FINAL

Report on Carcinogens Background Document for

Metallic Nickel and Certain Nickel Alloys

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Prepared for the:
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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary Statement

Metallic Nickel and Certain Nickel Alloys

Carcinogenicity

Metallic nickel and certain nickel alloys are *reasonably anticipated to be human carcinogens* based on evidence of malignant tumor formation at multiple tissue sites in multiple species of experimental animals.

Carcinogenicity testing in rodents indicates that metallic nickel produces tumors in a variety of studies when given by intratracheal instillation, or subcutaneous, intramuscular, or intraperitoneal injection. Tumors produced by intratracheal instillation of metallic nickel are primarily pulmonary adenocarcinomas while tumors produced by injection are most frequently sarcomas, indicating metallic nickel can induce both epithelial and connective tissue tumors. Tumors have been produced by metallic nickel exposures in both rats and hamsters.

A large number of nickel alloys exist that contain variable amounts of nickel as well as other metals like chromium, iron and cobalt. Although several studies indicate a carcinogenic effect for nickel alloys in rodents, interpretation of these results is complicated by the complex nature of the alloys involved. In general it appears that alloys of higher nickel content are carcinogenic in rodents when given by intratracheal instillation, or intraperitoneal or subcutaneous injection or when high content nickel alloys are directly implanted in the muscle or pierce the cartilaginous part of the ear pinna. The content of nickel in the alloy has been positively correlated with tumor production (Pott *et al.* 1989, 1990). Tumors have been observed after exposure to nickel alloys in rats, mice and hamsters. One of the nickel based alloys (which contained approximately 66% to 67% nickel, 13% to 16% chromium, and 6% to 7% iron) was tested independently by two laboratories, using different species (rats and hamsters), and different routes of administration (intratracheal instillation, intraperitoneal injection), and was carcinogenic in both studies.

The available studies of the carcinogenicity of metallic nickel and nickel alloys in humans are inadequate to make an evaluation.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Metallic nickel and nickel alloys probably are carcinogenic by dissolution and release of ionic nickel which is an active genotoxic and carcinogenic species. Human data indicate that elevated blood levels of nickel and chromosomal aberrations in bone marrow cells can occur after implantation of prosthetic devices comprised of metallic alloys containing nickel. Both soluble and insoluble nickel compounds are considered human carcinogens. Nickel exposure induces chromosomal aberrations, malignant cellular transformation,

mutation, chromosomal damage, chromatin condensation, DNA damage such as strand breaks, redox damage, and methylation changes and disrupted DNA repair.

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1 Introduction

Nickel and certain nickel compounds have been listed in the Report on Carcinogens (RoC) since 1980 as *reasonably anticipated to be human carcinogens*. In February 1998, the National Toxicology Program announced its intention to review nickel and nickel compounds for possible upgrading and/or listing for the first time in the RoC. The scientific review of nickel compounds for possible listing in the RoC was completed in 1998. The recommendation following that review was that nickel compounds be listed in the RoC as *known to be human carcinogens*. However, the new listing of nickel compounds in the RoC as *known to be human carcinogens* was deferred until the completion of the review of metallic nickel and nickel alloys. Nickel and certain nickel compounds remain listed in the Ninth RoC as *reasonably anticipated to be human carcinogens*.

This background document was prepared for the review of metallic nickel and nickel alloys for possible listing in the RoC. Nickel and nickel compounds, including metallic nickel and nickel alloys, were nominated for listing in the RoC by the National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP) RoC Review Group (RG1) based on the International Agency for Research on Cancer (IARC 1990) listing of nickel and nickel compounds as *carcinogenic to humans* (Group 1). Metallic nickel is currently listed as *reasonably anticipated to be a human carcinogen* in the ninth RoC (NTP 2000).

1.1 Chemical identification

Elemental nickel (Ni, atomic wt 58.69, CASRN 7440-02-0) is also known as Ni 233, Ni 270, nickel 270, nickel element, N1, C.I. 77775, Ni 0901-s, Ni 4303-s, NP 2, and rch 55/5.

Nickel alloys discussed in this review include the following:

ferronickel
nickel–aluminum alloys
nickel-containing steels
high-nickel alloys
alloys containing nickel used in prostheses

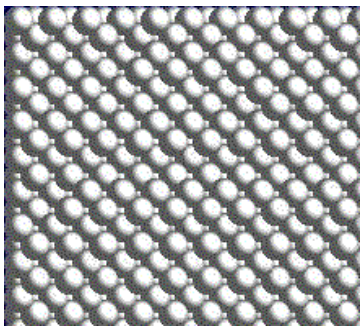
The U.S. Environmental Protection Agency (U.S. EPA) codes are K115 for nickel and P073 for nickel compounds. Shipping codes are UN1378 for nickel and UN2881 for nickel catalyst, dry.

1.2 Physical-chemical properties

Nickel is a silvery white metal, insoluble in water, with a boiling point of 2,730°C and a melting point of 1,455°C. Its appearance and odor depend upon the specific compound. The physical structure of nickel is cubic close-packed, as illustrated in Figure 1-1. It is

hard, malleable, ductile, somewhat ferromagnetic, and a fair conductor of heat and electricity. The physical and chemical properties of nickel are listed in Table 1-1.

Alloys are substances composed of two or more metals, or sometimes a metal and a nonmetal, which have been mixed intimately by fusion, electrolytic deposition, or other means (Dresher and Poirier 1997). Nickel alloys reviewed in this document include alloys that contain nickel and other alloying elements in varying proportions. The most important alloying constituents are iron, chromium, copper, and molybdenum. There are two classes of alloys: (1) alloys that depend primarily on the inherent corrosion characteristics of nickel itself, along with some influence of the alloying elements, and (2) alloys that contain chromium as the passivating alloying element. Corrosion takes place in a liquid film on the surface of a metal. It is an oxidation-reduction reaction in which the aggressive species is reduced as the metal is oxidized. Presence of chromium in these alloys forms an unreactive (passive) layer on the metal's surface, thereby minimizing oxidation-reduction reactions with the environment. This passive layer is composed of a tightly adhering film of oxides and hydroxides of chromium.



