, *Phalocrocorax atriceps*; muscle	0.29 DW	19
South giant petrel, *Macronectes giganteus*; muscle	0.06 DW	19
Redhead, *Aythya americana*; Texas and Louisiana; liver; winter 1987-88	<4.0 DW	33
Ring-necked duck, *Aythya collaris*; ducklings; contaminated vs. reference location		
Kidney	0.3 FW vs. 0.1 FW	29
Liver	0.5 FW vs. 0.2 FW	29
Greater scaup, *Aythya marila*; contaminated areas		
Ontario; muscle	0.2 FW	29
New Jersey; liver vs. salt gland	0.3-3.6 FW vs. 2.7 FW	30, 31
Canvasback, *Aythya valisineria*; Louisiana; winter 1987-88; liver	Usually <1.0 DW; Max. 2.0 DW	34

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Ruffed grouse, *Bonasa umbellus*		
Canada; nickel-contaminated vs. reference areas		
May		
Feathers, primaries	7.3 DW vs. 2.9 DW	35
Dung	19.4 DW vs. <0.5 DW	35
Kidney	2.8 DW vs. 1.7 DW	35
Liver	1.0 DW vs. 0.9 DW	35
Muscle	1.4 DW vs. <0.5 DW	35
September		
Feathers, primaries	4.8 DW vs. 0.8 DW	35
Dung	47.7 DW vs. <0.5 DW	35
Kidney	2.1 DW vs. <0.5 DW	35
Liver	3.5 DW vs. 0.7 DW	35
Muscle	0.2 DW vs. 0.2 DW	35
New England		
Kidney	5.0 DW	1
Liver	1.1-2.4 DW	1
Common goldeneye, *Bucephala clangula*; ducklings; Canada; contaminated vs. reference areas		
Kidney	0.3 FW vs. 0.1 FW	29
Liver	0.5 FW vs. 0.8 FW	29
Turkey vulture, *Cathartes aura*; California; kidney vs. liver	<0.1-0.4 FW vs. <0.1 FW	36
Common raven, *Corvus corax*; California; kidney vs. liver	<0.1-0.12 FW vs. <0.1 FW	36
American coot, *Fulica americana*; Ontario; muscle	1.5 FW	37
Domestic chicken, *Gallus* sp.; serum; United States	0.0036 (0.0033-0.0053) FW	3, 21
Common loon, *Gavia immer*; Ontario; muscle	1.1 FW	37
California condor, *Gymnogyps californianus*; feathers	0.5-2.0 DW	36
Willow ptarmigan, *Lagopus lagopus*; near nickel smelter; 1990-93; Norway; kidney	Max. 2.3 DW	38
Herring gull, *Larus argentatus*; Ontario; muscle	1.0 (0.6-1.3) FW	37
Lesser black-backed gull, *Larus fuscus*; Norway		
Kidney	5.0 DW	1
Liver	2.0 DW	1
Muscle	5.0 DW	1
Hooded merganser, *Lophodytes cucullatus*; ducklings; nickel-contaminated vs. reference areas		
Kidney	1.2 FW vs. 1.0 FW	29
Liver	0.07 FW vs. 0.14 FW	29
Turkey, *Meleagris gallopavo*; liver vs. muscle	0.002 FW vs. 0.015 FW	39
Black-crowned night-heron, *Nycticorax nycticorax*; liver; northeastern United States; nickel-contaminated vs.reference areas	<0.1-9.2 DW vs. <0.1 DW	40
Owl (species unidentified); Germany; polluted area vs. reference site; tail feathers		
Lower feather	2.0 FW vs. 1.6 FW	41
Upper feather	14.3 FW vs. 2.0 FW	41
Osprey, *Pandion haliaetus*; liver	<0.2-0.3 FW	42
Brown pelican, *Pelecanus occidentalis*		

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Egg	Max. 0.072 FW	1
Liver	Max. 0.078 FW	1
Common eider, *Somateria mollissima*; Norway		
Egg, liver	1.0 DW	1
Muscle, kidney	2.0 DW	1
Common tern, *Sterna hirundo*		
Rhode Island; 1981; immatures; liver vs. diet	Max. 1.0 DW vs. 0.8-2.1 DW	43
Hamilton Harbor, Ontario vs. Long Island Sound, New York		
Bone	Max. 19 DW vs. Max. 36 DW	44
Kidney	Max. 9 DW vs. Max. 26 DW	44
Liver	<5 DW vs. < 5 DW	44
Muscle	<2 DW vs. <2 DW	44
Tree swallow, *Tachycineta bicolor*; Hackensack River, New Jersey (contaminated area)		
Brain, prefledgling	27.6 FW	45
Eggshell	31.4 FW	45
Embryo, whole	1.6 FW	45
Feather	4.3 FW	45
Gizzard	9.4 FW	45
Liver	23.8 FW	45
Muscle	7.6 FW	45
American robin, *Turdus migratorius*; New England; kidney vs. liver	1.7 FW vs. 0.9 FW	1
Terrestrial Mammals		
Cow, *Bos* sp.		
Blood, whole	0.011 FW	39
Blood, plasma	0.0017-0.0044 FW	39
Bone	0.58 FW	1
Feces	0.75 FW	1
Kidney	0.01-0.66 FW	1
Liver	0.13 FW	39
Muscle	Not detectable	1
Pancreas	0.14 FW	39
Goat, *Capra hircus*; serum; England	0.0035 (0.0027-0.0044) FW	21
Common beaver, *Castor canadensis*		
Ontario, Canada; 1986-87; adults; near nickel smelter vs. reference site		
Kidney	2.6 DW vs. 1.5 DW	46
Liver	1.5 DW vs. 1.1 DW	46
Ontario; uncontaminated site		
Intestine	0.4 FW	47
Kidney	0.4 FW	47
Liver	0.5 FW	47
Muscle	0.9 (0.6-1.3) FW	48
Least shrew, *Cryptotis parva*; Virginia; whole body; polluted areas vs. reference sites	1.3-1.6 DW vs. 0.8 DW	49
Horse, *Equus caballus*; serum; United States	0.002 (0.0013-0.0025) FW	21
Human, *Homo sapiens*		
Adrenal gland	0.13 (0.05-0.34) DW	50
Average daily intake, in mg Ni/kg body weight (BW) daily; Canada		

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
General population; age >12 years vs. age <12 years		
Air	Max. 0.000007 vs. Max. 0.000009	51
Water	Max. 0.00016 vs. Max. 0.00077	51
Food	0.0044-0.0057 vs. Max. 0.022	51
Soil	Max. 0.000018 vs. Max. 0.00025	51
Tobacco smoking	Max. 0.00015 vs. no data	51
Canadians living near nickel point sources; age >12 years vs. age <12 years		
Air	Max. 0.000008 vs. Max. 0.000009	51
Water	Max. 0.0025 vs. Max. 0.012	51
Food	Max. 0.0057 vs. Max. 0.022	51
Soil	Max. 0.00013 vs. Max 0.0019	51
Blood, plasma		
Workers from nickel refinery	0.0064-0.0119 FW	52
Occupationally exposed workers vs. same workers after 2-week vacation	0.0102-0.0111 FW vs. 0.0053 FW	3
Normal	0.0016-0.0020 FW	3
Blood, whole; normal	0.003-0.007 FW	52, 53
Blood, serum		
Near nickel mine	0.0046 FW	52
Normal	0.0026 (0.0011-0.0046) FW	3, 21, 52, 53, 54
Diet		
Condiments		
Most	<1.0 FW	3
Baking powder	13.4 FW	54
Nutmeg	1.2 FW	54
Pepper, black	3.9 FW	54
Fish and seafoods		
Most	<0.3 FW	3, 55
Salmon, muscle	1.7 FW	3, 39
Oysters, soft parts	1.5 FW	3, 39
Shrimp, muscle	0.03 FW	39
Swordfish	0.02 FW	39
Fruits and vegetables	Usually 0.02-0.65 FW; Max. 2.6 FW	3, 55
Grains and grain products	Usually 0.2-1.3 FW; Max. 2.7-6.4 FW	3, 39, 55
Liquids		
Beer, wine, soft drinks	0.01-0.2 FW	3, 39
Cocoa	5.0 FW	54
Coffee	1.0 FW	39
Drinking water	0.0048 (0.001-0.2)FW	39
Tea, orange pekoe	7.6 FW	54
Meats		
Beef, pork	0.06-0.4 FW	39
Chicken	0.14-0.24 FW	39
Feces, normal	3.3 (2.1-4.4) FW; 14.2 (10.8-18.7) DW	54
Hair		
Near refineries	3.6 (1.1-32.0) DW	3

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Rural areas	2.1 (1.6-17.0) DW	3
Urban areas	2.4 (1.2-20.0) DW	3
Heart, normal	0.0061 FW; 0.023 DW	54
Kidney, normal	1.82 DW	3
Liver, normal	1.85 DW	3
Lung		
Bituminous coal miners vs. controls	2.5 DW vs. 0.6 DW	56
Normal	0.17 (0.07-0.37) DW	50
Perspiration; males vs. females	0.052 (0.007-0.182) FW vs.	53, 54
0.131 (0.039-0.270) FW		
Spleen, normal	1.72 DW	3
Thyroid, normal	0.14 (0.04-0.24) DW	50
Urine		
Normal	0.001-0.005 FW	3, 52, 53
Nickel battery workers	0.0117 FW	3
Nickel plate workers	0.0275 FW	3
Nickel refinery workers	0.222 FW	3
(atmospheric nickel =489 $\mu g/m^3$)		
Near nickel refinery	0.045-0.129 FW	52
Snowshoe hare, *Lepus americanus*;	0.2 FW	57
whole; Wisconsin		
River otter, *Lutra canadensis*; Ontario, Canada; reference areas vs. nickel-contaminated areas		
Kidney	0.7 FW vs. 0.44 FW	47, 58
Liver	0.4-0.5 FW vs. 0.5 FW	47, 58
Muscle	0.9 (0.6-1.0) FW vs. no data	47, 48
Mammals; serum; healthy adults		
Normal levels for horses, humans,	0.0020-0.0027 (0.0009-0.0046) FW	3
cattle, dogs, and rats		
Normal levels for goats, cats,	0.0035-0.0053 (0.0015-0.0083) FW	3
guinea pigs, hamsters, and swine		
Normal for rabbits	0.0093 (0.0065-0.0140) FW	3
Meadow vole, *Microtus pennsylvanicus*; whole		
Virginia; contaminated area vs. reference site	Max. 2.5 DW vs. Max. 1.8 DW	49
Wisconsin; near undeveloped ore deposits	Max. 2.6 FW	57
House mouse, *Mus musculus*		
Kidney	0.46-0.52 FW	1, 39
Liver	(0.02-0.62) FW	1, 39
Lung	(0.32-0.61) FW	1, 39
Mink, *Mustela vison*		
Illinois; 1984-89; trapped		
Kidney	1.1 (0.4-6.6) FW	59
Liver	0.9 (0.3-2.6) FW	59
Muscle	0.7 (0.3-1.5) FW	59
Ontario, Canada; nickel-contaminated area vs. reference area		
Kidney	0.6 FW vs. 0.6 FW (same)	58
Liver	0.7 FW vs. 0.7 FW (same)	58
Norway; 1990-91; near nickel processing plants vs. reference site		
Moose, *Alces alces*		
Kidney	0.19 FW vs. 0.12 FW	60

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Liver	0.02 FW vs. <0.01 FW	60
Domestic sheep, *Ovis aries*		
Kidney	0.03 FW vs. 0.03 FW (same)	60
Liver	0.01 FW vs. 0.01 FW (same)	60
Caribou, *Rangifer tarandus*		
Kidney	0.28 FW vs. 0.13 FW	60
Liver	0.09 FW vs. 0.02 FW	60
Mule deer, *Odocoileus hemionus*; Montana; kidney and liver	Max. 3 DW	61
White-tailed deer, *Odocoileus virginianus*; kidney vs. liver	0.0-2.9 FW vs. 0.0-2.5 FW	1
Rabbit, *Oryctolagus* sp.; serum; New Zealand	0.0093 (0.0065-0.0140) FW	21
White-footed mouse, *Peromyscus leucopus*; Virginia; whole; contaminated area vs. reference site	Max. 1.5 DW vs. Max. 3.1 DW	49
Raccoon, *Procyon lotor*; Ontario, Canada		
Kidney	0.7 FW	47
Muscle	1.0 (0.9-1.3) FW	48
Laboratory white rat, *Rattus* sp.		
Fur	0.16 FW	62
Kidney	0.32 FW	62
Muscle	0.17 FW	62
Shrews; southern Finland		
Common shrew, *Sorex araneus*; nickel-contaminated vs. reference site		
Liver	Max. 7.2 DW vs. <0.1 DW	63
Kidney	Max. 23.0 DW vs. Max. 37.5 DW	63
Long-tailed shrew, *Sorex minutus*; kidney vs. liver	Max. 0.7 DW vs. 3.4 DW; Max. 68.1 DW	63
Gray squirrel, *Sciurus carolinensis*; New England		
Heart	3.7 FW	1
Kidney	3.2 FW	1
Liver	1.5 FW	1
Masked shrew, *Sorex cinereus*; whole; nickel-contaminated area vs. reference site	Max. 0.9 FW vs. Max. 4.2 DW	63
Swine, *Sus* sp.		
Heart	Max. 0.43 FW	39
Kidney	Max. 3.4 FW	1
Muscle	Max. 0.02 FW	1
Serum	(0.0035-0.0083) FW	21, 39
Mole, *Talpa europaea*; rural areas; Finland; liver	0.13 DW; Max. 0.25 DW	63
Red squirrel, *Tamasciurus hudsonicus*		
New England; liver and kidney	<0.2 FW	1
Canada; fur; polluted area vs. reference site		
Spring (premoult)	3-9 DW vs. 2.2 DW	64
Fall (postmoult)	1-3 DW vs. 0.6 DW	64
Marine Mammals		
British Isles; eight species; 1988-89; livers limit of 0.5 FW	All values below detection	65
Wales coast and Irish Sea; eight species; 1989-91; livers	Usually <0.5 FW; Max. 2.1 FW	66
Vaquita (porpoise), *Phocoena sinus*; Baja California,		

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Mexico		
Heart	0.7 FW	67
Kidney	0.5 FW	67
Liver	<0.4 FW	67
Sperm whale, *Physeter macrocephalus*; North Sea; 1994-95; found stranded; livers	0.39 FW; Max. 2.1 FW	68
Sweden, three species (harbor seal, *Phoca vitulina*; gray seal, *Halichoerus grypus*; ringed seal, *Phoca hispida*); livers and kidneys	Usually <0.0006 FW; maximum concentrations were 0.17 FW in livers and 0.08 FW in kidneys	69
Integrated Studies		
Arctic; Spitsbergen, Svalbard; July-August 1988		
Surface water	0.0015 FW	70
Glacier ice	0.00725 FW	70
Algae, *Zygnema* sp.	3.25 DW	70
Lichen, *Cetraria nivalis*	1.6 DW	70
Mosses, *Tamenthypnum* sp., *Rhacomitrium* sp.	2.4-6.4 DW	70
Vascular plant, *Cassiope* sp.	4.1 DW	70
Herring gull, *Larus argentatus*; feathers	1.9-9.9 DW	70
Reindeer, *Rangifer tarandus*; fur	4.8 DW	70
Canada; Wanapitei River (near nickel smelter) vs. Pickerel River (reference site); Ontario; 1974		
Water	0.042 FW vs. 0.002 FW	71
Sediments	224 FW vs. 13 FW	71
Pondweed, *Potamogeton* sp.		
Leaves	480 FW vs. 39 FW	71
Stems	255 FW vs. 7 FW	71
Periphyton, whole	826 FW vs. 43 FW	71
Zooplankton, whole	27 FW vs. 7 FW	71
Crayfish, whole	39 FW vs. 9 FW	71
Clams, soft parts	11 FW vs. 4 FW	71
Fishes, six species		
Gills	11.1-31.7 FW vs. no data	71
Kidneys	11.8-51.6 FW vs. no data	71
Livers	10.7-17.0 FW vs. no data	71
Muscles	9.5-13.8 FW vs. no data	71
Florida; near sewage outfall; exposure for 120 days		
Turtle grass, *Thalassia testudinum*; leaves	45 DW	72
Mangrove, *Rhizophora mangle*; roots	10 DW	72
Sea urchin, *Lytechinus variegatus* (consumes *Thalassia*); whole	30 DW	72
Sea cucumber, *Holothuria mexicana*; whole	40 DW	72
Florida; stormwater ponds in Orlando vs. reference sites; 1991-92		
Sediments	2.4 FW vs. 0.07 FW	73
Fishes, whole		
Redear sunfish, *Lepomis microlophus*	5.3 FW vs. 0.6 FW	73
Bluegill, *Lepomis macrochirus*	0.2 FW vs. 0.08 FW	73
Largemouth bass, *Micropterus salmoides*	2.5 FW vs. 1.2 FW	73
French-Spanish border; Bidason estuary; four sites; April 1993		

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Sediments	35 (22-44) DW	74
Clam, *Scrobicularia plana*; soft parts	4.1 (2.9-5.7) DW	74
Sandworm, *Nereis diversicolor*; whole	5.4 (3.2-8.5) DW	74
Israel, Mediterranean coast; 1974		
Water	0.0028-0.0036 FW	75
Sediments	4.8 DW	75
Algae	5.2-5.8 DW	75
Fishes, 10 species; whole	0.1-10.8 DW	75
Lake Erie; near coal ash disposal basin; 1983-84		
Sediment	Max. 26.4 DW (vs. 19.8	76
DW in reference site)		
Coal ash	65.0 DW	76
Oligochaetes	Max. 32.5 DW	76
Chronomids	<9.1 DW	76
Fishes, whole		
Brown bullhead, *Ameiurus nebulosus*;	<9.1 DW vs. Max. 26.6 DW	76
adults vs. yearlings		
Yellow perch, *Perca flavescens*; white bass,	<9.1 DW	76
Morone chrysops		
Lebanon; near Ras Beirut		
Seawater	Max. 0.027 FW	77
Mollusks, three species; soft parts	27.4-40.1 DW	77
Mississippi River delta and northwestern Gulf of Mexico		
Sargassum weed, *Sargassum* spp. plus mixed	0.9-15.6 DW	78
phytoplankton; whole		
Zooplankton	<0.5-8.2 DW	78
New York; Hudson river; near nickel-cadmium battery plant; 1972		
Water; insoluble vs. soluble	0.043 FW vs. 0.068 FW	79
Sediments	Max. 7,000 DW	79
Cordgrass, *Spartina* sp.; roots	Max. 500 DW	79
New Guinea; Upper Fly River; September 1974		
Water	<0.001-0.005 FW	80
Sediments	24-38 DW	80
Gastropod, *Melanoides* sp.; soft parts	8-18 DW	80
Prawn, *Macrobrachium* sp.; whole	5-17 DW	80
Fishes, various species; liver and muscle	3-93 DW	80
Texas; outer continental shelf		
Sargassum weed, *Sargassum* spp.	5.2 DW	81
Squid, muscle	2.5 DW	81
Zooplankton, whole	4.6 DW	81
Shrimp, two species; whole	1.4-1.6 DW	81
Fish, various species; muscle	0.6-4.9 DW	81
Turkey; Tigris River (contaminated by wastes from smelter)		
Water	0.5-0.8 FW	82
Sediments with living organisms	41-305 DW	82
Sediments with no living organisms	403 DW	82
Fish, *Cyprinion macrostomus*		
Liver	105-502 FW	82
Muscle	8-95 FW	82
Fish, *Garra rufa*		

Table 6. Taxonomic group, organism, and other variables	Concentration (mg/kg)[a]	Reference[b]
Liver	Max. 380 FW	82
Muscle	Max. 43 FW	82

[a]Concentrations are shown as means, range (in parentheses), and maximum (Max.).