Source: WebElements2000 (1999)

Figure 1-1. Physical structure of nickel

Table 1-1. Physical and chemical properties of metallic nickel

Property	Information	Reference
Atomic weight	58.69	Budavari *et al.* 1996, ChemFinder 1999
Color	lustrous white or gray metal	Budavari *et al.* 1996, Lide 1999, ChemFinder 1999
Odor	odorless	Lide 1999, HSDB 1988
Physical state	solid (metal)	Budavari *et al.* 1996, Lide 1999, ChemFinder 1999
Melting point (°C)	1,455	Budavari *et al.* 1996, Lide 1999, HSDB 1988

Property	Information	Reference
Boiling point (°C)	2,730	Budavari *et al.* 1996, Lide 1999, HSDB 1988
Density g/cc (at 20°C)	8.90	HSDB 1988
Vapor pressure (mm Hg at 1810°C)	1	HSDB 1988
Crystal system	cubic close-packed	WebElements 1999
Young's modulus (/GPa)	200	WebElements 1999
Solubility: Water at 20°C Acids (dilute) Alkalies (dilute)	 insoluble soluble soluble	Budavari *et al.* 1996, Lide 1999, HSDB 1988

Nickel base alloys are characterized by having a face-centered-cubic crystal structure. In general, these alloys have high ductility and toughness over a wide temperature range. Other properties, such as corrosion resistance, oxidation resistance, and mechanical strength, make them useful for a variety of industrial uses. The physical and chemical properties of some nickel alloys are listed in Table 1-2.

Table 1-2. Physical and chemical properties of nickel alloys

Compound	CASRN	RTECS #	Synonyms	Physical and chemical properties
Ferronickel	11133-76-9	NO4570000	iron alloy (base), nickel alloy (nonbase)	gray solid Combined properties of metallic iron, nickel, ammonia, and alkali hydroxide. Fe, Ni
Nickel–aluminum alloys	61431-86-5 37187-84-1	WI6800000	Ranel alloy, Raney nickel	gray black powder or cubic crystals Insoluble in water and ethanol. Important hydrogenation catalyst prepared by treating Ni-Al alloy with 25% caustic soda solution; contains hydrogen and residual aluminum; ignites spontaneously in air; remains active in storage under a solvent for about 6 months NiAl
Nickel-containing steels	12681-83-3	NO4570200	alloy 21-6-9, AMS 5656C, Armco 21-6-9, 21-6-9 austenitic steel, iron alloy (base), Nitronic 40, Nitronic 40 stainless steel, Pyromet 538, Stainless steel 21-6-9, Steel 21-6-9, 21-6-9 Stainless steel, 21-6-9 Steel	Fe 60-69, Cr 18-21, Mn 8-10, Ni 5-7, Si 0-1, N 0.2-0.4, C 0-0.1, P 0-0.1
High nickel alloys	12605-70-8	QR6126310	Chromel C, 06Kh15N60, K15N60N, Nichrome, NiCr 60/15, PNKh, Tophet C	Ni 57-62, Fe 22-28, Cr 14-18, Si 0.8-1.6, Mn 0-1, C 0.0.2
	11121-96-3	NO4570100	AFNOR ZFeNC45-36, AISI 332, Alloy 800, Incoloy alloy 800, JIS NCF 8000, NCF Steel, NCF 800 HTB, Pyromet 800, Sanicro 31, Thermax 4876, TIG N800	Fe 39-47, Ni 30-35, Cr 19-23, Mn 0-1.5, Si 0-1, Cu 0-0.8, Al 0-0.6, Ti 0-0.6, C 0-0.1
	12675-92-2	GF9100000	Haynes alloy No 188	Ni(Co)
	11105-19-4	QR6126315	Alloy 400, H3261, Monel alloy 400, Monel (NiCu30Fe)	Ni 63-70, Cu 25-37, Fe 0-2.5, Mn 0-2, Si 0-0.5, C 0-0.3

Compound	CASRN	RTECS #	Synonyms	Physical and chemical properties
Titanium-6 percent aluminum-4 percent vanadium alloy	na	na	Ti-6-Al-4-V	< 0.2 % Ni by weight (used for prostheses)
Cobalt chromium molybdenum alloy	na	na	Co-Cr-Mo	< 0.1 % Ni by weight (used for prostheses)
Stainless-steel alloy	na	na	Fe-Cr-Ni	na
Cobalt chromium nickel tungsten alloy	na	na	Co-Cr-Ni-W	na
solid 316L	na	na	na	13.77% nickel, 65.2% iron, 17.2% chromium, 2.46% molybdenum, 0.47% manganese, 0.46% silicon, 0.24% copper, 0.11% cobalt, 0.10% phosphorus, 0.03% sulfur, 0.02% carbon
Powdered 316L	na	na	na	13.4% nickel, 67.8% iron, 16.1% chromium, 2.42% molybdenum, 0.11% manganese, 0.11% cobalt, 0.07% copper, 0.064% N, 0.024% carbon, 0.015% sulfur
CoCrWNi wire	na	na	na	12.44% nickel, 46.8% cobalt, 19.63% chromium, 13.76% tungsten, 3.78% iron, 2.21% magnesium, 1.39% silicon
CoCrWNi wire	na	na	na	10.36% nickel, 51% cobalt, 19.79% chromium, 14.47% tungsten, 2.35% iron, 1.67% manganese, 0.27% silicon, 0.09% carbon, 0.02% sulfur, 0.013 phosphorus
solid $MP_{35}N$	na	na	na	36.1% nickel, 32.5% cobalt, 20.0% chromium, 9.4% molybdenum, 1.5% iron, 0.74% titanium, 0.12% carbon, 0.09% silicon, 0.03% manganese
powdered $MP_{35}N$	na	na	na	35.4% nickel, 33.0% cobalt, 21.8% chromium, 8.7% molybdenum, 0.7% titanium, 0.4% iron
Neptune	na	na	na	63.36% nickel, 20.95% chromium, 8.40% molybdenum, 1.73% iron, 1% other (niobium, aluminum, silicon, manganese, titanium)
Rexalloy	na	na	na	67.21% nickel, 12.88% chromium, 6.76% molybdenum, 5.18% iron, 7.04% other (gallium, silicon, manganese, cobalt)

Compound	CASRN	RTECS #	Synonyms	Physical and chemical properties
Regalloy	na	na	na	71.20% nickel, 15.89% chromium, 4.50 molybdenum, 0.10% iron, 0.57% beryllium, 7.59% other (3.31% aluminum and silicon, 4.28% manganese)
Vera Bond	na	na	na	77.36% nickel, 12.27% chromium, 4.84% molybdenum, 0.14% iron, 1.67% beryllium, 2.76% other (aluminum, cobalt, titanium, silicon)

Source: IARC 1990, RTECS 2000, Urban *et al.* (2000)

na: not available.

1.3 Identification of metabolites

Nickel, being an element, is indivisible and thus cannot be metabolized *per se*. However, it is converted to Ni^{2+} in the target cells, where the ions may enter the nucleus and bind to nucleoproteins. Ionic nickel may also loosely bind to DNA (see Section 6). The crystal structure, particle size, surface area, and solubility of the nickel compound may be related to the carcinogenicity mechanism.