[b]1, Jenkins 1980b; 2, Memon et al. 1980; 3, U.S. Environmental Protection Agency 1980; 4, Richardson et al. 1980; 5, World Health Organization 1991; 6, Lee et al. 1978; 7, Anke et al. 1980a; 8, Frank et al. 1982; 9, Stoewsend et al. 1984; 10, Eisler 1981; 11, Bagatto and Shorthouse 1996; 12, Manly and George 1977; 13, Palmer and Rand 1977; 14, Bryan et al. 1977; 15, Stronkhorst 1992; 16, Greig et al. 1978; 17, Pesch et al. 1977; 18, Bryan and Hummerstone 1978; 19, Szefer et al. 1993; 20, Cheng et al. 1976; 21, Mushak 1980; 22, Greig et al. 1977; 23, Langlois and Langis 1995; 24, Sharif et al. 1993; 25, Greig and Wenzloff 1977; 26, Vas 1991; 27, Mathews 1994; 28, Sparling and Lowe 1996; 29, Outridge and Scheuhammer 1993; 30, Burger and Gochfeld 1985; 31, Gochfeld and Burger 1987; 32, Ranta et al. 1978; 33, Michot et al. 1994; 34, Custer and Hohman 1994; 35, Rose and Parker 1983; 36, Wiemeyer et al. 1986; 37, Wren et al. 1988; 38, Kalas et al. 1995; 39, Kasprzak 1987; 40, Custer and Mulhern 1983; 41, Ahmed and Stoeppler 1994; 42, Wiemeyer et al. 1987; 43, Custer et al. 1986; 44, Connors et al. 1975; 45, Kraus 1989; 46, Hillis and Parker 1993; 47, Wren 1984; 48, Wren et al. 1983; 49, Scanlon 1987; 50, Hausinger 1993; 51, Hughes et al. 1994; 52, Norseth 1986; 53, National Research Council of Canada 1981; 54, National Academy of Sciences 1975; 55, Norseth and Piscator 1979; 56, Sevin 1980; 57, Smith and Rongstad 1981; 58, Wren et al. 1988; 59, Halbrook et al. 1996; 60, Sivertsen et al. 1995; 61, Munshower and Neuman 1979; 62, Kirchgessner and Schnegg 1980; 63, Pankakoski et al. 1994; 64, Lepage and Parker 1988; 65, Law et al. 1991; 66, Law et al. 1992; 67, Villa et al. 1993; 68, Law et al. 1996; 69, Frank et al. 1992; 70, Drbal et al. 1992; 71, Hutchinson et al. 1975; 72, Montgomery et al. 1978; 73, Campbell 1994; 74, Saiz-Salinas et al. 1996; 75, Roth and Hornung 1977; 76, Hatcher et al. 1992; 77, Shiber and Shatila 1978; 78, Trefry and Presley 1976; 79, Kniep et al. 1974; 80, Boyden et al. 1978; 81, Horowitz and Presley 1977; 82, Gumgum et al. 1994.

Terrestrial vegetation within 3.5 km of one of the Sudbury, Ontario, smelters had as much as 140 mg Ni/kg DW; concentrations decreased with distance from the smelter, reaching a mean concentration of about 12 mg Ni/kg DW at a distance of 60 km (Chau and Kulikovsky-Cordeiro 1995). Some vegetation near a Sudbury smelter—including lawn grasses, timothy (*Phleum pratense*), and oats (*Avena sativa*)—showed signs of nickel toxicosis; concentrations in these species ranged between 80 and 150 mg Ni/kg DW. Vegetables—beets (*Beta vulgaris*), radishes (*Raphanus* spp.), cabbages (*Brassica oleracea capitata*), and celery (*Apium graveolans*)—grown in soils about 1 km from a nickel refinery had 40-290 mg Ni/kg DW in their top portions. All of these vegetables had reduced yield, stunted growth, and chlorosis and necrosis, which were attributed to the high levels of nickel in local soils (Chau and Kulikovsky-Cordeiro 1995).

Mosses and lichens accumulate nickel readily and at least nine species are used to monitor environmental gradients of nickel (Jenkins 1980a). Maximum concentrations of nickel found in whole lichens and mosses from nickel-contaminated areas range between 420 and 900 mg/kg DW versus 12 mg/kg DW from reference sites (Jenkins 1980a). Nickel concentrations in herbarium mosses worldwide have increased dramatically during this century. In one case, nickel concentrations in *Brachythecium salebrosum* from Montreal, Canada, rose from 6 mg/kg DW in 1905 to 105 mg/kg DW in 1971 (Richardson et al. 1980).

Nickel-tolerant or accumulator species of plants are likely to be found only on nickel-rich soils (Rencz and Shilts 1980). Hyperaccumulator species usually grow on relatively infertile, nickel-rich serpentine soils and contain more than 10,000 mg Ni/kg DW (Jenkins 1980b; NRCC 1981; WHO 1991; Table 6). Leaves from some genera of nickel hyperaccumulator plants, including *Alyssum*, *Homalium*, and *Hybanthus*, growing on soils derived from volcanic rocks, which are rich in nickel, accumulate nickel to concentrations of 120,000 mg/kg DW (Kasprzak 1987; Table 6). Nickel is bound as a citrate complex in hyperaccumulator plants from New Caledonia; however, nickel accumulator plants from other locations do not contain unusually high levels of citrate, and nickel is not present as a citrate complex but as a carboxylic acid complex (Lee et al. 1978).

Terrestrial plants take up nickel from soil primarily via the roots (NRCC 1981; WHO 1991). The nickel uptake rate from soil is dependent on soil type, pH, humidity, organic content, and concentration of extractable

nickel (NAS 1975; WHO 1991). For example, at soil pH less than 6.5 nickel uptake is enhanced due to breakdown of iron and manganese oxides that form stable complexes with nickel (Rencz and Shilts 1980). The exact chemical forms of nickel that are most readily accumulated from soil and water are unknown; however, there is growing evidence that complexes of nickel with organic acids are the most favored (Kasprzak 1987). In addition to their uptake from the soils, plants consumed by humans may receive several milligrams of nickel per kilogram through leaching of nickel-containing alloys in food-processing equipment, milling of flour, and catalytic hydrogenation of fats and oils by use of nickel catalysts (USEPA 1986). Nickel reportedly disrupts nitrogen cycling and this could have serious ecological consequences for forests near nickel smelters (WHO 1991), although adverse effects of nitrogen disruption by nickel need to be verified.

Data are limited on nickel concentrations in terrestrial invertebrates. Earthworms from uncontaminated soils may contain as much as 38 mg Ni/kg DW and workers of certain termite species may normally contain as much as 5,000 mg Ni/kg DW (Table 6). Larvae of the gypsy moth (*Porthetria dispar*) near a nickel smelter had 20.4 mg Ni/kg DW; concentrations in pupae and adults were lower because these stages have higher nickel elimination rates than larvae (Bagatto et al. 1996).

Aquatic Organisms

Nickel concentrations are comparatively elevated in aquatic plants and animals in the vicinity of nickel smelters, nickel-cadmium battery plants, electroplating plants, sewage outfalls, coal ash disposal basins, and heavily populated areas (Kniep et al. 1974; Eisler et al. 1978a; Montgomery et al. 1978; Jenkins 1980a; Eisler 1981; Kasprzak 1987; Chau and Kulikovsky-Cordeiro 1995; Table 6). For example, at Sudbury, Ontario, mean nickel concentrations, in mg/kg DW, were 22 for larvae of aquatic insects, 25 for zooplankton, and 290 for aquatic weeds; maximum concentrations reported were 921 mg/kg DW in gut of crayfish (*Cambarus bartoni*) and 52 mg/kg fresh weight (FW) in various fish tissues (Chau and Kulikovsky-Cordeiro 1995; Table 6). For all aquatic species collected, nickel concentrations were highly variable between and within species; this variability is attributable, in part, to differential tissue uptake and retention of nickel, depth of collection, age of organism, and metal-tolerant strains (Bryan et al. 1977; Bryan and Hummerstone 1978; Jenkins 1980a; Eisler 1981; Chau and Kulikovsky-Cordeiro 1995; Table 6).

The bioaccumulation of nickel under field conditions varies greatly among groups. Bioconcentration factors (BCF, which equals the milligrams of nickel per kilogram fresh weight of the sample divided by the milligrams of nickel per liter in the medium) for aquatic macrophytes range from 6 in pristine areas to 690 near a nickel smelter; for crustaceans these values are 10-39; for mollusks, 2-191; and for fishes, 2-52 (Sigel and Sigel 1988). Bioconcentration factors of 1,700 have been reported for marine plankton, 800 and 40 for soft parts and shell, respectively, of some marine mollusks, and 500 for brown algae, suggesting that some food chain biomagnification may occur (NAS 1975).

Concentrations of nickel in roots of *Spartina* sp. from the vicinity of a discharge from a nickel-cadmium battery plant on the Hudson River, New York, ranged between 30 and 500 mg/kg DW and reflected sediment nickel concentrations in the range of 100-7,000 mg Ni/kg DW (Kniep et al. 1974). The detritus produced from dead algae and macrophytes is the major food source for fungi and bacteria, and in this way nickel can again enter the food chain (NRCC 1981; Chau and Kulikovsky-Cordeiro 1995). Nickel concentrations in tissues of sharks from British and Atlantic water range between 0.02 and 11.5 mg/kg FW; concentrations were highest in fish-eating, mid-water species such as the blue shark (*Prionace glauca*) and tope shark (*Galeorhinus galeus*; Vas 1991). Concentrations of nickel in livers of tautogs *(Tautoga onitis*) from New Jersey significantly decreased with increasing body length in both males and females; however, this trend was not observed in bluefish (*Pomatomus saltatrix*) or tilefish (*Lopholatilus chamaeleonticeps*; Mears and Eisler 1977).

Amphibians

In Maryland, USA, nickel concentrations in tadpoles of gray treefrogs (*Hyla versicolor*) and northern cricket frogs (*Acris crepitans*) increased with increasing soil nickel concentrations, with maximum nickel concentrations recorded of 7.1 mg/kg DW in gray treefrogs and 10.0 mg/kg DW in northern cricket frogs (Sparling and Lowe 1996). In study sites 9-66 km from Sudbury, Ontario, populations of treefrogs (*Hyla crucifer*) and American toads (*Bufo americanus*) declined. Population abundance of adult treefrogs declined with increasing atmospheric deposition of nickel, and abundance of toad tadpoles declined as nickel concentrations in pond

water rose from 3.3 μg Ni/L at more distant sites to 19.5 μg Ni/L at sites near Sudbury (Glooschenko et al. 1992).

Birds

Nickel concentrations in the organs of most avian wildlife species in unpolluted ecosystems range from about 0.1 to 2.0 mg/kg DW and occasionally reach 5.0 mg/kg DW (Eisler 1981; Outridge and Scheuhammer 1993). In nickel-contaminated areas, nickel concentrations were elevated in feathers, eggs, and internal tissues of birds when compared to conspecifics collected at reference sites (Darolova et al. 1989; Outridge and Scheuhammer 1993; Table 6). In contaminated ecosystems, mean nickel concentrations between 31 and 36 mg/kg DW occur in primary feathers of mallards (*Anas platyrhynchos*) collected 20-30 km from a nickel smelter, bone of the common tern (*Sterna hirundo*) from Hamilton Harbor, Ontario, and eggshell of the tree swallow (*Tachycineta bicolor*) from the Hackensack River, New Jersey (Table 6).

Waterfowl feeding in areas subjected to extensive nickel pollution—such as smelters and nickel-cadmium battery plants—are at special risk because waterfowl food plants in those areas contain 500-690 mg Ni/kg DW (Eastin and O'Shea 1981). Dietary items of the ruffed grouse (*Bonasa umbellus*) near Sudbury, Ontario, had 32-95 mg Ni/kg DW, whereas nickel concentrations in grouse body tissues usually contain less than 10% of the dietary level. Nickel concentrations in aspen (*Populus tremula*) from the crop of ruffed grouse near Sudbury ranged from 62 mg/kg DW in May to 136 mg/kg DW in September (Chau and Kulikovsky-Cordeiro 1995), which shows the role of season in dietary nickel composition.

Mammals

Mammalian wildlife from uncontaminated habitats usually contain less than 0.1 to about 5 mg Ni/kg DW in tissues; in nickel-contaminated areas, these same species have 0.5 to about 10 mg Ni/kg DW in tissues (Outridge and Scheuhammer 1993; Chau and Kulikovsky-Cordeiro 1995), with a maximum of 37 mg/kg DW in kidneys of the common shrew (*Sorex araneus*; Table 6). Nickel accumulations in wildlife vary greatly between species. For example, tissues of mice have higher concentrations of nickel than rats and other rodents while beavers and minks have higher nickel concentrations in their liver than birds in similar sites near Sudbury (Chau and Kulikovsky-Cordeiro 1995).

The highest concentrations in wildlife tissues from nickel-contaminated locales are associated with tissues exposed to the external environment, such as fur and skin; nickel concentrations in internal organs are usually similar, regardless of degree of contamination (Outridge and Scheuhammer 1993; Table 6). However, nickel concentrations in bone, reproductive organs, and kidneys in certain herbivorous species of wildlife and livestock are elevated when compared to other internal tissues, especially in the vicinity of nickel smelters and other nickel point sources (Outridge and Scheuhammer 1993; Kalas et al. 1995). Trophic position in the food chain, sex, and reproductive state do not seem to significantly influence the nickel body burdens of mammals (Outridge and Scheuhammer 1993), but age is an important variable and nickel generally increases in various organs with increasing age of terrestrial and marine mammals. Fetuses of a variety of wildlife and domestic species contain concentrations of nickel significantly lower than those in their mothers or in juveniles, suggesting that placental transfer of nickel is restricted. Nickel concentrations in aquatic macrophytes and lower plants in the vicinity of nickel smelters may approach or exceed dietary levels known to cause adverse effects in young animals. Sensitive species of wildlife ingesting this vegetation for extended periods could experience nickel-related toxicity or risk alterations in community structure as nickel-sensitive taxa are eliminated or their abundance is reduced (Outridge and Scheuhammer 1993).

Elevated nickel concentrations in Norwegian wildlife are linked to emissions from Russian nickel smelters (Kalas et al. 1995). In Norway, nickel concentrations were elevated in livers and kidneys of moose (*Alces alces*) and reindeer (*Rangifer tarandus*) because of atmospheric transport of wastes from nickel-processing plants of nearby Russian towns (Sivertsen et al. 1995). In Russia between 1974 and 1992, three species of voles (*Clethrionomys glareolus*, *Clethrionomys rutilus*, *Lemmus lemmus*) were eliminated from the immediate vicinity of a copper-nickel smelter that discharged 2,700 metric tons of nickel annually to the atmosphere, and these species were scarce at a moderately contaminated area 28 km south of the smelter (Kataev et al. 1994). Declines were associated with a decrease of important food plants: lichens for *C. glareolus* and *C. rutilus*, mosses for *L. lemmus*, and seed plants for other species of *Clethrionomys*. Close to the smelter, direct toxic effects of accumulated nickel and other metals also may have reduced population densities (Kataev et al. 1994).

Nickel concentrations are also elevated in rodents, shrews, soil, vegetation, and earthworms in the vicinity of roads with high automobile density (Pankakoski et al 1993). In ruminant mammals, tissue nickel concentrations were higher in winter (WHO 1991), presumably because of increased combustion of fossil fuels.

Nickel is normally present in human tissues, and under conditions of high exposure, these levels may increase significantly (WHO 1991). Nickel enters the human body through the diet, through inhalation, by absorption through the skin, and in medications (NAS 1975). The diet accounts for about 97% of the total intake and drinking water about 2.5% (Kasprzak 1987). Foods rich in nickel include tea (7.6 mg/kg DW), cereals (6.5 mg/kg DW), vegetables (2.6 mg/kg DW), and fish (1.7 mg/kg DW) (IARC 1976; Table 6). The daily dietary intake of nickel by humans in the United States ranges between 0.15 and 0.6 mg, almost all of which is excreted in the feces (NAS 1975; Norseth and Piscator 1979; USEPA 1980; NRCC 1981; Sunderman et al. 1984). Minor amounts are also excreted in sweat, urine, and hair (Kasprzak 1987). Residents of the Sudbury, Ontario, area who consume homegrown garden products ingest an average of 1.85 mg of nickel daily, of which 0.6 mg comes from the drinking water (NRCC 1981). Inhalation intake of nickel for residents of New York City is estimated at 2.4 μg daily; for Chicago, a maximum value of 13.8 μg daily is recorded; and 14.8 μg are inhaled daily by smokers of 40 cigarettes (NAS 1975; WHO 1991). Canadians in urban areas inhale 0.06-0.6 μg Ni daily; near nickel smelters this may increase to 15 μg daily (NRCC 1981). In Connecticut, serum nickel levels in newborns were normal (3 μg/L) and similar to those of their mothers (Norseth and Piscator 1979). Nickel concentrations in human serum, however, are modified by disease and stress. Concentrations are usually elevated after strokes, pregnancy, and extensive burns and are depressed in cases of cirrhosis, hypoalbuminemia, extremes of heat, and uremia (Mushak 1980; USEPA 1980, 1986).

About 727,000 workers were potentially exposed to nickel metal, nickel alloys, or nickel compounds during the period 1980-83 (USPHS 1993). Worker exposure differs from that of the general population in that the major route of exposure for nickel workers is inhalation and for the general population it is dermal contact (Sevin 1980). Nickel workers with lung cancer had elevated concentrations of 1.97 mg/kg DW in their lungs when compared to the general population (0.03-0.15 mg/kg DW; USPHS 1977). Plasma concentrations of nickel quickly reflect current exposure history to nickel (USEPA 1980). Mean nickel concentrations in plasma of humans occupationally exposed to nickel have declined by about 50% since 1976, suggesting decreased exposure due to improved safety (Boysen et al.1980).

Integrated Studies

Beaver ponds downstream from an abandoned copper-nickel ore roast yard near Sudbury, Ontario, were devoid of fish and had reduced macroinvertebrate taxon richness and diversity when compared to upstream ponds. Nickel water concentrations, in μg Ni/L, were 57 in upstream ponds, 82 in downstream ponds, and 1,800 at the station directly on the roast pit (Rutherford and Mellow 1994). Beavers (*Castor canadensis*) near nickel smelters had elevated nickel concentrations in livers and kidneys when compared to conspecifics from a reference site; accumulations were attributed to food chain contamination (Hillis and Parker 1993).

Hutchinson et al. (1975) found nickel contamination in the Sudbury, Ontario, region to be the result of aerial transport and terrestrial drainage from mining and smelting activities. Nickel concentrations in soils were elevated as far as 52 km from the source. Erosion of soils following the death of vegetation was widespread and affected an area of more than 820 km^2. Soils increased in acidity, increasing the solubility of nickel. In aquatic ecosystems, nickel was accumulated from the water column by periphyton, rooted aquatic macrophytes, zooplankton, crayfish, clams, and fishes. However, there was no evidence of food chain biomagnification of nickel in the Sudbury ecosystem (Hutchinson et al. 1975). For example, in the nickel-contaminated Wanapitei River, bioconcentration factors during summer 1974 were highest for whole periphyton (19,667), followed by whole pondweeds (11,429), sediments (5,333), whole crayfish (929), whole zooplankton (643), muscle of carnivorous fishes (329), soft tissues of clams (262), and muscle of omnivorous fishes (226) (Hutchinson et al. 1975). Higher BCF values are recorded for acid- and metal-tolerant flora (Outridge and Scheuhammer 1993).

There is little convincing evidence for the biomagnification of nickel in the food chain. Most authorities agree that nickel concentrations do not increase with ascending trophic levels of food chains and that predatory animals do not have higher concentrations (Jenkins 1980a; WHO 1991; Outridge and Scheuhammer 1993; Chau and Kulikovsky-Cordeiro 1995). The potential for biomagnification exists because algae and macrophytes have comparatively elevated concentrations of nickel; however, animals seem to be able to regulate the nickel

content of their tissues by controlled uptake and increased excretion (Jenkins 1980a; Outridge and Scheuhammer 1993).

Nickel Deficiency Effects

General

Nickel is reportedly an essential micronutrient for maintaining health in certain species of plants, invertebrates, birds, and mammals, including humans (NAS 1975; Spears et al. 1979; Sunderman et al. 1984; Norseth 1986; USEPA 1986; Sigel and Sigel 1988; Hausinger 1993; USPHS 1993; Stangl and Kirchgessner 1996, 1997). However, nickel essentiality for humans has not yet been proven (Norseth and Piscator 1979; USPHS 1993), and the evidence for marine tunicates and land snails is inconclusive (Hausinger 1993). To prevent nickel deficiency in rats and chickens, diets should contain at least 50 μg Ni/kg ration; cows and goats require more than 100 μg Ni/kg ration, perhaps reflecting the increased use of nickel by rumen bacteria (USPHS 1993). In humans, nickel deficiency is not a public health concern because daily oral intake normally exceeds 170 μg of nickel (USPHS 1993).