2 Human Exposure

2.1 Use

Nickel has many uses in industry because of its unique properties. The majority (~80%) of all nickel is used in alloys, because it imparts such properties as corrosion resistance, heat resistance, hardness, and strength (ATSDR 1997). Currently, the principal uses of nickel are in the production of stainless steel, copper-nickel, and other corrosion-resistant alloys. Pure nickel metal is used (see Table 2-1) in plating, as a chemical catalyst, and in the manufacture of alkaline batteries, coins, welding products, magnets, electrical contacts and electrodes, spark plugs, machinery parts, and surgical and dental prostheses (HSDB 1988, IARC 1990).

Table 2-1. Pattern of U.S. consumption of nickel in 1983

Use	Consumption (%)
Transport	
Aircraft	10.3
Motor vehicles and equipment	10.2
Ship and boat building and repairs	4.3
Chemicals	15.6
Petroleum	8.2
Fabricated metal products	8.8
Electrical	10.7
Household appliances	7.9
Machinery	7.2
Construction	9.7
Other	7.1

Source: Sibley 1985

There are several categories of nickel alloys, based on the primary metal mixed with nickel (see Table 1-3). Monel alloys, composed of copper and nickel, are used mostly for industrial plumbing, marine equipment, petrochemical equipment, heat exchangers, pumps, and electrodes for welding. The alloy used to make coins contains 75% copper and 25% nickel. Nichrome alloys (composed of nickel and chromium) are used for heating elements. Hastelloy alloys are composed of nickel, chromium, iron, and molybdenum and are used with acids and salts, because they provide oxidation and corrosion resistance. Nickel-based superalloys are used in gas-turbine engines, owing to their high-temperature strength and creep and stress resistance. Nickel silvers, alloys containing silver, nickel, zinc, and copper, are used in coatings on tableware and as electrical contacts. Raney nickel (50% Ni and 50% Al) is used as a catalyst in hydrogenation reactions. Stainless steel may contain up to 25% to 30% nickel, but it typically contains 8% to 10%. Alloy steels contain approximately 0.3% to 5% nickel. Most permanent magnets are made of iron and nickel alloys (ATSDR 1997).

2.2 Production

Nickel is refined from either sulfide or silicate-oxide ore. These ores generally contain $\leq$ 3% nickel. Magmatic sulfide ores are mined underground or by open-pit methods. Pentlandite $(Ni, Fe)_9S_8$, is the principal sulfide ore; the known largest deposit is in Ontario, Canada, and substantial deposits also are found in Minnesota, South Africa, Russia, Finland, and western Australia. Silicate-oxide ores, or garnierites, originate in humid tropical regions (current or former) and are surface mined by open-pit methods. Nickel deposits in Oregon (U.S.) are the largest known source of nickel in the world, followed by Cuba which has 35% of all nickel reserves (IARC 1990, ATSDR 1997).

Sulfide ores are processed by a number of pyrometallurigical processes: roasting, smelting, and converting. Sulfur and iron are removed to produce a sulfur-deficient copper-nickel matte. The nickel in the matte consists primarily of nickel subsulfide, especially after roasting and converting. Nickel is refined electrochemically or by the carbonyl process after physical separation of the nickel and copper sulfides. The sulfide also can be roasted to form a nickel oxide sinter that is used directly in steel production. Lateritic ores are processed by pyrometallurgical or hydrometallurgical processes. Sulfur usually is added to the oxide ore to produce an iron-nickel matte in smelting during the pyrometallurgical process. Smelting without the addition of sulfur produces a ferronickel alloy that can be used directly in steel production. Hydrometallurgical processes involve leaching with ammonia or sulfuric acid followed by selective precipitation of nickel (ATSDR 1997).

Alloys, such as stainless steel, are produced by melting primary metals and scrap in large arc furnaces. Carbon content and concentration of alloying metals are adjusted to desired levels. The melt is then cast into ingots or continuously into casting shapes. Steel production is similar to nickel alloy production, except that the melting and decarbonizing units are generally larger. Alloy production also makes greater use of vacuum melting and remelting (IARC 1990).

Production of nickel in the United States stopped in 1986 after the main facilities, a mine and smelter in Oregon and a refinery in Louisiana, were shut down. In 1989, the Glenbrook Nickel Company purchased the Hanna mine and smelter in Riddle, Oregon, and restarted mining and smelting operations. Mining operations were phased out, and ore was imported from New Caledonia (ATSDR 1997) until the nickel smelter and the associated port facilities in Coos Bay, Oregon, were closed in early 1998. It was estimated that existing ore supplies were consumed by March 1998 (Cominco 1998).

Secondary nickel production from scrap is now a major source of nickel for industrial use. In 1988, 59,609 short tons of nickel were produced from ferrous scrap, and 3,700 short tons of nickel were produced from non-ferrous scrap. Secondary recovery of ferrous scrap was higher in 1988 than in the previous seven years, with the annual recovery ranging from 30,034 to 389,265 tons. Secondary recovery of non-ferrous scrap was lower than in the previous seven years, with recovery ranging from 8,392 to 19,776 tons. In 1994, the estimated U.S. production of refined nickel was 220,700 short tons. Table 2-2 provides data on U.S. mine and nickel plant production from 1982 to 1986. Plant production includes refined nickel, ferronickel, and nickel recycled from scrap.

Table 2-2. Mine and plant production of nickel in the United States from 1982 to 1986 (thousands of tons)

	1982	1983	1984	1985	1986
Mine production	2.9	--	13.2	5.6	1.1
Plant production	40.8	30.3	40.8	33.0	1.5

Source: Chamberlain 1988

--: not provided

2.3 Analysis

The most common methods of determining nickel concentration in the environment and biological media are atomic absorption spectrometry (AAS), either flame or graphite furnace, and inductively coupled argon plasma emission spectrophotometry–electrothermal atomic absorption spectrophotometry (ICP-EAS). The National Institute for Occupational Safety and Health (NIOSH) has recommended standard procedures for measuring nickel content in personal air samples. These routine procedures do not identify individual nickel compounds, however, and X-ray diffraction, which could do so, is impractical for routine monitoring (IARC 1990). Table 2-3 briefly describes methods for the analysis of nickel.

Table 2-3. Methods for the analysis of nickel

Sample matrix	Sample preparation	Assay procedure	Sensitivity or detection limit
Air	Collect on cellulose ester membrane and filter; digest with nitric acid and perchloric acid.	AAS	--
	Collect on cellulose ester membrane and filter; digest with nitric acid and hydrochloric acid.	AAS	1 ∝g absolute; 10 ∝g/m^3 (sample volume of 0.1 m^3)
	Collect on cellulose ester membrane and filter; digest with nitric acid and perchloric acid.	ICP	1.5 ∝g/sample
	Collect on cellulose ester membrane filter; digest with nitric acid.	AAS	20 ng/m^3 (sample volume 1.5 m^3)
Water	Chelate; extract with ammonium pyrrolidine dithiocarbamate:methyl isobutyl ketone.	AAS	0.04 ∝g/L
	Filter; irradiate with ultraviolet radiation.	DPASV (dimethylglyoxime-sensitized)	1 ng/L
	Chelate; extract with ammonium pyrrolidine dithiocarbamate:methyl isobutyl ketone	EAAS	0.2 ∝g/L
Food	Digest with acid.	AAS	--
	Wet digest with nitric acid, hydrogen peroxide, and sulfuric acid.	DPASV (dimethylglyoxime-sensitized)	1 ng/L digestion solution
	Dry ash.	DPASV (dimethylglyoxime-sensitized)	5 ng/sample
	Dry ash; chelate with sodium(ditrifluorethyl)dithiocarbamate.	Chelate-GC	100 ng/sample
Blood	Wet digest with nitric acid, hydrogen peroxide, and sulfuric acid.	DPASV (dimethylglyoxime-sensitized)	1 ng/L digestion solution
Serum or whole blood	Digest with nitric acid; heat.	EAAS (Zeeman)	0.05 ∝g/L serum 0.1 ∝g/L whole blood
Body fluids or tissues	Digest with nitric acid, perchloric acid, and sulfuric acid; chelate; extract with ammonium pyrrolidine dithiocarbamate:methyl isobutyl ketone.	EAAS	0.2 ∝g/L body fluids 0.4 ∝g/kg tissues

Sample matrix	Sample preparation	Assay procedure	Sensitivity or detection limit
Tissues	Homogenize; digest with nitric acid, perchloric acid, and sulfuric acid.	EAAS (Zeeman)	0.01 ∝g/g dry wt
	Digest with nitric acid and sulfuric acid.	EAAS (Zeeman)	0.8 ∝g/g wet wt
Serum or urine	Digest with nitric acid, perchloric acid, and sulfuric acid; chelate; extract with ammonium pyrrolidine dithiocarbamate:methyl isobutyl ketone.	EAAS	--
Urine	Chelate; extract with ammonium pyrrolidine dithiocarbamate:methyl isobutyl ketone.	EEAS	0.5 ∝g/L
	Digest with nitric acid, perchloric acid, and sulfuric acid.	DPASV	1 ∝g/L
	Chelate: extract with hexamethylene ammonium: hexamethylene dithiocarbamate: diisopropylketone.	AAS	0.2 ∝g/L
	Dilute with nitric acid.	EAAS (Zeeman)	0.5 ∝g/L
	Dilute directly with nitric acid.	EAAS	1.2 ∝g/L

Source: IARC 1990

AAS: flameless atomic absorption spectrometry; ICP: inductively coupled argon plasma spectrometry; DPASV: differential pulse anodic stripping voltammetry; EAAS: electrothermal atomic absorption spectrometry; GC: gas chromatography.

--: not provided

2.4 Environmental occurrence

Nickel is the 24th most common element in the crust of the earth, with an average concentration of 0.0086% (range: ″ 0.0001% to > 0.3%). In the overall composition of earth, nickel is the fifth most abundant element after iron, oxygen, silicon, and magnesium (ATSDR 1997). Meteorites contain 5% to 50% nickel. Nickel also is found in deep-sea nodules, typically comprising about 1.5% of the nodule (IARC 1990).

2.4.1 Air

Nickel is introduced into the environment from various natural sources (Table 2-4), such as volcanic emissions and windblown dusts from rocks and soils, from combustion of fossil fuels, from nickel mining and emissions of refining operations, from the use of metals in industrial processes, and from incineration of wastes (IARC 1990). The form of nickel released into the atmosphere depends upon the source. Nickel emitted during oil combustion is primarily nickel sulfate, with some complex metal oxides and nickel oxide. Most of the nickel in fly ash consists of complex oxides, primarily iron oxides. Nickel silicate and iron-nickel oxides are produced during the mining and smelting of lateritic nickel ore. Nickel subsulfide and metallic nickel are produced during nickel matte refining. Steel and nickel alloy production and secondary nickel smelting produce iron-nickel oxide (ATSDR 1997). In compliance with the Emergency Planning and Community Right-to-Know Act (EPCRA), 2,002 facilities reported their total nickel air release as 319,873 lb (TRI 1997).

Table 2-4. Emission rates of nickel into the atmosphere

Source	Emission rate (10^6 kg/year)
Natural	
Wind-blown dust	4.8
Volcanoes	2.5
Vegetation	0.8
Forest fires	0.2
Meteoric dust	0.2
Sea spray	0.009
Total	**8.5**
Anthropogenic[a]	
Residual and fuel oil combustion	27
Nickel mining and refining	7.2
Waste incineration	5.1
Steel production	1.2
Industrial applications	1.0
Gasoline and diesel fuel combustion	0.9
Coal combustion	0.7
Total	**43.1**

Source: IARC 1990

[a]Emissions during the mid-1970s.

2.4.2 Water

Nickel will enter groundwater from runoff associated with the natural weathering of soil and rocks, from disturbed soil, or from atmospheric fallout. Most nickel compounds are soluble in water at a pH of 6.5 or lower. Nickel usually is found as nickel hydroxides at a pH of 6.7 or higher. The U.S. EPA has determined that a nickel concentration of ″ 20 ∝g/L in groundwater is similar to that in municipal water that has been processed for distribution. U.S. drinking water nickel levels were reported to be mostly ″ 20 ∝g/L, with 90% of the samples containing ″ 10 ∝g/L. Mean effluent levels of nickel were higher around facilities that used nickel (IARC 1990). In compliance with EPCRA, 2,002 facilities reported their total nickel water release as 14,326 lb (TRI 1997).

2.4.3 Soil

Most of the nickel released into the environment is released into the soil. It has been estimated that, excluding mining and smelting releases, 66% of all anthropogenic environmental releases (median of 325 million kg/year) are to soil. Coal fly ash and bottom ash, waste from metal manufacturing, commercial waste, atmospheric fallout, urban refuse, and sewage sludge are significant sources of nickel release to soil (ATSDR 1997). In compliance with EPCRA, 2,002 facilities reported their total nickel land release as 232,469 lb and total underground injection releases as 25,642 lb in 1996 (TRI 1997).

2.5 Environmental fate

Nickel is an element, and therefore is not destroyed in the environment. Dry and wet precipitation processes remove nickel from the atmosphere and transfer it to soil and water. Nickel in the soil may then enter water by surface runoff or by percolation into ground water. Physical and chemical interactions occur once nickel is in the surface and ground water. Interactions include complexation, precipitation/dissolution, adsorption/desorption, and oxidation/reduction. Data regarding disposition of nickel compounds in the air, water, and soil are inadequate (HSDB 1988).