Nickel is considered essential to animals because it is present in the fetus or newborn, is homeostatically regulated, the metabolic pool of nickel is specifically influenced by hormonal substances or pathologic processes, certain metalloproteins contain nickel, and because nickel deficiency has been induced experimentally in certain species of birds and animals (NAS 1975; USPHS 1977; Kirchgessner and Schnegg 1980). In general, the nickel deficiency syndrome can be cured or prevented by trace amounts of nickel (NAS 1975). However, nickel administration may not be successful in reversing all abnormalities produced by nickel deprivation (USPHS 1977).

Nickel deficiency effects from dietary deprivation of nickel are now documented in at least 17 animal species, including chickens, cows, goats, pigs, rats, and sheep (USPHS 1977, 1993; Norseth and Piscator 1979; USEPA 1985; Norseth 1986; WHO 1991). According to Kirchgessner and Schnegg (1980), nickel deficiency can be induced only by very low nickel concentrations in the diet—not by its bioavailability. Signs of nickel deficiency include delayed gestation periods and fewer offspring; decreased growth and sometimes dwarfism; anemia; skin eruptions; brittle hair; reduced oxygen consumption; decreased levels of serum proteins; enhanced urinary nitrogen excretion; reduced tissue iron and zinc concentrations; reduced hemoglobin and hematocrit values; abnormal liver morphology and lipid metabolism; reduced liver glucose, lipids, glycogen, and triglycerides; and reduced activity of several enzymes, including dehydrogenases, transaminases, and alpha-amylases (USEPA 1980, 1985, 1986; WHO 1991; USPHS 1993; Stangl and Kirchgessner 1996).

Bacteria and Plants

Nickel is essential for the active synthesis of urease in plant cells and of various hydrogenases in bacteria (Thauer et al. 1980; USEPA 1986; WHO 1991; Hausinger 1993). In several species of higher plants, including jack beans (*Canavalia* sp.), soybeans (*Glycine max*), rice (*Oryza sativa*), and tobacco (*Nicotiana tabacum*), nickel is required for effective urea metabolism and urease synthesis (Kasprzak 1987; Sigel and Sigel 1988). Some terrestrial plants, such as *Alyssum* spp., accumulate nickel and require it for growth (Thauer et al. 1980). In bacteria, nickel is required for the growth of *Oscillatoria* sp. and *Alcaligenes* sp., for the synthesis of carbon monoxide dehydrogenase in *Clostridium posterianum*, and as a component of coenzyme F_{430} in *Methanobacterium* spp. (Babich and Stotzky 1982a; Kasprzak 1987). Nickel deficiency in bacteria may adversely affect reproductive processes, such as endospore formation, and cause a decrease in nickel-containing intracellular pigments in strains of *Bacillus cereus* (Thauer et al. 1980); however, both of these observations require verification.

Birds

All studies demonstrating nickel deficiency in birds were conducted on a single species, specifically, chicks of the domestic chicken, *Gallus* sp. The relevance of these results to avian wildlife species is unknown. Chicks grew normally when fed nickel-deficient diets (2-15 μg Ni/kg ration) for 3-4 weeks. But these chicks had liver histopathology, decreased concentrations of yellow lipochrome pigments in liver, low hematocrit, skin dermatitis, leg thickening, altered lengths of leg bones, and decreased plasma cholesterol (Nielsen et al. 1975a; Hausinger 1993). Adverse effects of nickel-deficient diets (<20 μg Ni/kg ration) were reversed by the addition of nickel to the diet (Ling and Leach 1979). Chicks fed diets containing 25-2,500 μg Ni/kg ration for 3-4 weeks grew

normally and all organs appeared normal (Nielsen et al. 1975a). Nickel-deficient chicks (40-80 µg Ni/kg ration), when compared to controls (3-5 mg Ni/kg ration), had swollen hock joints, reduced length-to-width ratios of tibias, scaly dermatitis of the legs, orange-yellow discoloration of the legs, fat-depleted livers, altered liver metabolism, and elevated concentrations of nickel in liver, spleen, and aorta (Sunderman et al. 1972; NAS 1975; USEPA 1980; USEPA 1985). Chicks fed nickel-deficient diets of 44 µg Ni/kg ration for 30 days had markedly lower nickel concentrations in serum and livers than did controls fed diets containing 3.4 mg Ni/kg ration; nickel-deficient chicks had 1.6 µg Ni/L in serum versus 4.2 in controls and 64 µg Ni/kg DW liver versus 82 in controls (Sunderman et al. 1972). Livers of nickel-deficient chicks had an altered gross appearance, reduced oxidative ability, and decreased lipid phosphorus concentrations (Nielsen et al. 1975a). Nickel deficiency in chicks may be associated with thyroid hormone imbalance (Nielsen et al. 1975a), but this needs verification.

Mammals

In humans, there is no evidence of a nickel deficiency syndrome (USEPA 1985) or proof that nickel is essential (Norseth and Piscator 1979; Norseth 1986).

Cows (*Bos* sp.) fed nickel-deficient diets containing less than 100 µg Ni/kg ration had reduced growth and survival (Hausinger 1993). Nickel deficiency in cows was exacerbated when diets were also low in protein, but effects were lessened when diets were supplemented with 5 mg Ni/kg ration (Spears et al. 1979). Lambs from domestic sheep (*Ovis aries*) fed a low nickel diet (30 µg Ni/kg ration) for 97 days had lower growth, higher mortality, and altered blood and tissue chemistry when compared to controls fed a diet containing 5 mg Ni/kg ration (Spears et al. 1979). Lambs given diets containing 65 µg Ni/kg DW ration had disrupted metabolism (USEPA 1980).

Adults and offspring of breeding goats (*Capra hircus*) and swine (*Sus* sp.) fed nickel-deficient diets (<100 µg Ni/kg ration) or control diets (10 mg Ni/kg ration) for 6 years had normal conception and abortion rates. However, nickel-deficient goats and pigs had delayed pregnancies, reduced litter sizes, lower birth rates, lower weight gains during suckling, and significant increases in mortality during the suckling period; mortality was 41% higher than controls in kids and 51% higher than controls in piglets (Anke et al. 1978). Nickel-deficient adult goats had lower nickel concentrations in kidneys, liver, and other tissues than did controls, specifically, 0.2-0.6 mg Ni/kg DW tissue versus 0.6-1.2 mg Ni/kg DW in controls (Anke et al. 1980a). Kids of nickel-deficient ewes (100 µg Ni/kg DW ration for 6 years vs. control diet of 300 µg Ni/kg ration) had inhibited growth starting at age 8 weeks and reduced survival (Anke et al. 1980b). During lactation, hemoglobin concentrations and hematocrits of nickel-deficient goats were significantly lower than control values (Anke et al. 1980b). Nickel-deficient pigs had rough coats, decreased growth, and impaired reproduction (USEPA 1980; Hausinger 1993).

Signs of nickel deficiency in the laboratory white rat (*Rattus* sp.) include retarded growth, anemia, a reduction in hematocrit and hemoglobin values, decreased enzyme activities (malate dehydrogenase, glucose-6-phosphate dehydrogenase, alpha amylase), a reduction in liver total lipids and phospholipids, and altered tissue concentrations of fatty acids, iron, copper, and zinc (Nielsen et al. 1975b; Norseth and Piscator 1979; Nielsen 1980b; Norseth 1986; Hausinger 1993; Stangl and Kirchgessner 1996, 1997). Nickel concentrations in fur, kidneys, and muscle of rats fed nickel-deficient diets (15 µg Ni/kg DW ration) were about 66% lower than those of controls given 20 mg Ni/kg ration (Kirchgessner and Schnegg 1980). Signs of nickel deficiency in rats were usually reversed by supplementing the diet with nickel (Ling and Leach 1979) at more than 50 µg Ni/kg ration (USEPA 1985). Rats fed nickel-deficient diets (<5 µg Ni/kg ration) for three generations produced offspring that were anemic and grew poorly in the first two generations and that had impaired reproduction in all generations (USEPA 1980; Sevin 1980). In another three-generation study, rats fed nickel-deficient diets containing 2-15 µg Ni/kg ration had increased perinatal mortality, unthrifty appearance of young rats, decreased physical activity, decreased liver cholesterol, and liver histopathology compared to controls fed diets containing 3 mg Ni/kg ration (Nielsen et al. 1975b).

Lethal and Sublethal Effects

General

Nickel toxicity reduces photosynthesis, growth, and nitrogenase activity of algae; fermentative activity of a mixed rumen microbiota; growth rate of marine bacteria; metabolism of soil bacteria; and mycelial growth, spore germination, and sporulation of fungi (Babich and Stotzky 1982a). Adverse effects of excess nickel have also been observed with yeasts, higher plants, protozoans, mollusks, crustaceans, insects, annelids, echinoderms,

fishes, amphibians, birds, and mammals (USEPA 1975). As discussed later, sensitive species of aquatic organisms are adversely affected at nominal concentrations of 11-113 μg Ni^{2+}/L.

In birds, mortality occurred in young individuals of sensitive species when rations contained more than 500 mg Ni/kg (Outridge and Scheuhammer 1993). Nickel accumulated in avian tissues at dietary loadings as low as 0.7-12.5 mg Ni/kg ration (Cain and Pafford 1981; Eastin and O'Shea 1981; Stoewsand et al. 1984); however, nickel intoxication in some species tested was not always reflected by elevated tissue nickel concentrations (Outridge and Scheuhammer 1993).

In mammals, the toxicity of nickel is a function of the chemical form of nickel, dose, and route of exposure. Exposure to nickel by inhalation, injection, or cutaneous contact is more significant than oral exposure. Toxic effects of nickel to humans and laboratory mammals are documented for respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, immunological, developmental, neurological, and reproductive systems (NAS 1975; Nielsen 1977; USEPA 1980, 1986; WHO 1991; USPHS 1993).

Terrestrial Plants and Invertebrates

In general, the effects of long-term, low-level exposure to nickel are shown in growth inhibition with no other visible signs (WHO 1991). However, many species of plants growing on soils contaminated with excess nickel show stunted and discolored roots and tops, wilting, chlorosis, necrosis, twisted stalks, thickening of leaf tissues, and failure of leaves to fold to form compact heads (NAS 1975; Frank et al. 1982; WHO 1991; Barman and Bhargava 1997; Donghua and Wusheng 1997). In solution culture, 1 mg of soluble nickel/L is toxic to sensitive plants (NRCC 1981; Outridge and Scheuhammer 1993). Accumulations of 50 mg Ni/kg DW plant and higher are toxic to most plants (NAS 1975; NRCC 1981; WHO 1991). Depending on soil conditions and chemical form, nickel in soil is toxic when concentrations exceed 500 mg Ni/kg DW soil with more than 25 mg Ni/L extractable in a 2.5% acetic acid solution (NRCC 1981). Accumulation and toxic effects occur in vegetables grown on soils treated with sewage sludge and in vegetation close to nickel-emitting sources (WHO 1991). Nickel was shown experimentally to decrease growth of soybeans (*Glycine max*) when administered as particulate nickel through the atmosphere or in the rooting medium (Ormrod et al. 1986). Crop plants are the most sensitive group of terrestrial vegetation tested against nickel. Adverse effects on chlorophyll metabolism and growth occur at soil water concentrations as low as 1 mg Ni/L (Outridge and Scheuhammer 1993). Radishes, beets, cabbages, celery, and lettuce planted in organic soils contaminated by aerial fallout from a nearby nickel smelter and containing between 1,570 and 6,550 mg Ni/kg DW soil had decreasing yields with increasing soil nickel concentrations (Frank et al. 1982). No radishes or cabbages were suitable for marketing. Celery, lettuce, and beets were reduced from a normal yield on soil with 1,300 mg Ni/kg to zero on soils with 4,800 mg/kg. Dried cabbage heads and celery tops had as much as 400 mg Ni/kg (Frank et al. 1982). Decreased yields of alfalfa (*Medicago sativa*) occur when plant nickel content exceeds 44 mg/kg DW (NAS 1975). Decreased yield of oats (*Avena sativa*) was associated with nickel concentrations more than 60 mg/kg DW grain, more than 28 mg/kg DW oat straw, or more than 500 mg Ni/kg DW soil (NAS 1975). Signs of nickel toxicity in oats decrease in severity with increasing magnesium concentrations in culture solution during exposure for 35 days (Proctor and McGowan 1976).

Temperature, pH, chlorophyll, and various metals all modify the toxicity of nickel to fungi (Babich and Stotzky 1982b). A reduction in the toxicity of nickel to the mycelial growth rates of five species of filamentous fungi occurs when pH increases from acidic to alkaline (*Achyla* sp., *Saprolegnia* sp.); at elevated concentrations of magnesium, zinc, or lead (*Achyla* sp.); at chlorophyll or humic acid contents equivalent to 1% (*Saprolegnia* sp., *Cunninghamella blakesleeana*, *Aspergillus clavatus*); and at increased temperatures of 33 C versus 23 C (*Aspergillus flavus*; Babich and Stotzky 1982b). Growth of sensitive species of filamentous fungi is inhibited at 10 mg Ni/L and abnormal mycelia occurs at 50 mg/L (Babich and Stotzky 1982a). Histidine may govern nickel accumulation in the approximately 400 known species of nickel-hyperaccumulating plants. Nickel hyperaccumulator plants, including 48 of 170 species of *Alyssum* spp., contain as much as 3% of the dry leaf biomass as nickel (Kramer et al. 1996). Exposing hyperaccumulator species of *Alyssum* to nickel elicits a large and proportional increase in the levels of free histidine, which is shown to be coordinated with nickel in vitro. Supplying histidine to a nonaccumulating species greatly increases both nickel tolerance and capacity for nickel transport to the shoot, indicating that enhanced production of the amino acid histidine is responsible for the nickel hyperaccumulation phenotype in *Alyssum* (Kramer et al. 1996).

Data on nickel toxicity to terrestrial invertebrates are scarce. A soil concentration of 757 mg/kg DW soil is lethal to 50% of earthworms (*Eisenia foetida*) in 14 days, and higher concentrations of 1,200-12,000 mg/kg DW soil for shorter periods produces reduced growth and survival in the same species (WHO 1991). Earthworms are less sensitive to nickel if the medium is rich in microorganisms and organic matter, thus making the nickel less bioavailable (WHO 1991).

Aquatic Organisms

Signs of nickel poisoning in fishes include surfacing, rapid mouth and opercular movements and, prior to death, convulsions and loss of equilibrium (Khangarot and Ray 1990). Destruction of the gill lamellae by ionic nickel decreases the ventilation rate and may cause blood hypoxia and death (Ellgaard et al. 1995). Other signs of nickel poisoning in fishes include decreased concentrations of glycogen in muscle and liver with simultaneous increases in levels of lactic acid and glucose in blood (Ghazaly 1992), depressed hydrogen peroxide production in tissues and a reduction in superoxide dismutase (Bowser et al. 1994), and contractions of vascular smooth muscle—signs similar to those associated with hypertension in mammals (Evans et al. 1990). Ionic nickel is lethal to sensitive species of aquatic organisms at 11-113 µg/L. Deaths occur among embryos of rainbow trout at 11-90 µg/L, daphnids at 13 µg/L, embryos of channel catfish at more than 38 µg/L, embryos of the narrow-mouthed toad at 50 µg/L, and embryos of largemouth bass at 113 µg/L (Table 7). Species intermediately resistant to nickel died at 150-410 µg Ni/L, including mysid shrimp at 150 µg/L, freshwater snails at 237 µg/L, clam embryos at 310 µg/L, and embryos of salamanders at 410 µg/L (Table 7). Aquatic bacteria and yeasts are comparatively tolerant to nickel. Sensitive species of freshwater eubacteria and actinomycetes show reduced growth at 5 mg Ni/L; for marine eubacteria, growth inhibition begins at 10-20 mg/L (Babich and Stotzky 1982a). Sensitive species of yeasts show growth inhibition at 1.0 mg Ni/L (*Torulopsis glabrata*); resistant species of yeasts (*Rhodotorula* sp., *Cryptococcus terrens*) show a reduction in growth at 5-20 mg Ni/L (Babich and Stotzky 1982a; WHO 1991).

Table 7. Nickel effects on selected aquatic plants and animals.

Table 7. Taxonomic group, organism, dose, and other variables	**Effect**	**Reference[a]**
Algae and macrophytes		
Alga, *Anabaena inequalis*		
125 µg/L	Growth inhibited	1
10.0 mg/L	Photosynthesis inhibited	1
20.0 mg/L	Nitrogenase activity inhibited	1
Blue-green alga, *Anacystis nidulans*		
160 µg/L	Growth of wild strains inhibited 50%	2
1.3 mg/L	Growth of nickel-tolerant strain inhibited 50%	2
10.0 mg/L	Decreased growth in 14 days	3
50.0 mg/L	No growth in 14 days	3
Freshwater algae, four species		
100-700 µg/L	Reduced growth at 50 mg $CaCO_3$/L	4
Green algae, four species		
100 µg/L	Growth inhibition at 20 C	1
Giant kelp, *Macrocystis pyrifera*		
2.0 mg/L	Photosynthesis inhibited 50%	4
Diatom, *Navicula pelliculosa*		
100 µg/L	Growth inhibited 50% in 14 days	1
Alga, *Phaeodactylum tricornutum*		
1.0 mg/L	Reduced growth	4
Alga, *Scenedesmus acutiformis*; from lake containing 2.5 mg Ni/L		
1.9 mg/L	Growth reduced 47%	1

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
3.0 mg/L	Growth reduced 82%	1
Marine diatom, *Thalassiosira rotula*		
30 μg/L	Growth inhibited	5
300 μg/L	Toxic threshold	5
Rotifers		
Rotifer, *Philodena acuticornis*		
2.9-7.4 mg/L	LC50 (96 h) at 25 mg $CaCO_3$/L	4
Mollusks		
Eastern oyster, *Crassostrea virginica*		
100 μg/L, embryos	None dead in 48 h	6
1.18 mg/L embryos	LC50 (48 h)	6
3.0 mg/L, embryos	All dead in 48 h	6
12.0 mg/L, larvae	LC50 (12 days); normal	7
growth in survivors		
Freshwater snail, *Juga plicifera*		
124 μg/L	No adverse effects in 96 h	1
237 μg/L	LC50 (96 h)	1
Freshwater mussel, *Lamellidens marginalis*		
Exposed for 15 days to 22 mg Ni/L; tissue concentrations, in mg/kg fresh weight (FW), experimental vs. controls		
Foot	218 vs. 122	8
Gills	570 vs. 153	8
Hepatopancreas	327 vs. 160	8
Mantle	277 vs. 145	8
Muscle	186 vs. 130	8
110 mg/L	LC50 (96 h)	8
Northern quahog, *Mercenaria mercenaria*		
100 μg/L, embryos	No deaths in 48 h	6
310 μg/L, embryos	LC50 (48 h)	6
600 μg/L, embryos	All dead in 48 h	6
5.7 mg/L, larvae	LC50 (8-10 days); survivors had reduced growth	7
Softshell clam, *Mya arenaria*; adults		
10.0-50.0 mg/L	No deaths in 168 h	9, 11
112.0 mg/L	LC50 (168 h)	9
200.0 mg/L	All dead in 168 h	9
320.0 mg/L	LC50 (96 h)	9
Common mussel, *Mytilus edulis*		
Exposed to 0, 13, 25, 30, 56 or 107 μg Ni/L for 4 weeks	No accumulations in soft parts at 30 μg/L and lower. After 4 weeks, the 56 μg/L group had 32 mg Ni/kg dry weight (DW) soft parts, and the 107 μg/L group had 41 mg Ni/kg DW soft parts vs. 12 mg/kg DW in controls	10
Exposed to 0, 20.0, 40.0, or 80.0 mg/L for 96 h	No deaths in any group. No byssal thread secretion in 40 and 80 mg/L groups. Nickel concentrations, in mg/kg DW soft parts, were 12 in controls, 400-420 in intermediate dose groups, and 820 in the high	10