2.6 Environmental exposure

Environmental exposure to nickel occurs through inhalation, ingestion, and percutaneous exposure. The general population is exposed to low levels of nickel, because it is widely present in the air, water, and food. Typical average levels of airborne nickel are 0.00001 to 0.003 ∝g/m^3 in remote areas, 0.003 to 0.03 ∝g/m^3 in cities with no metallurgical industry, and 0.07 to 0.77 ∝g/m^3 in nickel processing areas (HSDB 1988). The average intake of nickel by inhalation was calculated to be 0.1 to 1.0 ∝g/day, assuming that a person inhales 20 m^3 of air per day and using the range of average nickel concentrations in U.S. cities as 5 to 49 ng/m^3 (0.005 to 0.049 ∝g/m^3). The highest daily inhalation intake would be 18 ∝g, using 917 ng/m^3 as the highest ambient nickel level reported (ATSDR 1997).

The average intake of nickel from drinking water in the United States is around 2 ∝g/day. The dietary intake of nickel has been estimated at 69 ∝g/day for infants aged 6 to 11 months, 162 ∝g/day for teenage boys, and 146.2 ∝g/day for 25- to 30-year old males (ATSDR 1997). The U.S. EPA estimated that the average adult consumes 100 to 300 ∝g of nickel per day (U.S. EPA

1998). The estimated 47 million smokers in the United States are potentially exposed to nickel associated with tobacco (Spectrum 1999). Cigarette smoking increases daily intake of nickel by 0.12 to 0.15 ∝g/kg/day (ATSDR 1997).

Individuals are exposed to nickel in nickel alloys and nickel-plated materials via contact with steel, coins, and jewelry. Nickel also can be found in soaps, fats, and oils hydrogenated with nickel catalysts.

Individuals who have joint prostheses, sutures, clips, or screws containing nickel alloys for fractured bones may have elevated levels of nickel in the surrounding tissue, which is then released into the bloodstream. Elevated serum nickel concentrations were observed in some patients with Ti-Al-V prostheses (< 0.2% Ni by weight). Mean serum nickel concentrations ranged from 0.3-1.4 ∝g/L (n = 16, peak at 4-5 days, control mean = 0.2 ∝g/L). Serum nickel concentrations were also elevated in patients with Co-Cr prostheses (< 0.1% Ni by weight). Mean concentrations ranged from 0.4-3.3 ∝g/L (n = 28, peak at 1-2 days, control mean = 0.2 ∝g/L). In their review, Sunderman *et al.* (1989a) commented on increased plasma, blood and urine nickel concentrations in patients with stainless steel hip and knee prostheses. Patients receiving dialysis or transfusions also may be exposed to elevated amounts of nickel (ATSDR 1997).

2.7 Occupational exposure

Occupational exposure to nickel occurs mainly by inhalation or skin contact. Nickel workers also can ingest nickel-containing dusts. In 1977, NIOSH estimated that 1.5 million workers in the United States were occupationally exposed to nickel (IARC 1990). Based on the National Occupational Exposure Survey conducted from 1981 to 1983, NIOSH estimated that 727,240 U.S. workers were potentially exposed to nickel metal, alloys, dust fumes, salts, or inorganic nickel compounds (ATSDR 1997). NIOSH (1977) identified the following occupations as having potential for exposure to nickel:

battery makers, storage	catalyst workers
cemented carbide makers	ceramic makers
chemists	disinfectant makers
dyers	electroplaters
enamellers	gas mask makers
ink makers	metallizers
mond process workers	nickel-alloy makers
mould makers	nickel miners
nickel refiners	nickel smelters

nickel workers	oil hydrogenators
organic chemical synthesizers	paint makers
penpoint makers	petroleum refinery workers
spark plug makers	stainless-steel makers
textile dyers	vacuum tube makers
varnish makers	welders

Occupational exposure to nickel is measured by monitoring air and blood serum, plasma, or urine. Elevated nickel levels in biological fluids and tissue samples are indications of nickel uptake, and may not correlate directly to exposure levels (IARC 1990).

Many occupational processes lead to exposuretof nickel. Workers in different industries are exposed to different nickel species. Initial processes involved in the handling and purification of nickel, such as mining, milling, and smelting operations, typically involve higher levels of occupational exposure to insoluble than soluble nickel. As the refining process continues, occupational exposure to soluble nickel increases, while exposure to insoluble nickel decreases. Three industries, electroplating, electrowinning, and nickel chemicals industry segment, report occupational exposures almost exclusively to soluble nickel. Typical air sampling techniques, however, do not differentiate nickel species or particle size distribution (TERA 1999).

Table 2-5 summarizes measurements of occupational exposure to nickel in the U.S. nickel-producing industry. Table 2-6 summarizes measurements of occupational exposure in U.S. industries using primary nickel products. Table 2-7 summarizes measurements of occupational exposure in U.S. industries using nickel in special applications. Table 2-8 summarizes measurements of current nickel exposures, giving means and medians of nickel exposure in nickel-producing and nickel-using industries.

Table 2-5. Measurements of occupational exposure to nickel in the U.S. nickel-producing industry

Industry and activity (year, when available)	Number of workers	Air (∝g/m^3)		Reference
		Mean ± SD	Range	
Measurements in air samples				
Mines, Oregon (1981)	–	30	–	Rigaut 1983
Laterite mining and smelting, Oregon				
Ore handling	3	52	5–145	Warner 1984
Drying	4	17	9–21	
Calcining	4	90	37–146	
Skull drilling	8	16	4–43	
Ferrosilicon manufacturing	15	32	4–241	
Mixing	17	6	4–7	
Refining	10	11	4–34	
Handling of finished products	6	5	4–9	
Maintenance	9	39	7–168	
Miscellaneous	3	193	8–420	
Electrolytic refinery	15	489	20–2200	Bernacki *et al.* 1978
Measurements in urine samples		**Urine (∝g/L)**		
Electrolytic refinery	15	222 144 ∝g/g creatinine	8.6–813 6.1–287 ∝g/g creatinine	Bernacki *et al.* 1978

Source: IARC 1990

Table 2-6. Measurements of occupational exposure in U.S. industries using primary nickel products

Industry and activity	Number of workers	Air (∝g/m^3)		Reference
		Mean	Range	
Stainless-steel production				
Electric furnace shop	8	36	9–65	Warner 1984
Argon-oxygen decarburization	5	35	13–58	
Continuous casting	2	14	11–15	
Grinding/polishing (machine)	6	134	75–189	
Grinding/chipping (hand tool)	2	39	23–48	
Welding, cutting, and scarfing	5	111	13–188	
Heat treating	1	54	< 1–104	
Rolling and forging	6	49	< 11–72	
Other operations (maintenance, pickling)	5	58	10–107	
High-nickel alloy production				
Weighing and melting	369	83	1–4,400	Warner 1984
Hot working	153	111	1–4,200	
Cold working	504	64	1–2,300	
Grinding	96	298	1–2,300	
Pickling and cleaning	18	8	1–15	
Maintenance	392	58	1–73	
Production of wrought nickel and alloys via metal powder foundries	226	1,500	1–60,000	Warner 1984