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
	dose group	
Mud snail, *Nassarius obsoletus*; adults		
10.0 mg/L	No deaths in 168 h	9
25.0 mg/L	All dead in 168 h	9
72.0 mg/L	LC50 (96 h)	9
Arthropods		
Aquatic insects, five species		
4.0-33.5 mg/L	LC50 (96 h) at 42-50 mg $CaCO_3$/L	4
Caddisfly, *Clistoronia magnifica*		
295-734 µg/L	MATC[b] at 50 mg $CaCO_3$/L	4
Copepods, four species		
600-9,700 µg/L	LC50 (96 h)	4
Copepod, *Cyclops abyssorum prealpinus*		
15.0 (8.0-26.0) mg/L	LC50 (48 h)	12
Daphnid, *Ceriodaphnia dubia*		
13 µg/L	LC50 (48 h) at pH 8.0-8.5	13
>200 µg/L	LC50 (48 h) at pH 6.0-6.5	13
Daphnid, *Daphnia hyalina*		
1.9 (1.5-2.5) mg/L	LC50 (48 h)	12
Daphnid, *Daphnia magna*		
10.2-21.4 µg/L	MATC[b] at 51 mg $CaCO_3$/L	4
30-95 µg/L	Reproduction impaired in 21 days	4
100 µg/L	Growth inhibited in 9 days	4
101-150 µg/L	MATC[b] at 105 mg $CaCO_3$/L	4
220-570 µg/L	MATC[b] at 205 mg $CaCO_3$/L	4
360 (330-400) µg/L	LC50 (21 days)	14
500 µg/L	LC50 (9 days) at 60 mg $CaCO_3$/L	4
510 µg/L	LC50 (96 h) at 45 mg $CaCO_3$/L	4
540 µg/L	Population biomass reduced	14
10% in 21 days		
950 (670-1,300) µg/L	Population biomass reduced	14
50% in 21 days		
2.34 mg/L	LC50 (96 h) at 100 mg $CaCO_3$/L	4
4.96 mg/L	LC50 (96 h) at 206 mg $CaCO_3$/L	4
Daphnid, *Daphnia pulicaria*		
1.8-2.2 mg/L	LC50 (48 h) at 44-48 mg $CaCO_3$/L	4
2.4-3.8 mg/L	LC50 (48 h) at 194-244 mg $CaCO_3$/L	4
Copepod, *Eudiaptomus padanus*		
3.6 (2.8-4.6) mg/L	LC50 (48 h)	12
Amphipod, *Gammarus* sp.		
13.0 mg/L	LC50 (96 h)	4
Amphipod, *Hyalella azteca*		
890 µg/L	LC50 (96 h) at pH 8.0-8.5	13
2.0 mg/L	LC50 (96 h) at pH 6.0-6.5	13
Mysid shrimp, *Mysidopsis bahia*		
61-141 µg/L	MATC[b]	4
Mysid shrimp, *Mysidopsis bigelowi*		
510-640 µg/L	LC50 (96 h)	4
Mysid shrimp, *Mysidopsis formosa*		

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
150 μg/L	LC50 (96 h)	4
Copepod, *Nitocra spinipes*		
6.0 mg/L	LC50 (96 h)	15
Hermit crab, *Pagurus longicarpus*		
10.0 mg/L	No deaths in 168 h	9
47.0 mg/L	LC50 (96 h)	9
50.0 mg/L	All dead in 168 h	9
Annelids		
Oligochaete, *Lumbriculus variegatus*		
26.0 mg/L	LC50 (96 h) at pH 8.0-8.5	13
100.0 mg/L	LC50 (96 h) at pH 6.0-6.5	13
Sandworm, *Nereis diversicolor*; adults		
10.0 mg/L	No deaths in 168 h	9
25.0 mg/L	LC50 (96-168 h)	9
50.0 mg/L	All dead in 168 h	9
Polychaete annelids, three species		
17.0-49.0 mg/L	LC50 (96 h)	4
Oligochaete, *Tubifex tubifex*		
80-61,400 μg/L; various water hardnesses	LC50 (48 h) range; most sensitive in soft waters; survivors had increased respiration rate	16, 17
Echinoderms		
Sea urchin, *Arbacia punctulata*; embryos		
17.0 mg/L	More than 50% dead in 42 h	4
Starfish, *Asterias forbesi*; adults		
5.0 mg/L	No deaths in 168 h	9
13.0 mg/L	LC50 (168 h)	9
50.0 mg/L	All dead in 168 h	9
150.0 mg/L	LC50 (96 h)	9
Sea urchin, *Lytechinus pictus*; embryos; exposed continuously from fertilization through hatching to 5.8, 58, 580, 5,800, 58,000, or 580,000 μg Ni/L, as nickel chloride		
5.8 μg/L group	Normal growth and development	18
58 and 580 μg/L groups	Normal development through gastrulation, but larvae developed abnormally (no dorsoventral symmetry)	4, 18
58.0 mg/L and higher	Normal cleavage, but gastrulation unsuccessful	18
Sea urchin, *Strongylocentrotus purpuratus*		
Sperm held in 0.6, 5.9, 59, 590, or 5,900 μg Ni/L for 50 min	0.6 and 5.9 μg/L had no effect on sperm motility; 59 μg/L had initial depressing effect followed by increased motility; 590 μg/L had initial depressing effect in motility with recovery; 5,900 μg/L caused significant depression in sperm motility	19
Sea urchins, various species; embryos		
180 μg/L	No adverse effects on development	20
370-1,470 μg/L	Embryonic development inhibited	20
Fishes		

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
Rock bass, *Ambloplites rupestris*		
2.48 mg/L	LC50 (96 h) at 26 mg $CaCO_3$/L	4
Climbing perch, *Anabas testudineus*		
146.0 mg/L for 30 days	No deaths; significant depletion of glycogen and total proteins in liver and gonads	21
American eel, *Anguilla rostrata*		
13.0 mg/L	LC50 (96 h)	4
Zebradanio, *Brachydanio rerio*; exposed from 2 h after fertilization through hatching and larval stages until day 16; 11 different doses as nickel sulfate hexahydrate		
40 µg/L	No effect on hatching time	22
>40 µg/L	Delayed hatching time	22
80 µg/L	No effect on larval survival	22
1,024 µg/L	No effect on embryonic survival	22
Goldfish, *Carassius auratus*		
500 µg/L for 2 weeks	Some accumulation in scales and otoliths, but not statistically significant	23
25 mg/L in 96 h	Swimming activity reduced 31%	24
75 mg/L	LC25 (96 h)	24
100 mg/L	LC88 (96 h)	24
Giant gourami, *Colisa fasciata*; adults		
64 mg/L as nickel sulfate (equivalent to 0.8 x LC50 [96 h] value); gonads examined after 96 h	Testicular degeneration (spermatogonial activity reduced, germ cells in testicular lobules degenerating, congested blood vessels); ovaries histologically different, oocytes resorbed	25
Common carp, *Cyprinus carpio*		
750 µg/L, larvae	LC50 (257 h) at 128 mg $CaCO_3$/L	4
1.0 mg/L for 16 days (in mixture containing 1.0 mg/L each of Cd, Cr, and Pb salts); adults	Maximum nickel concentrations, in mg/kg DW, were 77 in liver, 49 in gill, 39 in brain, and 19 in muscle; other metals tested showed time-dependent increases in tissues	26
1.3-40.0 mg/L	LC50 (96 h)	4, 27
8.0 mg/L for 15 days, adults	No deaths; disrupted protein metabolism in gills and kidneys	8
8.0 mg/L for 15 days (sublethal exposure); nickel concentrations (in mg/kg FW) in tissues of experimentals at end of exposure vs. controls		
Brain	41 vs. 25	29
Gill	103 vs. 31	29
Kidney	80 vs. 50	29
Liver	97 vs. 32	29
Muscle	58 vs. 30	29
10.4-10.6 mg/L	LC50 (96 h) at 55 mg $CaCO_3$/L	4
Carp, *Cyprinus carpio communis*		
Fingerlings; exposed to 2.5, 5, 7.5, or 10 mg Ni/L for 30 days	No deaths; protein content significantly decreased over time	30

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
	in dose-dependent pattern in brain, intestine, and muscle	
Orange chromide, *Etroplus maculatus*		
Exposed to 10, 30, 60, 80, or 100 mg Ni/L for 96 h at 3 salinities (2.5, 5, and 15 ppt)	At 2.5 ppt salinity, whole body nickel concentrations increased from 19 to 232 mg/kg DW in a dose-dependent manner (vs. control of 12.5 mg/kg DW); for 15 ppt salinity, nickel increased from 20 to 113 mg/kg DW; in combination with copper salts, nickel uptake increased at intermediate salinities	31
Fishes; most species; adults		
4-14 mg/L	LC50 (96 h), soft water	1
24-44 mg/L	LC50 (96 h), hard water	1
Banded killifish, *Fundulus diaphanus*		
46.1 mg/L	LC50 (96 h) at 53 mg $CaCO_3$/L	4
Mummichog, *Fundulus heteroclitus*		
50 mg/L	No deaths in 168 h	9
150 mg/L	LC50 (96 h)	9
250 mg/L	All dead in 168 h	9
Channel catfish, *Ictalurus punctatus*; from fertilization through day 4 posthatch		
38 (18-68) µg/L	LC10	28
710 (490-1,010) µg/L	LC50	28
Spot, *Leiostomus xanthurus*		
70 mg/L	LC50 (96 h), adults	1
Pumpkinseed, *Lepomis gibbosus*		
5.2 mg/L	LC50 (96 h) at 20 mg $CaCO_3$/L	4
8.0 mg/L	LC50 (96 h) at 55 mg $CaCO_3$/L	4
Bluegill, *Lepomis macrochirus*		
5.4 mg/L	LC50 (96 h) at 20 mg $CaCO_3$/L	4
39.6 mg/L	LC50 (96 h) at 360 mg $CaCO_3$/L	4
Atlantic silverside, *Menidia menidia*		
8.0 mg/L	LC50 (96 h)	4
Tidewater silverside, *Menidia peninsulae*; larvae		
38.0 mg/L	LC50 (96 h)	1
Largemouth bass, *Micropterus salmoides*		
113 (61-185) µg/L; exposed from fertilization through day 4 after hatching	LC10	28
2.02 mg/L, embryos	LC50 (8 days) at 93-105 mg $CaCO_3$/L	4
2.06 (1.48-2.84) mg/L; exposed from fertilization through day 4 after hatching	LC50	28
White perch, *Morone americana*		
13.6 mg/L	LC50 (96 h) at 55 mg $CaCO_3$/L	4
Striped bass, *Morone saxatilis*		
6.2 mg/L	LC50 (96 h) at 54 mg $CaCO_3$/L	4
Coho salmon, *Oncorhynchus kisutch*		
16.7 mg/L	LC50 (96 h), alevins	32
18.0 mg/L	LC50 (96 h), juveniles	32
Rainbow trout, *Oncorhynchus mykiss*		

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
11 µg/L; embryos exposed from fertilization through day 4 after hatching	LC10	28
23.9 µg/L	Avoidance by adults	33
<35 µg/L; chronic exposure; newly fertilized eggs	No adverse effects	33
50 µg/L; embryos exposed from fertilization through day 4 after hatching	LC50 (28 days) at 93-105 mg $CaCO_3$/L	4, 28
60 µg/L; fertilization through day 4 after hatching	LC50 at 125 mg $CaCO_3$/L	1
90 µg/L; fertilization through day 4 after hatching	LC50 at 174 mg $CaCO_3$/L	1
134 µg/L; chronic exposure of eyed eggs and larvae	No adverse effects	33
230-535 µg/L	MATC[b] at 50 mg $CaCO_3$/L	4
1.0 mg/L, as hexahydrate nickel chloride; exposure for 6 months plus 3-month postexposure observation period in uncontaminated media; juveniles	All fish appeared outwardly normal at all times; after 6 months of exposure, nickel concentrations—in mg/kg FW—were 4.0 in kidneys, 2.9 in liver, and 0.8 in muscle. Nickel concentrations following the 3-month postexposure period (controls) in mg/kg FW, were 2.5 (1.5) in kidneys, 1.8 (1.5) in liver, and 0.6 (0.5) in muscle	34
7.8-10.9 mg/L	LC50 (96 h), juveniles	32, 33
25.1 mg/L	LC50 (96 h), alevins	32
31.7 mg/L	LC50 (96 h); adults; hard water	35
35.7 mg/L, adults	LC50 (48 h) at 42 mg $CaCO_3$/L	4
Fed diet containing 61 mg Ni/kg DW ration (and other metals found in activated sewage sludge) for 10 weeks	Whole body nickel concentration increased from 0.33 mg/kg DW to 0.63 mg/kg DW	36
Isolated R1 liver cells exposed to culture media containing 84 mg Ni/L	50% inhibition of neutral red dye uptake	35
Isolated liver cells in 116 mg Ni/L	Cytotoxic	35
Tilapia, *Oreochromis niloticus*		
1.5 or 3.0 mg/L for 10 days	Significant depletion in liver and muscle glycogen; significant increase in plasma glucose; differences more pronounced at higher dose	37
Fathead minnow, *Pimephales promelas*		
109-433 µg/L	MATC[b] at 44 mg $CaCO_3$/L	4
380-730 µg/L	MATC[b] at 210 mg $CaCO_3$/L	4, 38
730-1,600 µg/L; lifetime exposure	No adverse effects on growth or survival; reproduction inhibited	38
3.1 mg/L	LC50 (96 h) at pH 8.0-8.5	13
>4.0 mg/L	LC50 (96 h) at pH 6.0-6.5	13
4.6-9.8 mg/L	LC50 (96 h) at 20 mg $CaCO_3$/L	4

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
25.0-32.2 mg/L	LC50 (96 h) at 210 mg $CaCO_3$/L	4
42.0-44.5 mg/L	LC50 (96 h) at 360 mg $CaCO_3$/L	4
Guppy, *Poecilia reticulata*		
31.0 mg/L	LC50 (10 days)	39
36.0 mg/L	LC50 (96 h)	39
Brook trout, *Salvelinus fontinalis*		
54.4 mg/L	LC50 (48 h) at 42 mg $CaCO_3$/L	4
Lake trout, *Salvelinus namaycush*		
16.7 mg/L	LC50 (48 h) at 42 mg $CaCO_3$/L	4
Spiny dogfish, *Squalus acanthias*		
6.0-11.0 mg/L	Nickel causes in vitro contraction of vascular smooth muscle of ventral aorta	40
Nile tilapia, *Tilapia nilotica*		
1.0 mg/L for 16 days	Maximum nickel concentrations, in mg/kg DW, were 49 in liver, 42 in brain, 37 in gill, and 14 in muscle	26
Exposed to 19, 32 or 51 mg/L for up to 96 h	Dose- and time-dependent increase in blood glucose and lactic acid concentrations; liver glycogen decreased at all nickel levels and muscle glycogen decreased at the two higher levels; high nickel concentrations were associated with elevated erythrocyte number, hemoglobin, and hematocrit. Nickel accumulated in blood, liver, muscle, and especially in kidney	41
65 mg/L	LC50 (96 h)	41
Arctic grayling, *Thymallus arcticus*		
8.2 (5.6-12.0) mg/L	LC50 (96 h), alevins	32
8.7 (6.7-11.4) mg/L	LC50 (96 h), juveniles	32
Amphibians		
Marbled salamander, *Ambystoma opacum*		
410 µg/L as nickel chloride; fertilization through day 4 after hatching	LC50	28
420 µg/L, embryos	LC50 (8 days) at 93-105 mg $CaCO_3$/L	4
Fowler's toad, *Bufo fowleri*		
11.03 mg/L as nickel chloride; fertilization through day 4 after hatching	LC50	28
Egyptian toad, *Bufo regularis*		
Females given single subcutaneous injection of nickel sulphate at 3-160 mg Ni/kg BW		
73 mg/kg BW	Calculated LD50 (96 h)	42
120 mg/kg BW	Calculated LD50 (24 h)	42
Concentrations of nickel in selected tissues of nickel-exposed survivors (all groups) vs. controls at 96 h		
Whole blood	320 µg/FW (Max. 1,420 µg/L	42
at 24 h) vs. 40 µg/L		
Kidney	1.82 mg/kg FW (Max. 3.6 mg/kg	42

Table 7. Taxonomic group, organism, dose, and other variables	Effect	Reference[a]
FW at 24 h) vs. 0.11 mg/kg FW		
Liver	0.54 mg/kg FW (Max. 2.02 mg/kg	42
FW at 48 h) vs. 0.3 mg/kg FW		
Serum	0.3 mg/L vs. 0.05 mg/L	42
Skin	0.6 mg/kg FW (Max. 1.56 mg/kg	42
FW at 24 h) vs. 0.01 mg/kg FW		
Urine	2.12 mg/L (Max. 70.0 mg/L at	42
24 h) vs. not detectable		
Narrow-mouthed toad, *Gastrophryne carolinensis*		
50 µg/L as nickel chloride; fertilization through day 4 after hatching	LC50	28
50 µg/L; embryos	LC50 (7 days) at 195 mg $CaCO_3$/L	4

[a] 1, World Health Organization 1991; 2, Whitton and Shehata 1982; 3, Lee and Lustigman 1996; 4, U.S. Environmental Protection Agency (EPA) 1980; 5, Dongmann and Nurnberg 1982; 6, Calabrese and Nelson 1974; 7, Calabrese et al. 1977; 8, Sreedevi et al. 1992a; 9, Eisler and Hennekey 1977; 10, Friedrich and Felice 1976; 11, Eisler 1977b; 12, Baudouin and Scoppa 1974; 13, Schubauer-Berigan et al. 1993; 14, Enserink et al. 1991; 15, Bengtsson 1978; 16, Brkovic-Povic and Popovic 1977a; 17, Brkovic-Popovic and Popovic 1977b; 18, Timourian and Watchmaker 1972; 19, Timourian and Watchmaker 1977; 20, Kobayashi and Fujinaga 1976; 21, Jha and Jha 1995; 22, Dave and Xiu 1991; 23, Mugiya et al. 1991; 24, Ellgaard et al. 1995; 25, Nath and Kumar 1990; 26, Canli and Kargin 1995; 27, Alam and Maughan 1992; 28, Birge and Black 1980; 29, Sreedevi et al. 1992b; 30, Thatheyus et al. 1992; 31, Patterson and Fernandez 1995; 32, Buhl and Hamilton 1991; 33, Nebeker et al. 1985; 34, Calamari et al 1982; 35, Segner et al. 1994; 36, Singh and Ferms 1978; 37, Alkahem 1995; 38, Pickering 1974; 39, Khangarot and Ray 1990; 40, Evans et al. 1990; 41, Ghazaly 1992; 42; Daabees et al. 1991.

[b] MATC = maximum acceptable toxicant concentration. Lower value in each MATC pair is highest concentration tested producing no measurable effect on growth, survival, reproduction, or metabolism during chronic exposure; higher value is lowest concentration tested producing a measurable effect.

The biocidal properties of nickel are modified by many variables. For example, nickel is most lethal to freshwater crustaceans and fishes at pH 8.3 and least lethal at pH 6.3 (Schubauer-Berigan et al. 1993); less toxic to algae when copper is reduced or absent (NRCC 1981) and chelating agents, such as EDTA, are present (Lee and Lustigman 1996); most lethal to echinoderm embryos prior to gastrulation (Timourian and Watchmaker 1972); and more toxic to estuarine amphipods and clams under conditions of decreased salinity in the 0.5-3.5% range and increased temperature in the 5-15 C range (WHO 1991).

Representative nickel-sensitive aquatic species show sublethal effects at 11.7-125 µg Ni/L. These effects include altered immunoregulatory mechanisms in tissues of the rainbow trout at 11.7 µg/L (Bowser et al. 1994), inhibited reproduction of daphnids at 30 µg/L, growth inhibition of freshwater and marine algae at 30-125 µg/L, reduced growth of rainbow trout at 35 µg/L, accumulation from the medium by mussels at 56 µg/L, and abnormal development of sea urchin embryos at 58 µg/L (NRCC 1981; WHO 1991; Outridge and Scheuhammer 1993; Table 7).

Bioconcentration factors (BCF) for nickel vary among organisms under laboratory conditions. For freshwater species, typical BCF values for nickel are about 10 for algae, 61 for fathead minnows, and 100 for cladocerans; for marine mussels and oysters, typical BCF values range between 299 and 414 (USEPA 1980). The alga *Thalassiosira rotula* can accumulate as much as 90 mg Ni/kg DW (Dongmann and Nurnberg 1982). Other species of aquatic plants can extract nickel from water and concentrate it to as much as 10,000 mg/kg DW (NRCC 1981). The alga *Anacystis nidulans* can develop tolerance to nickel and other metals under laboratory conditions (Whitton and Shehata 1982), and this may account for high BCF values in this species. Nickel at 50 µg/L was accumulated from seawater by softshell clams (*Mya arenaria*) more rapidly during summer at water temperatures of 16-22 C than during winter temperatures of 0-10 C; no accumulations occurred at 10 µg Ni/L in winter, but clams accumulated twice as much nickel over controls in summer (Eisler 1977a). Embryos of sea urchins actively accumulate nickel from seawater at all dose levels tested (Timourian and Watchmaker 1972).