Industry and activity	Number of workers	Air (∝g/m^3)		Reference
		Mean	Range	
Six jobbing foundries processing alloys containing 0 to 60% nickel, averaging 10% to 15% nickel				
Melting	15	21	< 5–62	Scholz and Holcomb 1980
Casting	7	14	< 4–35	
Cleaning room:				
Cutting and gouging	11	233	7–900	
Welding	14	94	20–560	
Hand grinding	24	94	< 5–440	
Swing grinding	3	19	13–30	
Jobbing foundry processing carbon, alloy, and stainless steel containing 0-10% nickel				
Melting and casting	16	13	ND–70	Warner 1984
Cleaning room:				
Air arc gouging	7	310	40–710	
Welding	34	67	10–170	
Three low-alloy (0 to 2% nickel) iron and steel foundries				
Melting and casting	16	13	4–32	Warner 1984
Cleaning room (grinding, air arc gouging, welding)	18	54	7–156	

Source: IARC 1990

Table 2-7 Measurements of occupational exposure in U.S. industries using nickel in special applications

Industry and activity	No. of workers	Air (∝g/m^3)		Urine (∝g/L)		Serum (∝g/L)		Reference
		Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Ni/Cd battery production with nickel and nickel hydroxide; assembly and welding of plates	36	378	20–1910	–	–	–	–	Warner 1984
Ni/Cd or Ni/Zn battery production	6	–	–	11.7 ± 7.5 10.2	3.4–25 7.2–23 ∝g/g creatinine	–	–	Bernacki *et al.* 1978
Ni/H_2 battery production	7	–	–	32.2 ± 40.4	2.8-103	–	–	Bernacki *et al.* 1978
Ni/Cd battery production	–	–	12–33	–	24–27 ∝g/g creatinine	–	–	Adamsson *et al.* 1980
Ni catalyst production from nickel sulfate	7 5	150 370	10–600 190–530	–	–	–	–	Warner 1984
Ni catalyst use; coal gasification workers	9			4.2 3.2	0.4–7.9 0.1–5.8 ∝g/g creatinine	–	–	Bernacki *et al.* 1978
Electroplating								Warner 1984
Sulfate bath, 45°C				–	–	–	–	
Area 1 samples	16	< 6	< 5–< 8					
Area 2 samples	3	< 4	< 2–< 7					
Personal samples	6	< 11	< 7–< 16					
Sulfate bath, 70°C								
Area samples	6	< 3	< 2–< 3					
Sulfamate bath, 45–55°C								
Area 1 samples	9	< 4	< 4					
Area 2 samples	6	< 4	< 4					

Industry and activity	No. of workers	Air (∝g/m^3)		Urine (∝g/L)		Serum (∝g/L)		Reference
		Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Electroplating	–	9.3	0.5–21.2	48	5–262	–	–	Bernacki *et al.* 1980
Electroplating	21	–	–	30.4 21.0 ∝g/g creatinine	3.6–85 2.4–62 ∝g/g creatinine	–	–	Bernacki *et al.* 1978
Flame spraying	5	2.4	< 1–6.5	17.2 16.0 ∝g/g creatinine	1.4–26 1.4–54 ∝g/g creatinine	–	–	Bernacki *et al.* 1978
Painting								
Spray painting in a construction shipyard	13	–	–	3.2	< 0.5–9.2	4.4	< 0.5–17.2	Grandjean *et al.* 1980
Painting in a repair shipyard	18	–	–	–	–	5.9	< 0.5–13	
Manufacturing plants	10	–	–	15.3 ± 11.1	6–39	–	–	Tandon *et al.* 1977
Buffing, polishing, grinding								
Buffer and polishers (aircraft engine factory)	7	26	< 1–129	4.1 2.4 ∝g/g creatinine	0.5–9.5 0.5–4.7 ∝g/g creatinine	–	–	Bernacki *et al.* 1978
Grinders (abrasive wheel grinding of aircraft parts)	9	1.6	< 1–9.5	5.4 3.5 ∝g/g creatinine	2.1–8.8 1.7–6.1 ∝g/g creatinine	–	–	
Miscellaneous exposure								
Bench mechanics (assembling, fittings, and finishing aircraft parts made of Ni-alloys)	8	52	< 1–252	12.2 7.2 ∝g/g creatinine	1.4–41 0.7–20 ∝g/g creatinine	–	–	Grandjean *et al.* 1980
Riggers/carpenters (construction shipyard)	16	–	–	3.7	1.1–13.5	3.3	1.1–13.5	
Riggers/carpenters (repair shipyard)	11	–	–	–	–	3.6	< 0.5–7.4	

Industry and activity	No. of workers	Air (∝g/m^3)		Urine (∝g/L)		Serum (∝g/L)		Reference
		Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Shipfitters/pipefitters (construction shipyard)	6	–	–	4.9	3.7–7.1	4.1	1.5–6.8	
Shipfitters/pipefitters (repair shipyard)	15	–	–	–	–	9.1	0.5–3.8	

Source: IARC 1990

-: not available

Table 2-8. Summary of current nickel exposures in nickel producing- and using-industries

Industry sector	Range of exposure concentrations (mg Ni/m^3)[a]	Range of mean aerosol exposure concentrations (mg Ni/m^3)[a]	Predominant species[b]
Mining	0 – < 1.0	0.003 – 0.15	SU, O[c]
Milling	0.001 – 4.0	0.01 – < 0.70	SU
Smelting	0.001 – 77.0[d]	0.01 – < 3.0	SU, O[c]
Refining	0.001 – 20.0[e]	0.003 – ~1.50[f]	SU, O, M, SO[g]
Stainless and alloy steels	0 – < 1.0	0.001 – 0.10	O, M
Nickel alloy steels	0.001 – 9.0[h]	0.002 – ~0.50[i]	O, M
Welding and hot cutting	Trace – 7.0[h]	0.001 – ~0.5[j]	O, M[k]
Nickel plating	Trace – ~3.0[i]	0.0004 – ~0.10	SO[l]
Production of chemicals	0.001 – ~3.0	0.02 – ~1.50	SO, O, M
Nickel catalysts	0 – 26.0[m]	0.004 – ~1.0[n]	SO, O, M[o]
Nickel-cadmium batteries	0 – ~2.0	0.005 – ~0.50	O, M, SO
Others	Trace – 14.0	Trace – 0.5[p]	mixed

Source: NiPERA 1996

[a]Total nickel, unless otherwise indicated.

[b]M = metallic nickel, O = oxidic nickel, NC = nickel carbonyl, SU = sulphidic nickel, SO = soluble nickel salts.

[c]Dependent upon the type of ore.

[d]Upper limits of ranges for most data sources did not exceed 2.0 mg Ni/m^3.

[e]Upper limits of ranges for most data sources did not exceed 5.0 mg Ni/m^3.

[f]A few mean aerosol concentrations exceeded 1.5 mg Ni/m^3. The highest mean value reported was 4.84 mg Ni/m^3.

[g]Dependent upon the operation and job.

[h]Upper limits of ranges for most data sources did not exceed 1 mg Ni/m^3.

[i]A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest mean value reported was 3.2 mg Ni/m^3.

[j]A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest mean value reported was 3.58 mg Ni/m^3.

[k]In some instances, soluble nickel was noted to be present, although it was not the predominant form of nickel found.

[l]In instances where speciation was conducted, insoluble nickel compounds were noted to be present although they were not the predominant forms of nickel found.

[m]Upper ranges for most data sources did not exceed 4.0 mg Ni/m^3.

[n]A few mean aerosol concentrations exceeded 1.0 mg Ni/m^3. The highest mean value reported was 1.55 mg Ni/m^3.

[o]In addition to potential exposures to oxidic and/or metallic nickel species, sulfidic nickel also is believed to be present in the spent nickel catalyst.

[p]A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest mean value reported was 4.1 mg Ni/m^3.

2.8 Biological indices

Nickel exposure can be assessed from plasma and urine samples if the exact nickel compound is identified. The estimated average body burden of nickel in adults is 0.5 mg/70 kg (7.4 ∝g/kg

body weight) (IARC 1990). Urine and serum levels of nickel in workers who have inhaled soluble nickel compounds reflect the amount of nickel absorbed in the previous one or two days. The best correlations between exposure concentrations and urine levels were found with end-of-shift urine sampling or next-morning urine sampling. Serum and urine are the most useful biomarkers for biological monitoring (ATSDR 1997).

2.9 Regulations

The U.S. EPA regulates nickel compounds under the Clean Air Act (CAA), the Clean Water Act (CWA), the Resource Conservation and Recovery Act (RCRA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Superfund Amendments and Reauthorization Act (SARA). The nickel salt of an organo compound containing nitrogen is regulated under the Toxic Substances Control Act. Effective in 1990, liquid hazardous wastes containing nickel compounds at concentrations $\geq$ 134 mg/L are prohibited from underground injection. Reportable quantities (RQs) have been established for the release of certain nickel compounds. An RQ of 100 lb has been designated for nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate, and an RQ of 10 lb has been set for nickel carbonyl, nickel cyanide, and nickel hydroxide. Under the Federal Water Pollution Control Act (FWPCA), nickel compounds are designated toxic pollutants. Effluent limitations and pretreatment and performance standards have been created for point sources producing nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, and nickel carbonate.

The U.S. Food and Drug Administration (FDA) regulates the amount of nickel oxide in the color additive chromium-cobalt-aluminum oxide to less than 1%. NIOSH has recommended an exposure limit of 0.007 mg/m^3 as a time-weighted average (TWA; time not specified) for nickel carbonyl and 0.015 mg/m^3 for inorganic nickel compounds (as Ni) in the workplace (NIOSH 1988). NIOSH considers nickel and its compounds to be potential occupational carcinogens and recommends that occupational exposures to carcinogens be limited to the lowest feasible concentration (Ludwig 1994). The Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit (PEL) for nickel carbonyl (as Ni) at 0.007 mg/m^3 as an 8-hour TWA. For other nickel compounds, soluble and insoluble, the PEL is 1 mg/m^3. OSHA also regulates the compounds as hazardous chemicals in laboratories and under the Hazard Communication Standard. Table 2-9 summarizes U.S. EPA regulations that affect nickel and nickel compounds. Table 2-10 summarizes FDA regulations that affect nickel and nickel compounds. Table 2-11 summarizes OSHA regulations that affect nickel and nickel compounds.

Table 2-9. U.S. EPA Regulations

Regulatory action	Effect of regulation and other comments
40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANT FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Code: 42 U.S.C. 7401 et seq.	This part contains national emission standards for hazardous air pollutants established pursuant to section 112 of the CAA, which regulates specific categories of stationary sources that emit (or have the potential to emit) one or more hazardous air pollutants listed in this part pursuant to section 112(b) of the CAA.
40 CFR 63—Subpart D—Regulations Governing Compliance Extensions for Early Reductions of Hazardous Air Pollutants.	The provisions of this subpart apply to an owner or operator of an existing source who wishes to obtain a compliance extension from a standard issued under section 112(d) of the CAA. Nickel compounds are listed as high-risk pollutants; the weighting factor is 10.
40 CFR 63—Subpart JJ—National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/07/95.	The affected source to which this subpart applies is each facility that is engaged, either in part or in whole, in the manufacture of wood furniture or wood furniture components and that is located at a plant site that is a major source as defined in section 63.2. Nickel subsulfide is listed as a pollutant excluded from use in cleaning and wash-off solvents. Nickel carbonyl is listed as a volatile hazardous air pollutant of potential concern.
40 CFR 68—PART 68—CHEMICAL ACCIDENT PREVENTION PROVISIONS. Promulgated: 59 FR 4493, 01/31/94. U.S. Code: 42 U.S.C. 7412(r), 7601(a)(1), 7661–7661f.	This part sets forth the list of regulated substances and thresholds, the petition process for adding or deleting substances to the list of regulated substances, the requirements for owners or operators of stationary sources concerning the prevention of accidental releases, and the State accidental release prevention programs approved under section 112(r). Nickel carbonyl is a regulated toxic substance; the threshold quantity for accidental release prevention is 1,000 lb. Its toxic endpoint is 0.00067 mg/L.
40 CFR 116—PART 116—DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/78. U.S. Code: 33 U.S.C. 1251 et seq.	This regulation designates hazardous substances under section 311(b)(2)(A) of the FWPCA and applies to discharges of substances designated in Table 116.4.
40 CFR 116.4—Sec. 116.4 Designation of hazardous substances. Promulgated: 43 FR 10474, 03/13/78 through 54 FR 33482, 08/14/89.	Nickel ammonium sulfate, nickel chloride, nickel hydroxide, nickel nitrate, and nickel sulfate are listed as hazardous substances.
40 CFR 117—PART 117—DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. Promulgated: 44 FR 50776, 08/29/79. U.S. Code: 33 U.S.C. 1251 et seq.	
40 CFR 117.3—Sec. 117.3 Determination of reportable quantities. Promulgated: 50 FR 13513, 04/04/85 through 60 FR 30937, 06/12/95.	A reportable quantity of 100 lb (45.4 kg) has been established for nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate, and of 10 lb for nickel hydroxide, pursuant to section 311 of the CWA.
40 CFR 148—PART 148—HAZARDOUS WASTE INJECTION RESTRICTIONS. Promulgated: 53 FR 28154, 07/26/88. U.S. Code: 42 U.S.C. 6901 et seq.	