Bioconcentration factors for rainbow trout after exposure for 6 months to 1.0 mg Ni/L were 0.8 for muscle, 2.9 for liver, and 4.0 for kidneys (Calamari et al. 1982). Fish can accumulate nickel from food and water. Levels up to 13 mg Ni/kg DW occurred in northern pike (*Esox lucius*) and pickerel (*Esox* sp.) from a contaminated river (NRCC 1981). Common carp (*Cyprinus carpio*) and tilapia (*Tilapia nilotica*) exposed for 16 days to 1.0 mg Ni/L had elevated concentrations in livers of 49-77 mg Ni/kg DW (Canli and Kargin 1995). Goldfish (*Carassius auratus*) that died during immersion in solutions containing more than 35 mg Ni/L showed elevated concentrations in tissues; however, most of the nickel was washed off with water, and it is not clear if accumulation occurred after death (Kariya et al. 1968). Nickel accumulates in fish tissues and causes alterations in gill structure, including hypertrophy of respiratory and mucus cells, separation of the epithelial layer from the pillar cell system, cauterization and sloughing, and necrosis of the epithelium (Nath and Kumar 1989). Although aquatic organisms can accumulate nickel from their surroundings, there is little evidence of significant biomagnification of nickel levels along food chains (NRCC 1981; Sigel and Sigel 1988; WHO 1991).

Birds

In mallards (*Anas platyrhynchos*), nickel accumulates in tissues when diets contain as little as 12.5 mg Ni/kg DW ration (Table 8). Metabolic upset and altered bone densities occur in mallards fed diets containing 800 mg Ni/kg ration for 90 days (Cain and Pafford 1981; Eastin and O'Shea 1981). Inhibited growth and reduced survival occur in mallards at dietary loadings of 1,200 mg Ni/kg ration (Table 8). Dietary nickel concentrations of 0.074 mg Ni/kg ration have no adverse effects on Coturnix quail (*Coturnix risoria*). However, Japanese quail (*Coturnix japonica*) fed diets containing 0.71 mg Ni/kg ration have significantly elevated nickel concentrations in liver compared to controls fed diets containing 0.48 mg Ni/kg (Table 8). Increased concentrations of nickel in the diets of domestic chickens (*Gallus* sp.) were associated with decreased growth and survival and increased nickel concentrations in bone and kidney (Ling and Leach 1979). Dietary loadings of 500 mg Ni/kg ration and higher were associated with reduced growth and high mortality in some strains of chickens, but not others (Table 8). No developmental abnormalities occurred in chicks from survivors challenged by nickel during embryogenesis (USPHS 1977). Chick embryos receiving a single injected dose of 3.6 mg Ni/kg embryo, however, experienced 50% mortality within 18 days (Ridgway and Karnofsky 1952). Chicks are more resistant than embryos to injected nickel. Chicks injected with 10 mg Ni/kg BW survived but had disrupted glucose metabolism; effects were exacerbated by starvation (Nielsen 1977).

Table 8. Nickel effects on birds.

Variables		
Mallard, *Anas platyrhynchos*		
Breeding adults 20-months old fed diets containing 0, 12.5, 50, 200, or 800 mg Ni/kg ration for 90 days. All birds killed at day 90 and examined		
All groups	No effect on egg production, hatchability, or survival of ducklings; adults had normal blood chemistry and no organ histopathology; nickel accumulated in kidneys at all doses and in feathers, blood, and livers of birds fed high doses	1, 9
50 mg/kg group	Feathers contained 5.2 mg Ni/kg dry weight (DW) vs. 0.9 mg/kg DW in controls	1
800 mg/kg group	Abnormal black, tarry feces in test birds. Mean nickel concentrations, in mg/kg fresh weight (controls), were 1.9 (0.09) in kidneys, 0.52 (0.12) in livers, and 0.14 (0.005) in blood. Newly grown feathers had 68 (range 8-558) mg Ni/kg DW vs. 0.9 (0.5-1.6) mg/kg DW in controls	1
Ducklings age 1 day fed diets containing 0, 200, 800, or 1,200 mg Ni/kg fresh weight (FW) ration, as nickel sulfate, for 90 days		
800 mg/kg group and lower	No effect on growth or survival	2
800 mg/kg group	Lower bone density in females at day 60	2
1,200 mg/kg group	Tremors and paresis beginning at day 14; 71% dead by day 60. Survivors weighed less at day 28 than did birds fed other diets. Lower bone density evident at day 30. Livers and kidneys of survivors had <1.0 mg Ni/kg FW; dead birds had as much as 22.7 mg Ni/kg FW liver and 74.4 mg Ni/kg FW kidney	2
Japanese quail, *Coturnix japonica*		
For 2 generations quail ate diets containing wheat (*Triticum aestivum*) grown on sludge-amended soils (980 µg Ni/kg DW wheat) or control wheat (400 µg Ni/kg DW). Total diets contained 710 µg Ni/kg DW (sludge-grown wheat) or 480 µg Ni/kg DW (controls)	Nickel concentrations in livers of birds fed sludge-grown wheat were significantly elevated in males (210 µg Ni/kg DW vs. 130 in controls) and females (120 vs. 80 µg Ni/kg DW); mixed function oxidase activities were elevated in livers of both sexes when compared to controls	3
Coturnix quail, *Coturnix risoria*		
Fed diets containing 74 µg Ni/kg ration for 4 generations	No observed adverse effects	4
Domestic chicken, *Gallus* sp.		
Chicks given single intraperitoneal injection of 10 mg Ni (as nickel chloride)/kg body weight (BW)	Initial increase in plasma glucose after 15 min followed by hypoglycemia 60-120 min after injection. Starved chicks remained hyperglycemic during 120 min postinjection observation period	5
Day-old Plymouth Rock males fed semi-purified diets for 3 weeks		
300 mg Ni/kg diet	Reduced growth rate; elevated kidney nickel concentration of 4.2 mg/kg FW vs. 0.13 in controls	6, 9

[a]1, Eastin and O'Shea 1981; 2, Cain and Pafford 1981; 3, Stoewsand et al. 1984; 4, National Academy of Sciences 1975; 5, Nielsen 1977; 6, Ling and Leach 1979; 7, Weber and Reid 1968; 8, Ridgway and Karnofsky 1952; 9, Outridge and Scheuhammer 1993.

Mammals

Outridge and Scheuhammer (1993), in their excellent review of nickel hazards, draw six major conclusions regarding nickel toxicity to mammals. (1) Lifetime exposure of resistant species of mammals to diets containing 2,500 mg Ni/kg DW or to drinking water containing 10,000 mg Ni/L are not lethal. (2) Lethal nickel doses in mammals are usually derived from studies with laboratory animals injected with nickel and its compounds, not from realistic exposure regimens. (3) Inhaled nickel is at least 100 times more toxic than ingested nickel because it is more readily absorbed from the lungs than from the gastrointestinal tract, and death is more often the result of respiratory failure than of nervous system effects. For example, oral ingestion of 0.05 mg Ni/kg BW and inhalation at 0.005 mg Ni/m^3 are equally effective threshold doses in rats (USPHS 1977). (4) Large differences in sensitivity to nickel exist between closely related taxonomic species, such as rats and mice. (5) Threshold effects on lung function or morphology in several species of laboratory mammals occur at airborne nickel concentrations of 0.1-0.2 mg/m^3, depending on nickel compound and duration of exposure. (6) Juveniles were usually more sensitive to nickel than were adults.

Nickel salts administered by intravenous or subcutaneous injection are comparatively toxic. For all routes of parenteral administration, the LD50 (lethal dose to 50% of the sample) range for injected nickel salts is 6 mg Ni/kg BW for dogs given nickel oxide intravenously to 600 mg Ni/kg BW for mice given nickel disodium EDTA intraperitoneally (Nielsen 1977).

Several trends were evident among sensitive species of mammals tested against nickel through administration routes other than injection (Table 9). (1) Nickel carbonyl is lethal to mice, rats, and cats at 0.067-0.24 mg Ni/L. (2) Inhalation of nickel compounds other than nickel carbonyl causes significant effects in humans, rats, mice, rabbits, and dogs, with respiratory effects being most common. (3) Nickel-contaminated drinking water has adverse effects on rat reproduction and may neurologically affect the eyes of humans, although this needs to be verified. (4) Diets containing nickel carbonate, nickel chloride, or nickel sulfate cause reduced growth, disruptions of food intake and thyroid function, and emphysema and pneumonia in calves, dogs, mice, or rats. (5) Dermal application of nickel sulfate hexahydrate causes skin and testicular damage. (6) Single oral doses of 136-410 mg Ni/kg BW as nickel acetate are lethal to mice.

Table 9. Nickel effects on selected mammals.

Table. 9. Organism, route of exposure, dose, and other variables	**Effect**	**Reference[a]**
Cow, *Bos* sp.		
Diet		
63 mg Ni/kg ration for 8 weeks as nickel carbonate; male calves	Normal growth and food consumption	1, 2
250 mg Ni/kg ration for 42 days; lactating cows	Negligible transfer of nickel from diet to milk	3
250 mg Ni/kg DW ration for 8 weeks as nickel carbonate; male calves; equivalent to daily intake of 1,218 mg nickel	No accumulations in tissues; slight (13%) reduction in food intake and growth rate (11%)	1, 2
1,000 mg Ni/kg dry weight (DW) ration for 8 weeks as nickel carbonate; male calves; equivalent to daily intake of 1,410 mg nickel	Abnormal rumen fluid composition; nickel accumulations in tissues; marked reduction in food intake and growth rate. During a 6-week post exposure recovery period, growth rate was same as in controls	1,2
1,750 mg Ni/kg ration; adult females	No detectable nickel in milk	2
In vitro culture; isolated brain cells exposed for 20 h to graded concentrations of nickel chloride up to 116 mg Ni/L	Time- and dose-dependent effects on kinetics of brain microtubule polymerization; effects reversed on removal of Ni^{2+} from culture media	4
Domestic dog, *Canis familiaris*		
Diet		
0, 100, 1,000, or 2,500 mg Ni/kg ration for 2 years as nickel sulfate hexahydrate	No significant adverse effects at 1,000 mg Ni/kg ration and lower. At 2,500 mg Ni/kg, adverse effects observed on growth and blood chemistry; livers and kidneys enlarged; lung lesions; hyperplasia of bone marrow	5
Equivalent to 25 or 63 mg Ni/kg BW daily, as nickel sulfate, for 2 years	No serious adverse effects at low dose; high dose group had emphysema, pneumonia, low hematocrit, increased liver and kidney weight, and a 40% decrease in body weight gain	6
Inhalation		
2.7 mg Ni/L, as nickel carbonyl ($Ni(CO)_4$), for 75 min	LC80 (1-5 days postexposure)	8
5 to 6 mg Ni powder/m^3, 10 min daily for 6 months; observed for additional 19 months following treatment	No change in weight or general condition. At 3 months after treatment, leucocyte and primary neutrophil counts were low, and nickel was elevated in liver and kidneys. At 12 months, blood flow was reduced in small vessels of lungs. At 19 months, survivors had increased pulse and respiration rates	7
Intravenous injection, single dose		
6 to 7 mg Ni/kg BW, as nickel oxide	Lethal	2
10 to 20 mg Ni/kg BW as colloidal nickel	Death preceded by gastroenteritis,	2,9

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
	tremors, and paralysis	
10 to 20 mg Ni/kg BW as nickel chloride Oral	Some deaths	2, 9
12 mg/kg BW daily for 200 days	Tolerated without ill effects	10
1,000-3,000 mg Ni/kg BW as powdered nickel	Tolerated	9
Subcutaneous injection; single dose of 500 mg Ni/kg BW as nickel sulfate hexahydrate	Some deaths	2
Domestic goat, *Capra* hircus; pulmonary macrophages cultured in vitro for 20 h with media containing 14.5-58.0 mg Ni/kg as nickel chloride	Concentration-dependent decrease in viability of alveolar macrophages; highest dose had survival of <50%. Death associated with release of superoxide anions	11
Guinea pig, *Cavia* sp.		
Drinking water; 2.5 mg Ni/L for 4 months were between 3.4 and 4.6 mg Ni/kg DW hair	No accumulations in hair; all values	12
Inhalation; 15 mg Ni/m^3 as elemental nickel; lifetime exposure	Excess blood, swelling, hemorrhage, and increased frequency of lesions in the pharyngeal area	7
Intravenous injection; 62 mg Ni/kg BW as nickel sulfate; single injection	LD50	2
Subcutaneous injection; males given 0.0001, 0.001 or 1.0 mg Ni/kg BW daily as nickel chloride for 15 days were mated with fertile females	No effect on female gestation period, number of litters or offspring, weight of offspring, or offspring development	7
Hamster, *Cricetus* sp.		
Gavage; 5 mg of nickel oxide	After 24 h, no increase in nickel content of lungs, liver, kidney or carcass	7
Inhalation		
Exposed to nickel oxide aerosols at concentrations of 2-160 µg/L (2 to 160 mg/m^3) and particle size of 1 to 2.5 µm	45 days after exposure about 50% of the original dose remained in lungs with no significant accumulations in other tissues	10
15 mg Ni/m^3 as elemental nickel; lifetime exposure	No significant effect on survival or health	7
39 mg Ni/m^3 as nickel oxide for 3 weeks	Inflammation and congestion of lungs; emphysema	7
48.4 mg Ni/m^3 as nickel oxide for 61 days	No deaths	6
Domestic cat, *Felis domesticus*		
Inhalation; nickel carbonyl		
0.19 mg/L for 30 min	LC50 (0.2 h-6 days after exposure)	8
3.0 mg/L for 75 min	LC50 (1-5 days after exposure)	8
Oral; 12-25 mg/Ni kg BW daily for as long as 200 days as elemental and inorganic nickel salts	Tolerated, with no apparent ill effects	2, 9, 10
Human, *Homo sapiens*		
Dermal; <59 µg Ni/L; nickel-sensitive persons	No contact allergic reaction	14
Dialysis; 23 patients; nickel leached into dialysate from a nickel-plated stainless	At plasma nickel concentrations of about 3 mg/L, patients had adverse	8

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
steel water heater tank	effects including headaches, nausea, vomiting, and weakness; recovery occurred 3 to 13 h after cessation of dialysis	
Drinking water		
Equivalent to 0.012 or 0.05 mg Ni/L as nickel sulfate	Neurological effect on eyes at high dose; no adverse effects at low dose	6
250 mg Ni/L in contaminated drinking water	Stomach ache, increased red blood cell number, increased protein in urine	6
32 workers in an electroplating plant drank water accidentally contaminated with nickel sulfate and nickel chloride at 1,630 mg Ni/L;estimated intake of 0.5-2.5 g, equivalent to 8.3-41.6 mg/kg BW	Symptoms included nausea, vomiting, abdominal discomfort, diarrhea, giddiness, lassitude, headache, cough, and shortness of breath, and persisted for at least 2 h and sometimes 2 days. Serum nickel concentrations on day 1 after exposure were 286 (13-1,340) µg/L vs. 50 µg/L in nonaffected workers; for urine these concentrations were 5.8 (0.2-37.0) mg/L vs. 4.0 µg/L	8
Inhalation		
>0.04 mg Ni/m^3 air, usually as nickel oxide or metallic nickel	Chronic bronchitis, emphysema, reduced lung capacity, and increased incidence of deaths from respiratory disease among workers occupationally exposed	6
30 mg Ni/L air as nickel carbonyl for 30 min	Lethal	13
Chronic exposure		
Nickel aerosols, occupational exposure	Lung cancer, nasal sinusitis, chronic rhinitis	10
Nickel particulates	Chronic respiratory infections	10
Oral		
Low nickel diet fed to patients with chronic nickel dermatitis	Significant improvement in 6 weeks; adverse effects when placed on normal diet	10
Accidental ingestion of nickel sulfate crystals (15-20 grams) by 2.5 year-old female child	Death in 4 h of heart failure; blood had 7.5 mg Ni/kg, urine 50 mg/L, and liver 25 mg Ni/kg FW	6,8
Monkeys, various species; different forms of nickel in diet; as much as 1,000 mg Ni/kg ration for 24 weeks	No adverse effects on growth, behavior, or blood chemistry	10,13
Domestic mouse, *Mus* spp.		
Diet		
Young mice fed diets containing 0, 1,100 or 1,600 mg Ni/kg ration as the acetate salt for 4 weeks	Food consumption and growth reduced in the male 1,600 mg/kg group and the female 1,100 and 1,600 mg/kg groups. All nickel groups had significant decreases in liver cytochrome oxidase and isocitric dehydrogenase activities; in heart and kidney homegenates, malic dehydrogenase activity decreased in the high nickel groups	15, 16
Equivalent to >1.4 mg Ni/kg BW daily for 2 years as nickel chloride or nickel sulfate	Decreased liver weight	6

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
Equivalent to 108 mg Ni/kg BW daily for 180 days as nickel sulfate Drinking water	Renal tubular damage at the corticomedullary junction	6
Equivalent to >23 mg Ni/kg BW for 6-30 h as nickel chloride, nickel sulfate, or nickel nitrate	Abnormal sperm in mature males	6
150 mg/L as nickel sulfate for 6 months	No deaths	6
160 mg/L as nickel chloride in drinking water of pregnant females from gestation day 2 to day 7	Increased incidence of spontaneous abortions	6
Inhalation		
Nickel carbonyl		
0.01 mg/L for 120 min	All dead	8
0.067 mg/L for 30 min	LC50 (0.2 h-6 days after exposure)	8, 9
Nickel oxide		
>3.9 mg/m^3 for as long as 13 weeks	Adverse respiratory effects including chronic inflammation, fibrosis, macrophage hyperplasia, interstitial infiltrates, and increased lung weight	6
23.6 mg/m^3 for 16 days	No deaths	6
Nickel subsulfide		
>0.11 mg/m^3 for 16-91 days	Adverse respiratory effects	6
7.3 mg/m^3 for 16 days	All dead	6
Nickel sulfate		
>0.1 mg/m^3 for 16-91 days	Adverse respiratory effects	6
1.6 mg/m^3 for 16 days	All dead	6
Single intramuscular injection of 18.3 mg Ni/kg BW as nickel chloride	Involution of thymus and suppression of cellular and humoral activity and transient immunosuppressive effects within 2 days of injection with responses returning to normal within a few days	17
Single intraperitoneal injection		
Nickel acetate		
11 mg/kg BW	Adverse effects	21
32 mg/kg BW	LD50 (48 h)	7
39-50 mg/kg BW; adult males; age 9-15 weeks	LD50 (5 days postinjection)	20
48-54 mg/kg BW; adult females; age 9-15 weeks	LD50 (5 days postinjection)	20
89-97 mg/kg BW; juveniles; age 3 weeks	LD50 (5 days postinjection)	20
Nickel chloride		
Pregnant females given 1.2, 2.0, 3.0, 3.5, 4.6, 5.7, or 6.9 mg Ni/kg BW between days 7 and 11 of gestation	Dose-related increase in fetal deaths and malformations	8
3.1 mg Ni/kg BW	Normal spleen lymphocyte function	18
Pregnant mice given 4.6 mg Ni/kg BW on day 16 of gestation and killed 2 to 48 h after injection	Maximum nickel concentrations in tissues (in mg/kg FW) were reached in blood (19.8) and placentas (3.9) 2 h following injection; those in liver (4.9), spleen (1.3), and kidneys (56.2) were	19

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
	reached 4 h after injection; and maximum concentration in fetal tissues (1.1) was reached after 8 h. Authors estimate that all nickel is excreted in 42 to 84 h	
9.3-12.3 mg Ni/kg BW	Immunosuppression in spleen lymphocyte function	18
26 mg Ni/kg BW	LD50 (48 h)	7
Nickel chloride hexahydrate; 48 mg Ni/kg BW	LD50 (48 h)	7
Nickelocene; 27 mg Ni/kg BW	Adverse sublethal effects	21
Nickel oxide; >744 mg/kg BW	LD50 (72 h)	7
Nickel perchlorate heptahydrate; 100 mg Ni/kg BW	LD50 (12 h)	7
Nickel sulfate; 21-38 mg Ni/kg BW	LD50 (10-30 days)	7
Oral, single dose		
Nickel acetate; 136-410 mg Ni/kg BW	LD50 (72-120 h)	7, 21
Nickelocene; 186 mg/kg BW	LD50	21
Rabbit, *Oryctolagus* sp.		
Inhalation		
Metallic nickel dust		
>0.2 mg/m^3 for about 8 months	Alterations in alveolar macrophages; impaired cellular function	6
1.0 mg/m^3 for 3 or 6 months, 5 days weekly, 6 h daily; lungs examined	At both 3 and 6 months, there was a twofold to threefold increase in volume density of alveolar Type II cells; after 6 months, lungs had foci of pneumonia, suggesting a higher susceptibility to pulmonary infections due to a decrease in function of alveolar macrophages	22
Nickel carbonyl; 1.4 mg/L for 50 min	Alveolar cell degeneration within 5 days; LC80 (120 h)	8, 10
Nickel chloride; >0.2 mg/m^3 for about 8 months	Alterations in alveolar macrophages	6
Single intravenous injection; nickel chloride		
10 mg/kg BW	Transient hyperglycemia 1-4 h after injection	7
15 mg/kg BW	Pronounced hyperglycemia 1-4 h after injection, returning to normal after 24 h	7
15-20 mg/kg BW	Pancreas histopathology	7
Single subcutaneous injection; various nickel salts; 1,300 mg Ni/kg BW	Lethal	9
Laboratory white rat, *Rattus* sp.		
Dermal; nickel sulfate hexahydrate; dose equivalent to 40, 60, or 100 mg Ni/kg BW daily for 30 days (rats licked skin so exposure route may be oral in part)	No adverse effects in 40 mg/kg BW group. High dose groups had skin damage (atrophy, acanthosis, hyperkeratinization) and testicular damage abnormal seminiferous tubules, tubular lumens filled with degenerated sperm)	6,8,10
Diet		
Weanlings fed rations containing 0, 100, 500, or 1,000 mg Ni/kg, as nickel	At high doses (500, and 1,000 mg/kg), rats had depressed growth, low	38

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
acetate, for 6 weeks	hematocrit and hemoglobin, and low tissue cytochrome oxidase and alkaline phosphatase activities; the 1,000 mg/kg group (vs. controls) had elevated nickel concentrations—in mg Ni/kg DW—of 2.1 (0.9) in heart, 40.7 (5.0) in kidney, 4.0 (0.7) in liver, and 7.2 (1.6) in testes	
0, 100, 1,000, or 2,500 mg Ni/kg ration, as nickel sulfate hexahydrate, for 2 years	No histopathology in any group; at 1,000 and 2,500 mg Ni/kg ration, rats had depressed growth, lower liver weights, and increased heart weights	5
0, 250, 500, or 1,000 mg Ni/kg ration, as nickel sulfate hexahydrate, for 3 generations; equivalent to 0.7, 12.5, 25, or 50 mg Ni/kg BW daily; reproductive study	Higher incidence of stillborns and fetal mortalities noted only in the first generation at all nickel dietary levels; weanling body weight was lower at 1,000 mg Ni/kg ration in all generations	5,6,21
0.08 mg Ni/kg ration for 55 days	No adverse effects	2
250 mg Ni/kg ration for 16 months	Normal growth	16
1,000 mg Ni/kg ration (as nickel carbonate or nickel catalysts) for 8 weeks	Normal growth	10
1,000 mg Ni/kg ration for 13 days; juveniles	Altered blood chemistry, diminished food intake, and reduced growth within a few days	39
Dietary equivalent of 1, 25, or 100 mg/kg BW daily for 4 months; nickel chloride	Thyroid function affected; decreased iodine uptake at 1 mg/kg BW, increased at 25 mg/kg BW, and decreased at 100 mg/kg BW	7
Dietary equivalent of >1.4 mg Ni/kg BW daily for 2 years; nickel chloride or nickel sulfate	Decreased liver weight	6
Drinking water		
5 mg/L; lifetime exposure	No effect on growth or survival	35, 36
5 mg/L for 3 generations; diets contained 0.31 mg Ni/kg FW ration	Significant increase in mortality of young rats in all generations; significant increase in runts in first and third generations; litter size decreased with each generation; total number of rats reduced; few males were born in the third generation	35
225 mg/L for 4 months as nickel chloride	Depressed growth rate; lower serum triglyceride and cholesterol concentrations	13,40
Inhalation		
Nickel carbonyl ($Ni(CO)_4$)		
0.1 mg/L for 20 min	Some deaths after exposure	8
0.24 mg/L for 30 min	LC50 (0.2 h-6 days)	2, 8, 9
0.24-1.0 mg/L for 30 min	Lung histopathology within 10 days	10
0.9 mg/L for 30 min	LC80 (2 h-several months)	8
100 mg/L for 15 min	About 26% of the inhaled nickel was excreted in urine within 4 days; absorption estimated at 50%	10
160 mg/m^3 on days 7-8 of gestation or 300 mg/m^3 on day 7	Increased fetal mortality; reduced body weight in live pups; 16% incidence of fetal malformations	8

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
	(anophthalmia, microphthalmia, cystic lungs, hydronephrosis)	
Nickel chloride ($NiCl_2$); 0.05-5.0 mg/m^3	Significant decrease in iodine uptake	10
for 2 to 4 weeks	by thyroid	
Nickel dust; 15 mg/m^3; lifetime exposure	Increased frequency of adenoidal lesions and chronic sinus inflammation and ulceration	7
Nickel oxide (NiO)		
0.06 mg/m^3; lifetime exposure	Survival time decreased from 125 weeks in controls to 88 weeks; body weight loss after 13 months; alveolar proteinosis and marked lung enlargement	6
0.2 mg/m^3 for 1 year	Pneumonia and bronchial epithelial metaplasia	6
0.5 mg/m^3 for 1 month	Bronchial gland hyperplasia 20 months after exposure	6
1.6 mg/m^3 on gestation days 1-21	Decrease in fetal body weight	6
>3.9 mg/m^3 for as long as 13 weeks	Adverse respiratory effects	6
11.7 mg/m^3, 8 h daily, 5 days weekly, for 4 weeks	Significant increase in tumor necrosis factor for alveolar macrophages	24
23.6 mg/^{3} for 16 days	No deaths	6
Nickel subsulfide (Ni_3S_2)		
Equivalent to 0, 0.4, or 1.8 mg Ni/m^3; 6 h daily for as long as 22 days	The high dose group had reduced survival, nose and lung histopathology, and disrupted enzyme activity levels; survivors were lethargic and grew poorly. At day 22, nickel concentrations in lungs, in mg/kg FW, were<1.8 in controls, 12 in the low dose group and 34.0 in the high dose group	26
Equivalent to 0.11, 0.44, or 1.8 mg Ni m/^{3} for as long as 13 weeks; exposures were 6 h daily and 5 days weekly	Dose-dependent increase in pulmonary lesions; atrophy of the nasal olfactory epithelium at 0.44 mg/m^3 and higher	26
Equivalent to 0.73 mg/m^3 for 78 weeks plus 30 weeks of postexposure observation; exposure for 6 h daily and 5 days weekly	Pulmonary tumor growth (14% incidence in lung tumors vs. 1% in controls) and increased mortality (95% dead vs. 69% in controls)	6,25
7.3 mg/m^3 for 16 days	LC20	6
Nickel sulfate ($NiSO_4$)		
50 µg/rat	Half-time persistence in lung of 32 h; lung inflammatory responses disrupted lung enzyme activity	29
>0.1 mg/m^3 for as long as 13 weeks	Adverse respiratory effects	6
0.635 mg/m^3 for 16 days, 6 h daily	Induced lesions of olfactory epithelium but no measurable changes in olfactory	31

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
	function	
1.6 mg/m^3 for 16 days	No deaths	6
Single intramuscular injection, unless noted otherwise		
Metallic nickel; 110 mg/kg BW	Lowest toxic dose	2
Nickel acetate		
Males and females given 2.32 mg Ni/kg BW daily for 4 days	Males had inhibited testosterone levels and reduced growth, while females had increased uterine weights	7
420 mg/kg BW	Lowest toxic dose	2
Nickel chloride		
Females given 1.5-2.0 mg/kg BW daily on days 6-10 of gestation	Significant intrauterine mortality, but body weight of live pups was normal	8
Females given 2.0 mg/kg BW twice daily	No congenital abnormalities on days 6-10 of gestation	34
12 mg/kg BW to pregnant and nonpregnant females; tissues analyzed 24 h following injection	Relative tissue concentrations were kidney >serum > adrenal = lung = ovary > spleen = heart = liver > muscle. Nickel concentration in pituitary gland was significantly higher in pregnant rats	34
16 mg Ni/kg BW on day 8 of gestation	Reduction in number of live pups and diminished body weight of fetus on day 20 of gestation and of weanlings 4 to 8 weeks after birth; no developmental abnormalities	34
23-98 mg/kg BW	LD50 (7 days)	7,21,23,80
Nickel oxide		
7 mg Ni/kg BW	Significantly increased levels of serum alkaline phosphatase, amylase, aspartate transaminase, and lipoperoxide. Daily injections of copper-zinc superoxide dismutase prevented these changes	28
180 mg/kg BW	Toxic	2
Nickel subsulfide		
80 mg Ni/kg BW on day 6 of gestation	Reduction in mean number of live pups	34
90 mg/kg BW	Lowest toxic dose	2
Nickel sulfate; 12-16 mg/kg BW on day 8 of gestation	Reduction in mean number of live pups; reduced body weight in fetuses on day 20 of gestation and in pups 4-8 weeks after birth	8
Nickel sulfide; 7 mg/kg BW	Disrupted serum enzyme activity	28
Single intraperitoneal injection, unless indicated otherwise		
Nickel acetate		
8 mg/kg BW	Toxic	21
24 (19-28) mg/kg BW	LD50 (48 h)	7, 8
Nickel carbonyl; 13 mg/kg BW	LD50	8
Nickel chloride		
4 mg/kg BW	Tissue concentrations at 24 h	33

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
	(and at 15 min) after injection, in mg/kg FW, were 2.7 (16.1) in kidney, 0.3 (4.7) in liver, 1.2 (5.9) in blood, and 0.9 (1.4) in placenta	
6.0 (5.5-6.5) mg/kg BW	LD50 (7 days) for females pregnant 19 days	33
6.3 (5.6-7.1) mg/kg BW	LD50 (7 days) for females pregnant 12 days	33
8.0 mg/kg BW	Rapid transient increase in serum glucose and decrease in serum insulin	40
9.3 (8.5-10.2) mg/kg BW	LD50 (7 days) for virgin females	33
11-19 mg/kg BW	LD50 (7 days)	2, 7, 8
Nickelocene; 16-59 mg/kg BW	LD50, usually within 14 days	8, 21
Nickel oxide; >690 mg/kg BW	LD50 (3 days)	7
Nickel sulfate; 3 or 6 mg/kg BW daily for 7 or 14 days; killed 48 h after last injection	Highest nickel concentrations were in myocardium (5.7 mg/kg FW vs. 2.2 in controls) and spleen (2.1 vs. 0.6), followed by kidney, bone, and other tissues	37
Single intrarenal injection of nickel subsulfide equivalent to 39 mg/kg BW	Pronounced erythrocytosis; increased hematocrit and reticulocyte count	30
Intratracheal injection		
Nickel chloride; 1.0 mg/kg BW; examined 6 and 72 h after injection	At 6 h, tissue nickel concentrations were elevated in kidneys, lungs, adrenals, liver, pancreas, spleen, heart, and testes, in that order; by 72 h, 90% of the nickel was excreted, mostly (75%) in the urine	7
Nickel oxide; >110 mg/kg BW	LD50 (72 h)	7
Single intravenous injection of nickel carbonyl		
11 mg/kg BW; day 7 of gestation	High incidence of fetal deaths and malformations; reduced body weight in live pups	8
22 mg/kg BW	LD50, usually within 14 days	8
65 mg/kg BW	Massive lung histopathology within 6 days	10
Single oral exposure, unless indicated otherwise		
Nickel acetate		
116-120 mg/kg BW	Toxic	21
304-410 mg/kg BW	LD50 (7 days)	7, 8
Nickel chloride		
0.35 mg/kg BW daily for 28 days	Hyperglycemia, decreased body weight, reduced food and water intake	6
8.6 mg/kg BW daily for 91 days	LD25; decreased body weight in survivors	6
116 mg/kg BW	Toxic	6, 21
285 mg/kg BW	LD50, usually within 14 days	7
Nickel fluoborate ($Ni(BF_4)_2$); 500 mg/kg BW	Lethal	2
Nickel hexahydrate; 8.5 mg/kg BW daily for 91 days	Death preceded by lethargy, ataxia, irregular breathing, hypothermia, salivation, squinting, and loose stools	6

Table. 9. Organism, route of exposure, dose, and other variables	Effect	Reference[a]
Nickel nitrate ($Ni(NO_3)_2$); 1,620 mg/kg BW	LD50, usually within 14 days	2
Nickelocene		
154 mg/kg BW	Toxic	21
471-525 mg/kg BW	LD50, usually within 14 days	8
Nickel sulfate		
25 mg/kg BW daily for 120 days	Infertility	8
66 mg/kg BW	LD50, usually within 14 days	6
Single subcutaneous injection		
Nickel carbonyl; 21 mg/kg BW	LD50 within several days	8
Nickel chloride		
10 or 20 mg/kg BW; young males; observed for 7 days	Increased prolactin levels that persisted for 4 days;increased insulin levels on days 1 and 2	8
11.9 mg/kg BW	5% dead	27
59.5 mg/kg BW given 16 h prior to sacrifice	Significant increase in hepatic glutathione S-transferase activity	32

[a] 1, O'Dell et al. 1970; 2, National Academy of Sciences 1975; 3, Stevens 1991; 4, Lin and Chou 1990; 5, Ambrose et al. 1976; 6, U.S. Public Health Service (USPHS) 1993; 7, USPHS 1977; 8, World Health Organization 1991; 9, Sunderman 1970; 10, U.S. Environmental Protection Agency (USEPA) 1980; 11, Waseem et al. 1993; 12, Scheiner et al. 1976; 13, Nielsen 1977; 14, USEPA 1975; 15, Weber and Reid 1969; 16, Ling and Leach 1979; 17, Smialowicz et al. 1984; 18, Graham et al. 1975; 19, Lu et al. 1981; 20, Hogan 1985; 21, USEPA 1985; 22, Hohansson et al. 1981; 23, Sunderman et al. 1983; 24, Morimoto et al. 1995; 25, Ottolenghi et al. 1974; 26, Benson et al. 1995; 27, Iscan et al. 1992; 28, Novelli et al. 1995; 29, Hirano et al. 1994; 30, Oskarsson et al. 1981; 31, Evans et al. 1995; 32, Iscan et al. 1993; 33, Mas et al. 1985; 34, Sunderman et al. 1978; 35, Schroeder and Mitchener 1971; 36, Schroeder et al. 1974; 37, Mathur et al. 1978; 38, Whanger 1973; 39, Schnegg and Kirchgessner 1976; 40, Clary 1975; 41, Ho and Furst 1973.

Nickel carbonyl ($Ni(CO)_4$) is the only nickel compound known to cause severe acute effects, such as pulmonary damage and death; acute toxic effects of other nickel compounds to mammals are a minor risk (Norseth and Piscator 1979; Sevin 1980; WHO 1991). In fatal cases, death occurs 3-13 days after exposure; recovery from nickel carbonyl poisoning usually occurs within 70 days after exposure, but sometimes may take up to 6 months (Sunderman 1970; Sevin 1980; WHO 1991). Nickel carbonyl is a volatile, colorless liquid formed when finely divided nickel or its compounds come into contact with carbon monoxide. It is unstable under atmospheric conditions, and if inhaled, nickel is deposited in a highly active form on the respiratory mucosa on contact. Nickel carbonyl is widely used commercially as a catalyst but is one of the most toxic gases encountered in industrial operations (Sunderman 1970; Norseth and Piscator 1979; USEPA 1980, 1986). Exposure to air containing more than 50 mg $Ni(CO)_4/m^3$ for 0.5-2.0 h may be fatal to humans (WHO 1991). Intraperitoneal injection of nickel carbonyl was the most toxic route of administration; for all routes of administration, LD50 values to various tested mammals ranged between 13 and 65 mg/kg BW (WHO 1991; Table 9). Nickel carbonyl toxicity is due, in part, to its volatility and lipophilicity (Sigel and Sigel 1988). Signs of nickel carbonyl poisoning—which strongly resemble those of viral pneumonia—include headache, vertigo, nausea, vomiting, insomnia, and irritability followed by an asymptomatic interval and then the onset of insidious, persistent signs that include chest pains, dry coughing, cyanosis, sweating, visual and gastrointestinal disturbances, severe weakness, paralysis of the hind limbs, and convulsions; the lungs are the primary target organs in all animals tested, although the liver, kidneys, adrenal glands, spleen, and brain are also affected (Sunderman 1970; Nielsen 1977; Mushak 1980; USEPA 1980, 1986; Norseth 1986; WHO 1991).

Adverse effects in mammals by inhalation of nickel compounds other than nickel carbonyl occur with aerosols of both soluble and insoluble nickel compounds (USEPA 1980). Inhalation of nickel by humans and other mammals produces respiratory, hepatic, renal, dermal, immune system, and body weight effects (WHO 1991; USPHS 1993). Respiratory effects of nickel include asthma, nasal septal perforations, chronic rhinitis and

sinusitis, and increased risk for chronic respiratory tract infections (USPHS 1977; USEPA 1986; WHO 1991); immunological, genotoxic, and carcinogenic effects were also observed (USPHS 1993). Lung reactions in the form of asthma were attributed to sensitization by nickel (Norseth and Piscator 1979). Insoluble forms of inhaled nickel are more persistent in lungs than are soluble forms, as judged by 90-day studies with nickel chloride (soluble) and nickel oxide (insoluble) given to rodents by intratracheal administration (English et al. 1981). Severity of respiratory toxicity was higher with increasing solubility of the nickel compound tested and not with increasing burden of nickel on the lung; insoluble nickel oxide had the lowest toxicity but the highest lung burden. Nickel sulfate was more toxic than nickel subsulfide, which was more toxic than nickel oxide (USPHS 1993).

Local effects noted in guinea pigs, rats, mice, and hamsters caused by inhalation of metallic nickel powder (15 mg/m^3), nickel subsulfide (0.97 mg/m^3), or nickel oxide (53 mg/m^3) include nasal sinus inflammations, ulcers, lung irritation, nickel accumulations in lungs, emphysema, and increased viral respiratory infections (Norseth 1986; WHO 1991). Rats inhaling nickel subsulfide at 2.5 mg/m^3 for 22 days had nasal and lung histopathology within 4 days and disrupted enzyme activities and elevated nickel accumulations within 7 days (Benson et al. 1995). Repeated inhalation of nickel subsulfide by rats for 3 months resulted in chronic inflammation in the lung and atrophy of the olfactory epithelium (Benson et al. 1995). Rats exposed via inhalation of nickel sulfate hexahydrate of 635 μg Ni/m^3 for 6 h daily over 16 days had no outward signs of toxicity; however, internal examination revealed lesions on the olfactory epithelium (Evans et al. 1995). Rats and mice died following inhalation exposure for 16 days to equal doses of nickel sulfate or nickel subsulfide, but not nickel oxide (USPHS 1993). Rats showed epithelial hyperplasia after inhalation exposure to aerosols of nickel chloride or nickel oxide and pulmonary fibrosis after inhalation exposure to nickel subsulfide; a similar syndrome was reported in rabbits after high level inhalation exposure to nickel-graphite dust (WHO 1991). Dogs exposed to nickel powder for 6 months by way of inhalation developed lung pneumosclerosis causing cardiac insufficiency (USPHS 1977). Rats exposed to airborne nickel dusts (100 μg Ni/m^3, 12 h daily for 2 months) had respiratory irritation (NRCC 1981). Single exposures of mice to 250 μg Ni/m^3 for 2 h depressed the humoral immune response (NRCC 1981). Rats exposed to 1,000 μg Ni dust/m^3 (5 days/week for 3-6 months) had high accumulations of nickel in the lungs and kidneys and interstitial fibrosis (NRCC 1981).

Nickel and nickel salts are comparatively nontoxic when taken orally because of homeostatic mechanisms that control nickel metabolism and limited intestinal absorption (Nielsen 1977). In cattle, young calves fed nickel carbonate at concentrations as high as 1,000 mg Ni/kg ration for 8 weeks had nephritic kidneys, with degree of severity increasing with dietary nickel level. However, dietary nickel did not affect growth or food consumption of calves or cause histopathology of the rumen, abomasum, duodenum, liver, or testes (O'Dell et al. 1970). Human and animal data indicate that death is unlikely from oral nickel exposure except when exposed accidentally to high levels (USPHS 1993). Oral exposure studies for humans were limited to acute intoxication and include death (due to cardiac arrest) and the effects of gastrointestinal (nausea, cramps, diarrhea, vomiting), hematological (increase in reticulocytes), hepatic (increase in serum bilirubin), renal (albuminuria), and neurological damage. A child that accidentally ingested 20.36 grams of Ni/kg BW as crystals of nickel sulfate died from heart failure (USPHS 1993). Oral LD50 doses of nickel chloride to rats produced depression of the nervous system, edema of the mucous membranes of the mouth and nose, diffusions from the oral cavity, lacrimation, bleeding from the nose, and diarrhea (USPHS 1977). Prior to death, rats were lethargic, ataxic, and with irregular breathing and cool body temperatures (USPHS 1993).

Nickel is a reproductive toxicant in animals. Specific effects of nickel on reproduction include degenerative changes in the testes, epididymis, and spermatozoa of rats; adverse effects on embryo viability of rats and hamsters; and delayed embryonic development of rodents (Smialowicz et al. 1984; USEPA 1986; USPHS 1993). Nickel salts given by injection cause intrauterine mortality and decreased weight gain in rats and mice (WHO 1991). Inhibited testosterone and reduced growth occur in male rats given 2.32 mg Ni/kg BW as nickel acetate via intramuscular injection. Females given the same treatment had increased uterine weights (USPHS 1977). Nickel given in drinking water of rats for three generations at concentrations which do not interfere with growth or survival (i.e., 5 mg/L) were intolerable for normal reproduction (Schroeder and Mitchener 1971). All generations of rats given nickel in drinking water had increased proportions of runts and increased neonatal mortality when compared to controls. In the third generation of nickel-treated rats, there were reductions in litter size and a reduction in the proportion of males (Schroeder and Mitchener 1971). Excess nickel also inhibits

prolactin secretion in rats. Because prolactin influences milk production, the observation that suckling pups from nickel-exposed dams were most severely affected lends support to the concept that nickel plays a role in lactation at the pituitary level (Nielsen et al. 1975b).

The most commonly observed toxic reaction to nickel and nickel compounds in the general human population is nickel dermatitis and skin sensitivity arising from dermal contact with metals containing nickel (Sunderman 1970; NAS 1975; Norseth and Piscator 1979; USEPA 1980, 1986; WHO 1991; USPHS 1993). Studies on occupational dermatitis—which is the most prevalent occupational disease—show that 8% of the cases are due to nickel (Sunderman et al. 1984). Nickel dermatitis in occupational exposure begins as an itching or burning in the web of the fingers, spreading to the fingers, the wrists, and the forearms; the eruption is similar to atopic dermatitis (NAS 1975; USEPA 1980, 1986). Once an individual is dermally sensitized to nickel, even minimal contact (i.e., 0.007-0.04 mg Ni/kg BW daily) by any route of exposure may elicit a reaction (USEPA 1980; WHO 1991; USPHS 1993; Hughes et al. 1994). Nickel, in fact, is the most common allergin tested in North America; about 1-5% of human males and 7-14% of females are contact sensitized to nickel (NAS 1975; Nielsen 1977; Sevin 1980; USEPA 1980, 1986; Sunderman et al. 1984; USPHS 1993; Ikarashi et al. 1996). Nickel contact hypersensitivity has been documented worldwide, with 10% of the female population and 1% of the male population affected. Of these, 40-50% have vesicular hand eczema that, in some cases, can be severe and lead to loss of working ability (WHO 1991). Nickel contact dermatitis is decreasing in occupational exposure, but increasing elsewhere due to increasing contact with nickel alloys in jewelry, coins, zippers, tools, pots and pans, stainless steel, detergents, prostheses, and certain hair dressings (NAS 1975; Nielsen 1977; USEPA 1980; Sunderman et al. 1984; WHO 1991; USPHS 1993). Nickel is a major allergen for women, and between 1970 and 1980 there was a two- to threefold increase in the number of cases (Sunderman et al. 1984). In recent years, the incidence of nickel allergy has increased disproportionately in young females due to an increased frequency of ear piercing by this group to accommodate nickel-plated jewelry (Ikarashi et al. 1996).

Although contact allergy to nickel is common in humans, experimental sensitization in animals is only successful under special conditions (WHO 1991). Dermal studies with nickel salts and small laboratory mammals show that primary nickel sensitization typically takes place beneath nickel-containing metal objects that are in contact with the skin for hours and exposed to friction and sweating; nickel is released from nickel-containing objects by the action of blood, sweat, or saliva; ionic nickel diffuses through the skin at sweat-duct and hair-follicle openings, with a special affinity for keratin; and that nickel subsequently binds to proteins, including animo and carboxyl groups of keratin and serum albumin (NAS 1975; USEPA 1980; USPHS 1993). Rats, guinea pigs, and rabbits absorbed and subsequently distributed 55-77% of nickel applied dermally (USPHS 1977, 1993). Dermal effects in animals after dermal exposure to nickel include distortion of the dermis and epidermis, hyperkeratinization, atrophy of the dermis, and biochemical changes (USPHS 1993; Ikarashi et al. 1996). For example, in rats treated dermally with more than 40 mg Ni/kg BW daily as nickel hexahydrate for 30 days, distortion of the epidermis and dermis occurred by day 15 and hyperkeratinization, vacuolization, hydropic degeneration of the basal layer, and atrophy of the epidermis occurred by day 30 (USPHS 1993). Skin irritation and death from nickel salts is reported in rabbits when nickel was applied dermally to abraded skin; no negative effects occurred in rabbits when the same dose was applied to intact skin (USPHS 1977). As was the case for humans, allergic reactions occur in laboratory animals after oral nickel challenge in sensitized individuals (USPHS 1993).

Nickel affects endocrine and enzymatic processes. Nickel-induced endocrine effects include inhibition of insulin production in pancreas, prolactin in hypothalamus, amylase excretion in parotid gland, and iodine uptake in thyroid (Mushak 1980; USEPA 1980, 1986; USPHS 1977; WHO 1991). Inhibition of enzyme activity by nickel is reported for RNA polymerase, ATPase, dialkyl fluorophosphate, and aspartase (NAS 1975). Inhibition of ATPase is associated with neurological abnormalities, such as tremors, convulsions, and coma; altered hormone release or action; and internal rearrangement of calcium ions in muscle that might cause paralysis and abnormal heart rhythm (Nielsen 1977). Nickel increases the duration of the action potential of excitable membranes of nerve and muscle tissues; this effect is competitive with and imitative of those of calcium (NAS 1975). Nickel hexahydrate at 14.8 mg Ni/kg BW disrupts hepatic monooxygenases; mice were more sensitive to this disruption than rats or guinea pigs (Iscan et al. 1992). Nickel is also reported to activate various enzymes, including bovine pancreatic ribonuclease, pancreatic deoxyribonuclease, carboxypeptidase, arginase, phosphoglucomutase (Sevin 1980), and calcineurin—a calmodulin-dependent phosphoprotein phosphatase (USEPA 1986). Nickel affects the activity of heme oxygenase, thereby affecting the absorption of hemoglobin iron. Nickel, like many other metals and metalloids, induces heme oxygenase activity in tissues of mice,

hamsters, and guinea pigs in a dose-related manner (Sunderman et al. 1983).

Systemic effects of nickel exposure include hyperglycemia, increased levels of plasma glucagon, damage to the pancreatic islet cells, decreased body weight, reduced food and water intake, and hypothermia (NAS 1975; USEPA 1980; USPHS 1993). Acute administration of nickel salts caused prompt hyperglucagonemia and subsequent hyperinsulinemia in rats, rabbits, and guinea pigs (WHO 1991). Nickel chloride given orally to young male rabbits at 500 µg daily for 5 months produced a decrease in liver glycogen and an increase in muscle glycogen, with prolonged hyperglycemia (NAS 1975). Nickel increased glucose metabolism in rats injected intratracheally with 0.5 mg ionic nickel. This phenomenon probably reflected the influence of nickel on the production or secretion of insulin through decreased production of pituitary hormone secretions—specifically, prolactin—which control insulin concentrations (USPHS 1977). Nickel significantly affects the activity of hepatic glutathione S-transferases (GST); these compounds play important roles in the detoxification of electrophilic xenobiotics, such as nickel, epoxides, and diolepoxides (Iscan et al. 1993), and readily eliminate the cytotoxic products of lipid peroxidation, particularly the organic peroxides (Coban et al. 1996). The influence of nickel chloride on hepatic GST activity levels depends on the animal species tested, being depressed in mice, unchanged in rats, and increased in guinea pigs (Iscan et al. 1992). In humans, nickel toxicity is not related to GST depletion or increased lipid peroxidases in vitro, whereas in rat kidney, nickel toxicity may be due to GST depletion and stimulation of lipid peroxidases (Coban et al. 1996).

Nickel affects the immune, cardiac, and excretory systems. Nickel adversely affects the immune system by reducing host resistance to bacterial and viral infections, suppressing phagocytic activity of macrophages, reducing the number of T-lymphocytes (thereby suppressing the natural kill cell activity), and increasing susceptibility to allergic dermatitis (WHO 1991; USPHS 1993). In mice, nickel chloride suppresses the activity of natural killer cells within 24 h of a single intramuscular injection (USEPA 1986). Nickel-induced cardiovascular effects include vasoconstriction, inhibition of contraction by myocardial muscle, and a reduction in coronary vascular flow (USEPA 1986; WHO 1991; USPHS 1993). Nickel salts are demonstrably cardiotoxic in dogs (Sigel and Sigel 1988). Cats injected intravenously with $NiCl_2$ had altered heart rhythms, conductivity, and calcium metabolism (Nielsen 1977). Nickel is a nephrotoxin with greatest adverse effect on the glomerular epithelium of the kidney. Kidneys from mammals exposed to nickel showed renal tubular damage, protein loss, and weight changes (USPHS 1993).

Nickel accumulations in tissues and organs of mammals vary significantly with species, route of administration, sex, and general health. No significant accumulations of nickel were observed in liver or kidney of Holstein calves fed diets containing 1,000 mg Ni/kg ration for 21 weeks (Stevens 1992). In lactating dairy cows, no transfer of soluble nickel was observed from diet to tissues (Stevens 1992). In rats, guinea pigs, rabbits, sheep, dogs, and other species of mammals, nickel tends to accumulate in kidneys and other tissues after nickel exposure (as quoted in Eastin and O'Shea 1981). Nickel-poisoned rats had elevated accumulations primarily in myocardium (5.7 mg/kg FW vs. 2.2 in controls) and spleen (2.1 mg/kg FW vs. 0.6), followed by kidney, bone, and other tissues (Mathur et al. 1978). In rats, nickel accumulated mainly in lung and secondarily in heart tissues after intratracheal administration of nickel chloride; nickel was retained for at least 40 days after dosing (Novelli and Rodrigues 1991). In rodents, nickel accumulates in endocrine tissues, including the pituitary, adrenals, and pancreas (Mushak 1980; USEPA 1980). High nickel concentrations in the pituitary gland of rodents were associated with inhibition of insulin release and decreased prolactin secretion (Clary 1975). Rat weanlings fed diets containing 500 mg Ni/kg ration as nickel acetate show elevated nickel accumulations in plasma, erythrocytes, heart, liver, testes, and especially kidneys; high accumulations were associated with reductions in growth, hematocrit, hemoglobin, cytochrome oxidase, and alkaline phosphatase (Whanger 1973; Nielsen 1977). Male guinea pigs accumulated higher concentrations of nickel in hair than did females after exposure for 4 months to drinking water containing 2.5 mg Ni/L (Scheiner et al. 1976). Invading microorganisms can change the distribution of ^{63}Ni in mice infected with coxsackie B3 virus. Infected mice had high accumulations of ^{63}Ni in the pancreas and the wall of the ventricular myocardium. Healthy mice had almost no ^{63}Ni accumulations in these tissues, but residues were elevated in blood, kidney, and lung (Ilback et al. 1992).

Excretion of ingested nickel by rats, regardless of amount ingested, usually occurs through the feces within 48 h (Ho and Furst 1973). Most nickel administered to rats through a variety of routes, and irrespective of chemical form, is usually excreted within a few days; however, excretion is slower for nickel powder and from lungs (USPHS 1977). Nickel caused a twofold increase in urinary corticoid excretion in guinea pigs (USPHS

1977), increased urinary excretion of protein in rats (USPHS 1977), and increased urinary excretion of B-2-macroglobulin in nickel refinery workers (USPHS 1993). Nickelemia was associated with increased urinary B-2-macroglobulin levels, and 5 of 11 workers with urinary nickel concentrations more than 100 µg/L had increased urinary B-2-macroglobulin (>240 µg/L; USPHS 1993).

Proposed Criteria and Recommendations

While nickel may be carcinogenic, perhaps in all forms, there is little or no detectable risk in most sectors of the nickel industry at current exposure levels, including in some processes that had previously been associated with very high lung and nasal cancer risks (WHO 1991). More research is in progress to clarify the hazards of nickel to humans, including chronic inhalation carcinogenicity studies of nickel subsulfide, nickel oxide, and nickel sulfate hexahydrate in rats and mice (USPHS 1993). Nevertheless, additional research on nickel-induced cancer has been proposed, including research on (1) route of administration (USPHS 1993); (2) oxidative state of nickel (Kasprzak 1987); (3) effect of nickel on nucleic acid synthesis (Sunderman 1981); (4) interaction effects with asbestos (USEPA 1980), zinc and magnesium (Furst and Radding 1980), tobacco smoke (NRCC 1981), and agents thought to inhibit nickel carcinogenesis, such as manganese, copper, and aluminum (Furst and Radding 1980); (5) role of diet in nickel carcinogenesis (Furst and Radding 1980) and specificity and mechanism of uptake of nickel ion from the gastrointestinal tract (Hausinger 1993); and (6) nickel immunosuppressive mechanisms, especially effects of nickel on natural killer cell activity and the relation between suppression of these cells and the known carcinogenesis of nickel compounds (Smialowicz et al. 1984). Large-scale studies are needed to establish the upper limits of cancer risk from nickel (WHO 1991).

Humans have been shown to develop sensitivity to nickel (USPHS 1993). The use of nickel in products that may release the metal when in contact with the skin should be regulated (WHO 1991). Among various subgroups of the U.S. population who may be at special risk for adverse effects of nickel are those who have nickel hypersensitivity and suffer chronic flare-ups of skin disorders with frank exposure (USEPA 1986). The role of oral nickel exposure in dermatic responses by sensitive individuals suggests that nickel-limited diets resulted in marked improvement of hand eczema and that nickel added to the diets appeared to aggravate the allergic response (USEPA 1986). More research is needed on the role of nickel in contact dermatitis, including the role of oral nickel exposure, and the pathogenesis and therapy of nickel dermatitis (NAS 1975; Sunderman et al. 1984; USEPA 1986). Additional dermal exposure studies are needed to determine if testicular effects result from both oral and dermal exposure to nickel (USPHS 1993).

Animal experimental models of nickel-induced skin sensitivity are few and have been conducted only under very specialized conditions (USEPA 1986). Studies examining the mechanism of nickel contact sensitization and its extent in wildlife are needed (USPHS 1993). The importance of the surface properties and crystalline structure of nickel compounds in relation to their reactivity and protein-binding activities is well documented. It is therefore necessary to identify clearly the nickel compounds to which exposure occurs (Sunderman et al. 1984). Acute and chronic dermal and inhalation studies using all nickel compounds would determine if certain compounds are more effective in eliciting allergic dermatitis (USPHS 1993).

To protect terrestrial vegetation against decreased growth and other toxic effects, nickel residues in leaves should contain less than 44 to less than 50 mg/kg DW, soils should contain less than 50 to less than 250 mg Ni/kg DW, and sewage sludge applied to agricultural soils should be limited to 30-140 kg Ni/surface ha at the low end and 50-560 kg/ha at the high end (Table 10). Research is needed on the direct effects on vegetation of nickel from airborne deposition, the effects of soil acidification on mobility and toxicity of nickel in soil, differences in nickel metabolism between tolerant and nickel-sensitive plants (NRCC 1981), and on the interactions of nickel and organic acids in nickel-accumulating plants and in the surrounding soils (Lee et al. 1978).

To protect freshwater plants and animals against nickel, a proposed range of less than 25 to 96 µg total recoverable Ni/L is recommended by various authorities (Table 10). This range will protect most species of freshwater biota; however, certain species have reduced survival within this range, including embryos of rainbow trout (*Oncorhynchus mykiss*) at 11 µg/L (Birge and Black 1980), daphnids (*Ceriodaphnia dubia*) at 13 µg/L (Schubauer-Berrigan et al. 1993), and embryos of the narrow-mouthed toad (*Gastrophryne carolinensis*) at 50 µg/L (Birge and Black 1980; USEPA 1980). Mixtures of metals are additive or more-than-additive in toxicity and, in some cases, will exceed the recommended water quality criteria based on the individual metals. Such additive effects were demonstrated for daphnids and rainbow trout using water quality criteria developed in the

Netherlands for mixtures of nickel salts and those of arsenic, cadmium, chromium, copper, lead, mercury, or zinc (Enserink et al. 1991). To protect marine life, the 24-h average for total recoverable Ni/L should not exceed 7.1 μg/L, and the maximum concentration should not exceed 140 μg/L at any time (Table 10). The maximum concentration level for marine life protection needs to be reexamined because 30 μg Ni/L adversely affects growth of marine diatoms (Dongmann and Nurnberg 1982), 56 μg/L results in nickel accumulations in mussels (Friedrich and Filice 1976), 58 μg/L causes abnormal sea urchin development (Timourian and Watchmaker 1972), and 59 μg/L has adverse effects on motility of sperm of sea urchins (Timourian and Watchmaker 1977). In aquatic systems, research is needed to determine the mechanisms of nickel toxicity to biota, the transport of nickel, the interaction of nickel with other inorganic and organic chemicals, and the mobility of nickel in sediments under various environmental conditions (NRCC 1981).

Table 10. Proposed nickel criteria for protection of natural resources and human health.

Table 10. Resource, criterion, and other variables Aquatic life, freshwater	**Effective nickel concentration**	**Reference a**
Sediments		
Great Lakes		
Safe	Less than 20 mg/kg dry weight (DW)	1
Moderately polluted	20-50 mg/kg DW	1
Heavily polluted	More than 50 mg/kg DW	1
Wisconsin; for disposal in water	Less than 100 mg/kg DW	1
Water		
Canada; safe level	Less than 25 µg/L	2
Rainbow trout, *Oncorhynchus mykiss*; safe level	Less than 29 µg/L	3
Toxic effects expected	30-50 µg/L	4
Ontario, Canada; from sediment disposal in water; final water concentration	Less than 50 µg/L	1
The Netherlands; safe level	Less than 50 µg/L	5
United States; water hardness of 50 mg $CaCO_3$/L	24-h average not to exceed 56 µg total recoverable Ni/L; maximum concentration not to exceed 1,100 µg/L at any time	6
Sweden; safe level	Less than 80 µg/L	7
United States; water hardness of 100 mg $CaCO_3$/L	24-h average not to exceed 96 µg total recoverable Ni/L; maximum concentration not to exceed 1,800 µg/L at any time	6
United States; water hardness of 200 mg $CaCO_3$/L	24-h average not to exceed 160 µg total recoverable Ni/L; maximum concentration not to exceed 3,100 µg/L at any time	6
Aquatic life, marine		
Water	24-h average not to exceed 7.1 µg total recoverable Ni/L; maximum concentration not to exceed 140 µg/L at any time	6
Birds		
Diet		
Domestic chicken, *Gallus* sp.; to prevent nickel deficiency in chicks	More than 50 µg/kg ration	8,9,10
Mallard, *Anas platyrhynchos*		
Ducklings; no adverse effects	Less than 200 mg/kg ration	4
Adults; no adverse effects	Less than 800 mg/kg ration	4
Adults; adverse effects	More than 800 mg kg fresh weight (FW) ration	11
Tissue concentrations		
Adverse effects expected; most species		
Kidney	More than 10 mg/kg DW	4

Table 10. Resource, criterion, and other variables Aquatic life, freshwater	Effective nickel concentration	Reference a
Liver	More than 3 mg/kg DW	4
Internal organs, most species		
Normal	Less than 3 mg/kg DW	4
Nickel-contaminated environments	As much as 30 mg/kg DW	4
Mallard; liver or kidney; significant exposure to dietary nickel that may be harmful	More than 1.0 mg/kg FW	11
Crops and other terrestrial vegetation		
Plant residues		
Alfalfa, *Medicago sativa*		
Normal	0.3-3.2 mg/kg DW	12
Decreased growth	44.0 mg/kg DW	12
Terrestrial vegetation		
Hyperaccumulator plants	More than 1,000 mg/kg DW	13
Most species		
Normal	0.05-5.0 mg/kg DW	13
Toxic	More than 50 mg/kg DW	13
Sewage sludge; maximum addition to agricultural soils		
Europe	30-75 kg/ha	1
South Africa	200 mg/kg DW	24
United States; soils with low exchange capacity vs. soils with high exchange capacity		
Maryland	140 kg/ha vs. 280 kg/ha	1
Massachusetts	56 kg/ha vs. 112 kg/ha	1
Minnesota and Vermont	56 kg/ha vs. 112-224 kg/ha	1
Missouri	140 kg/ha vs. 280-560 kg/ha	1
New York, all soils	34-50 kg/ha	1
Oregon	50 kg/ha vs. 100-200 kg/ha	1
Wisconsin	50-100 kg/ha vs. 150-200 kg/ha	1
Soils; suitability for crop production		
Canada; Alberta; acidic soils; acceptable	Less than 250 mg/kg DW	1
The Netherlands		
Background	50 mg/kg DW	1
Moderate contamination	100 mg/kg DW	1
Unacceptable and requires cleanup	More than 500 mg/kg DW	1
Russia; maximum acceptable concentration; extractable by ammonium acetate buffer at pH 4.6	4.0 mg/kg	1
South Africa, no phytotoxicity or elevated nickel concentrations in crops	38 mg/kg DW	24
United States; New Jersey; acceptable	Less than 100 mg/kg DW	1
Mammals, except humans		
Air		
Laboratory white rat, *Rattus* sp.		
Adverse effects; nickel sulfate	More than 0.1 mg/m^3	9
No adverse effects		
Nickel refinery dust	Equivalent to less than 0.84 mg/kg BW daily	9
Nickel subsulfide	Equivalent to less than 1.7 mg/kg BW daily	9
Nickel sulfate	Less than 0.1 mg/m^3	9
Rodents, *Mus* spp., *Rattus* spp.		

Table 10. Resource, criterion, and other variables Aquatic life, freshwater	**Effective nickel concentration**	**Reference a**
Adverse effects; nickel oxide, nickel sulfate	More than 0.02 mg/m^3	14
No adverse effects; nickel chloride, nickel subsulfide	Less than 0.1 mg/m^3	4
Diet		
To prevent deficiency		
Rats, *Rattus* spp.	More than 50 µg/kg ration	9, 10, 15
Ruminants (*Bos* spp.), swine (*Sus* spp.)	More than 100 µg/kg DW ration[b]	9, 10
No observable adverse effects during chronic exposure		
Cattle, *Bos* spp.	Less than 0.5 mg/kg DW ration	10
Dogs (*Canis* sp.), rats (*Rattus* spp.), monkeys (*Macaca* spp.)	Less than 1.0 mg/kg ration	4
Rat	Equivalent to 16.7 µg/kg BW daily[c]	9
Various species	Less than 100 mg/kg ration, equivalent to 0.8 to less than 40.0 mg/kg BW daily	4
Adverse effects expected		
Cattle		
Adults	More than 50 mg/kg ration	16
Calves	More than 5 mg/kg ration, equivalent to more than 0.16 mg/kg BW daily	4,16
Dogs	Equivalent to more than 1.3 mg/kg BW daily	14
Mammals, most species	More than 500 to 2,500 mg/kg diet, equivalent to 10-50 mg Ni/kg BW daily	4
Drinking water		
Adverse effects observed		
Rat	5 mg/L, equivalent to 0.35 mg/kg BW daily	4
Most species	200-225 mg/L	4
Tissue residues		
Evidence of significant nickel exposure		
Kidney	More than 10 mg/kg DW	4
Liver	More than 3 mg/kg DW	4
Human health		
Air		
Cancer risk		
Increased risk; soluble nickel compounds	More than 1 to 2 mg/m^3	13
No increased risk; metallic nickel	Less than 0.5 mg/m^3	13
Industrial plant; United States; nickel carbonyl		
Safe	Daily average less than 1.0 µg/L; single air sample less than 40 µg/L	17
Discontinue operations	More than 1 to 5 µg/L daily average; single air sample more than 200 to 2,000 µg/L	17
Shut down plant	Daily average more than 5 µg/L; single air sample more than 2,000 µg/L	17
Outside industrial plant; nickel carbonyl		
Acceptable	Less than 0.3 µg/L monthly average	17
Shut down plant	More than 1.0 µg/L monthly average	17

Table 10. Resource, criterion, and other variables Aquatic life, freshwater	Effective nickel concentration	Reference a
Safe		
Canada		
Soluble nickel compounds	Less than 0.1 mg/m^3	18
Sparingly soluble nickel compounds	Less than 1.0 mg/m^3	18
Nickel carbonyl	Less than 0.12 mg/m^3 (equivalent to less than 0.35 mg $Ni(CO)_4/m^3$)	18
Former Soviet Union		
Nickel metal, nickel monoxide and sulfide dust, soluble nickel compound	Less than 0.5 mg/m^3	19
Nickel carbonyl	Less than 0.005 mg/m^3	19
Germany; nickel carbonyl	Less than 0.7 mg/m^3	19
Sweden; nickel metal	Less than 0.01 mg/m^3	19
United States		
Nickel carbonyl	Less than 0.007 mg/m^3	19
Nickel metal and relatively insoluble nickel compounds; 8 h daily, 40 h weekly	Less than 1.0 mg/m^3	6, 9, 19
Inorganic nickel in workplace (elemental and all nickel compounds except organonickel compounds with a covalent C-Ni bind, such as nickel carbonyl); 10-h work shift, 40-h workweek, over a working lifetime	Less than 0.015 mg/m^3	20
Water soluble nickel compounds; 8 h daily, 40 h weekly	Less than 0.1 mg/m^3	9 ,19
Oral, via diet and drinking water		
Safe chronic exposure via diet or drinking water; soluble nickel compounds	Less than 0.002 mg/kg BW daily	9
Diet; Australia; marine fish muscle; acceptable concentration	Less than 1.0 mg/kg FW	21
Drinking water		
Acceptable daily intake for 70-kg person (with a safety factor of 1,000)	0.031mg daily (equivalent to 0.443µg/kg BW daily)	6
Concentrations developed for noncarcinogenic effects		
Daily intake, lifetime exposure, 70-kg adult (safety factor of 100)	Less than 350 µg/L	15
Daily intake, 10-day health advisory for 10-kg child (with safety factor of 100)	Less than 1.0 mg/L	15
Daily intake, 10-day health advisory for 70-kg adult with safety factor of 100)	Less than 3.5 mg/L	15
Water containing edible fishery products		
From ingestion through water and nickel-contaminated fishery products	Less than 13.4 µg total recoverable Ni/L	6
From consumption of fish and shellfish products alone	Less than 101.1 µg/L	6
Tissue residues		
Plasma; total nickel; nickel workers; considered elevated	More than 11.9 µg/L	22
Serum; total nickel		

Table 10. Resource, criterion, and other variables Aquatic life, freshwater	Effective nickel concentration	Reference a
Normal	Less than 2.6 µg/L, excretion of 2.6 µg daily	22
Elevated (near nickel mine)	More than 4.6 µg/L, excretion of 7.9 µg daily	22
Urine; nickel carbonyl		
Mild exposure	Less than <0.1 mg/L during the first 8 h after exposure	22,23
Significant exposure	More than 0.1 mg/L during the first 8 h after exposure	23
Urine; total nickel; nickel workers; considered elevated	More than 129 µg/L	22

a 1, Beyer 1990; 2, Rutherford and Mellow 1994; 3, Nebeker et al. 1985; 4, Outridge and Scheuhammer 1993; 5, Enserink et al. 1991; 6, USEPA 1980; 7, Sreedevi et al. 1992a; 8, Nielsen et al. 1975a; 9, USPHS 1993; 10, Hausinger 1993; 11, Cain and Pafford 1981; 12, Jenkins 1980b; 13, WHO 1991; 14, Hughes et al. 1994; 15, USEPA 1985; 16, Stevens 1991; 17, NAS 1975; 18, NRCC 1981; 19, Sevin 1980; 20, USPHS 1977; 21, Sharif et al. 1993; 22, Norseth and Piscator 1979; 23, Norseth 1986; 24, Steyn et al. 1996.

b Elevated requirement may reflect increased use by rumen bacteria.

c Based on no observable adverse effects during chronic exposure to diets containing 100 mg Ni (as soluble salts) per kg ration (=5 mg Ni/kg BW daily) divided by uncertainty factor of 300.

To protect birds, diets should contain at least 50 μg Ni/kg ration to prevent nickel deficiency but less than 200 mg Ni/kg ration in the case of young birds and less than 800 mg/kg ration in the case of adults to prevent adverse effects on growth and survival (Table 10). Nickel residues in avian kidneys in excess of 10 mg/kg DW or in liver in excess of 3 mg/kg DW are sometimes associated with adverse effects (Outridge and Scheuhammer 1993); however, nickel accumulates in kidneys of mallards (*Anas platyrhynchos*) at dietary concentrations as low as 12.5 mg Ni/kg ration (Eastin and O'Shea 1981). In general, tissue concentrations of nickel were not reliable indicators of potential toxicity in mammals and birds because adverse effects, including death, frequently occurred in the absence of elevated tissue nickel concentrations (Outridge and Scheuhammer 1993). For monitoring birds, analysis of kidneys, bone, and feathers is most likely to reveal elevated exposure to environmental nickel contamination; nickel concentrations in liver and spleen often do not reflect elevated exposure (Outridge and Scheuhammer 1993).

To protect humans and other mammals, proposed air quality criteria range from 0.01 to less than 1.0 mg/m^3 for metallic nickel and slightly soluble nickel compounds, 0.015-0.5 mg/m^3 for water-soluble nickel compounds, and 0.005-0.7 mg/m^3 for nickel carbonyl (Table 10). Inhalation of nickel subsulfide concentrations (0.11-1.8 mg Ni/m^3) near the current threshold limit value of 1 mg Ni/m^3 can produce detrimental changes in the respiratory tract of rats after only a few days of exposure (Benson et al. 1995). Additional animal studies are recommended to identify minimally effective inhalation exposure levels for the various nickel compounds (USPHS 1993). Continued monitoring of nickel refining, nickel-cadmium battery manufacture, and nickel powder metallurgy installations is recommended because ambient air levels of bioavailable nickel at these installations in excess of 1 mg/m^3 can sometimes still be found (NAS 1975; Sevin 1980; Sunderman et al. 1984; Chau and Kulikovsky-Cordeiro 1995).

Most species of mammals had normal growth and survival during chronic exposure to diets equivalent to 0.8-40 mg Ni/kg BW daily (Outridge and Scheuhammer 1993). Reduced growth and survival sometimes occurred when sensitive species of wildlife were fed diets containing 500-2,500 mg Ni/kg ration, equivalent to 10-50 mg Ni/kg BW daily (Outridge and Scheuhammer 1993). Proposed criteria for nickel by way of the diet or drinking water range from 2 μg total Ni/kg BW daily (USPHS 1993) to 443 μg total Ni/kg BW daily (USEPA 1980) for soluble nickel compounds, less than 1.0 mg Ni/kg FW diet, and less than 350 μg Ni/L drinking water (Table 10). Further research is needed to clarify the role of nickel in mammalian nutrition, including dietary requirements of nickel and identification of the chemical forms of nickel present in foods and their bioavailability

(NAS 1975; Sunderman et al. 1984; Hausinger 1993). Studies are needed on the absorption and cellular uptake, transport, and metabolism of well-characterized nickel species following different routes and types of administration (NAS 1975; WHO 1991; Hausinger 1993) and on the transfer of dietary nickel to tissues of lactating dams and juveniles (Stevens 1992). Because young female laboratory mice were more susceptible to dietary nickel than were adults, it is possible that no-observable-adverse-effect-levels (NOAELs) derived from adult animals may be inappropriately high for neonates and juveniles (Outridge and Scheuhammer 1993). Studies that compare the toxicokinetics of humans and animals concurrently could be helpful in determining which species of animal is the most appropriate model for assessing the effects of nickel in human health (USPHS 1993). Animal studies designed to examine neurological effects after inhalation or oral exposure are needed to determine, in part, if human exposure to nickel will cause permanent neurological damage (USPHS 1993).

Nickel affects reproduction of selected mammals. Drinking water containing 5 mg Ni/L—equivalent to 0.2-0.4 mg Ni/kg BW daily—had adverse effects on rat reproduction and iron metabolism (Outridge and Scheuhammer 1993). Dogs given the equivalent of 1.3 mg Ni/kg BW daily had decreased litter survival (Hughes et al. 1994). Nickel is known to cross the placental barrier and reach the fetus in mammals and humans. More information is needed on the effects of in utero nickel exposure in pregnant women (USEPA 1986; Chashschin et al. 1994). Such information may be obtained using appropriate animal models (USPHS 1977). Multigenerational inhalation studies are recommended to determine if developmental effects result from both inhalation and oral exposure (USPHS 1993).

Biomarkers of nickel exposure and effects include nickel concentrations in feces and urine and changes in serum antibodies and serum proteins (USPHS 1993). Levels of carnosine, a dipeptide, seem to reflect the extent of nickel-induced damage to olfactory mucosa of rats, although the rodent olfactory system is more resilient than is the human (Evans et al. 1995). Studies on the availability of trace levels of nickel in food and water and in air would be helpful to relate levels of nickel found in the hair, nails, blood, and urine to levels of nickel in internal organs (USPHS 1993). Nickel concentrations in human tissues now considered elevated include 4.6 μg/L in serum, 11.9 μg/L in plasma, and 100-129 μg/L in urine (Table 10). Treatment of mammals suffering from nickel poisoning is usually through administration of various classes of chelating agents, including dithiocarb (sodium diethyl-dithiocarbamate—the drug of choice in the management of nickel carbonyl poisoning), EDTA salts, BAL (2,3-dimercaptopropanol), and penicillamine (Norseth and Piscator 1979; Norseth 1986). In all cases, the agents accelerate urinary excretion of absorbed nickel before extensive tissue injury occurs (USEPA 1980).

The nomenclature of nickel compounds should be further standardized (WHO 1991). Analytical methods must be developed and standardized in order to facilitate speciation of nickel compounds in atmospheric emissions, biological materials, and in other environmental samples (NAS 1975; WHO 1991). Studies are needed to elucidate the biogeochemical nickel cycle on a global scale and determine its potential for long-range transport (WHO 1991).

Conclusions

Nickel is found in air, soil, water, food, and household objects; ingestion or inhalation of nickel is common, as is dermal exposure. Recent estimates suggest that as much as 28,100 tons of nickel are introduced into the atmosphere each year from natural sources and as much as 99,800 tons from human activities. In the atmosphere, nickel is mostly suspended onto particulate matter. In natural waters the dominant chemical species is Ni^{2+} in the form of $(Ni(H_2O)_6)^{2+}$. In alkaline soils the major components of the soil solution are Ni^{2+} and $Ni(OH)^{+}$; in acidic soils the main solution species are Ni^{2+}, $NiSO_4$, and $NiHPO_4$.

Nickel is an essential micronutrient for maintaining health in certain species of plants and animals. Nickel deficiency effects from dietary deprivation of nickel have been induced experimentally in many species of birds and mammals. To prevent nickel deficiency in rats and chickens, diets should contain at least 50 μg Ni/kg ration, while cows and goats require more than 100 μg Ni/kg rations, perhaps reflecting the increased use by rumen bacteria. Nickel deficiency is not a public health concern for humans because daily oral intake is sufficient to prevent deficiency effects.

Nickel contamination from anthropogenic activities occurs locally from emissions of metal mining, smelting, and refining operations; combustion of fossil fuels; nickel plating and alloy manufacturing; land disposal of sludges, solids, and slags; and disposal as effluents. Nickel concentrations in living organisms and abiotic materials tend to be elevated in the vicinity of nickel smelters and refineries, nickel-cadmium battery plants, sewage outfalls, and coal ash disposal basins.

Adverse effects of excess nickel are documented for bacteria, algae, yeasts, higher plants, protozoans, mollusks, crustaceans, insects, annelids, echinoderms, fishes, amphibians, birds, and mammals. To protect terrestrial vegetation against decreased growth and other toxic effects, nickel concentrations in leaves should contain less than 50 mg Ni/kg DW (and in some cases less than 44 mg Ni/kg DW), growing soils should contain less than 250 mg Ni/kg DW (and in some cases <50 mg Ni/kg DW), and sewage sludge applied to agricultural soils should be limited to 30-140 kg Ni/surface ha at the low end and 50-560 kg/surface ha at the high end. To protect freshwater plants and animals against nickel, a proposed range of less than 25 to 96 μg total recoverable Ni/L is recommended by various authorities; however, certain species have reduced survival within this range. To protect marine organisms, the 24-h average for total recoverable nickel per liter should not exceed 7.1 μg/L and the maximum concentration should not exceed 140 μg/L at any time; however, certain marine organisms show adverse effects to as little as 30 μg Ni/L.

To protect young birds against adverse effects of excess nickel on growth and survival, diets should contain less than 200 mg Ni/kg ration, and diets of older birds should contain less than 800 mg Ni/kg ration. Nickel concentrations in avian tissues in excess of 10 mg/kg DW kidney or 3 mg/kg DW liver are sometimes associated with adverse effects.

Toxic effects of nickel to humans and laboratory mammals are documented for respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, immunological, developmental, neurological, and reproductive systems. Nickel toxicity in mammals is governed by the chemical form of nickel, dose, and route of exposure. Mammalian exposure to nickel by inhalation or cutaneous contact was more significant than oral exposure. To protect humans and other mammals against respiratory effects, proposed air quality criteria are 0.01 to less than 1.0 mg/m^3 for metallic nickel and sparingly soluble nickel compounds and 0.005-0.7 mg/m^3 for nickel carbonyl. Most species of mammals tested had normal growth and survival during chronic exposure to dietary nickel (equivalent to 0.8-40 mg Ni/kg BW daily) and reduced growth and survival when fed diets containing 500-2,500 mg Ni/kg ration (equivalent to 10-50 mg Ni/kg BW daily). Proposed nickel criteria for sensitive species by way of the diet or drinking water now range from 2 to less than 443 μg total Ni/kg BW daily for soluble nickel compounds, less than 1.0 mg Ni/kg FW diet, and less than 350 μg Ni/L in drinking water. Nickel concentrations in human tissues now considered elevated include 4.6 μg/L serum, 11.9 μg/L plasma, and 100-129 μg/L urine; comparable data for mammalian wildlife are lacking.

Some forms of nickel are carcinogenic to humans and animals, but only when exposure is by the respiratory route. Toxic and carcinogenic effects of nickel compounds are associated with nickel-mediated oxidative damage to DNA and proteins and to inhibition of cellular antioxidant defenses. Some nickel compounds are weakly mutagenic in a variety of test systems, but much of the evidence is inconclusive or negative. In mammals, no teratogenic effects of nickel compounds occur by way of inhalation or ingestion, except from nickel carbonyl. Inhaled nickel carbonyl results in comparatively elevated nickel concentrations in lung, brain, kidney, liver, and adrenals and is the most hazardous form of nickel.

Overall, nickel is not an immediate threat to the health of plants, animals, and humans at environmentally encountered levels, except in the case of nickel carbonyl, and progress has been made toward minimizing or eliminating occupational nickel exposure.

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