Regulatory action	Effect of regulation and other comments
40 CFR 148.1—Sec. 148.1 Purpose, scope, and applicability. Promulgated: 61 FR 15596, 04/08/96. Effective 04/08/98.	This part identifies wastes that are restricted from disposal into Class I wells and defines those circumstances under which a waste otherwise prohibited from injection may be injected.
40 CFR 148.12—Sec. 148.12 Waste specific prohibitions—California list wastes. Promulgated: 53 FR 30918, 08/16/88, as amended at 53 FR 41602, 10/24/88.	Liquid hazardous wastes, including free liquids associated with any solid or sludge, containing the nickel and/or nickel compounds at concentrations $\geq$ 134 mg/L are prohibited from underground injection, effective August 8, 1990.
40 CFR 192—PART 192—HEALTH AND ENVIRONMENTAL PROTECTION STANDARDS FOR URANIUM AND THORIUM MILL TAILINGS. Promulgated: 48 FR 602, 01/05/83. U.S. Code: 42 U.S.C. 2022, as added by the Uranium Mill Tailings Radiation Control Act of 1978.	The provisions of this part control the residual radioactive material at designated processing or depository sites under section 108 of the Uranium Mill Tailings Radiation Control Act of 1978, and applies to the restoration of such sites following any use of the subsurface minerals under section 104(h) of the Uranium Mill Tailings Radiation Control Act of 1978.
40 CFR 192—Subpart E—Standards for Management of Thorium Byproduct Materials Pursuant to Section 84 of the Atomic Energy Act of 1954, as Amended. Promulgated: 48 FR 45947, 10/07/83.	Nickel and nickel compounds (not otherwise specified), nickel carbonyl, and nickel cyanide are listed as constituents (Appendix I).
40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTE. Promulgated: 45 FR 33119, 05/19/80. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, 6922, 6924(y), and 6938.	
40 CFR 261—Subpart D—Lists of Hazardous Wastes, Appendix VIII—Hazardous Constituents. Promulgated: 53 FR 13388, 04/22/88 through 62 FR 32977, 06/17/97. Nickel compounds (not otherwise specified), nickel carbonyl, and nickel cyanide are listed as hazardous constituents.	Appendix VIII is a consolidated list of hazardous constituents identified in this part. Solid wastes containing these constituents are subject to notification requirements of RCRA section 3010 and must be disposed of in RCRA-permitted facilities.
40 CFR 261.33—Sec. 261.33 Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. Promulgated: 45 FR 78529 and 78541, 11/25/80.	Nickel carbonyl and nickel cyanide are listed as hazardous waste.
40 CFR 266—Subpart M—Military Munitions. Promulgated: 62 FR 6654, 02/12/97.	The regulations in this subpart identify when military munitions become a solid waste and, if these wastes also are hazardous under this subpart or 40 CFR part 261, the management standards that apply to these wastes. The reference air concentration for nickel cyanide is 0 µg/m. The risk-specific dose for nickel subsulfide is 2.1 x 10^{-22} µg/m^3. The residue concentration limit for nickel cyanide is 0.7 mg/kg.
40 CFR 268—PART 268—LAND DISPOSAL RESTRICTIONS. Promulgated: 51 FR 40638, 11/07/86. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, and 6924.	
40 CFR 268—Subpart E—Prohibitions on Storage.	Nickel cyanide is a metal-bearing waste prohibited from dilution in a combustion unit according to 40 CFR 268.3 (Appendix XI).

Regulatory action	Effect of regulation and other comments
40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Code: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	This regulation designates under section 102(a) of the CERCLA those substances in the statutes referred to in section 101(14) of the CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This regulation also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.
40 CFR 302.4—Sec. 302.4 Designation of hazardous constituents.	**Compound** — **RQ (lb)** Nickel ammonium sulfate — 100 Nickel carbonyl — 10 Nickel chloride — 100 Nickel cyanide — 10 Nickel hydroxide — 10 Nickel nitrate — 100 Nickel sulfate — 100
40 CFR 355—PART 355—EMERGENCY PLANNING AND NOTIFICATION. Promulgated: 52 FR 13395, 04/22/87. U.S. Code: 42 U.S.C. 11002, 11004, and 11048.	This regulation establishes the list of extremely hazardous substances, threshold planning quantities, and facility notification responsibilities necessary for the development and implementation of State and local emergency response plans. Nickel carbonyl is listed as an extremely hazardous substance; its threshold planning quantity is 1 lb.
40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Code: 42 U.S.C. 11023 and 11048.	This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of the SARA of 1986. The information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, to aid in the development of regulations, guidelines, and standards, and for other purposes.
40 CFR 372.65—Sec. 372.65 Chemicals and chemical categories to which this part applies. Promulgated: 53 FR 4525, 02/16/88; 53 FR 12748, 04/18/88.	The requirements of this subpart apply to nickel compounds—any unique chemical substance that contains nickel as part of that chemical's infrastructure—and became effective on January 1, 1987.
40 CFR 401—PART 401—GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74. U.S. Code: 33 U.S.C. 1251, 1311, 1314 (b) and (c), 1316 (b) and (c), 1317 (b) and (c) and 1326(c).	This part sets forth the legal authority and general definitions which will apply to all regulations issued concerning specific classes and categories of point sources under parts 402 through 699 of this subchapter.
40 CFR 401.15—Sec. 401.15 Toxic pollutants. Promulgated: 44 FR 44502, 07/30/79, as amended at 46 FR 2266, 01/08/81; 46 FR 10724, 02/04/81.	Nickel compounds are toxic pollutants designated pursuant to section 307(a)(1) of the FWPCA.

Regulatory action	Effect of regulation and other comments
40 CFR 415—PART 415—INORGANIC CHEMICALS MANUFACTURING POINT SOURCE CATEGORY. Promulgated: 47 FR 28278, 06/29/82. U.S. Code: 33 U.S.C. 1311, 1314 (b), (c), (e), and (g), 1316 (b) and (c), 1317 (b) and (c), and 1361. 40 CFR 415—Subpart A—Aluminum Chloride Production Subcategory.	
40 CFR 415.1—Sec. 415.1 Compliance dates for pretreatment standards for existing sources. Promulgated: 49 FR 33420, 08/22/84; 49 FR 37594, 09/25/84.	The compliance date for discharges from nickel sulfate manufacturing operations and for all subparts in part 415 not listed in paragraphs (a) and (b) of this section is June 29, 1985.
40 CFR 415—Subpart AU—Nickel Salts Production Subcategory. Promulgated: 49 FR 33423, 08/22/84.	
40 CFR 415.470—Sec. 415.470 Applicability; description of the nickel salts production subcategory.	This subpart is applicable to discharges and to the introduction of pollutants into treatment works which are publicly owned resulting from the production of nickel salts, including nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, and nickel carbonate.
40 CFR 415.472—Sec. 415.472 Effluent limitations guidelines representing the degree of effluent reduction attainable by the application of the best practicable control technology currently available (BPT).	Except as provided in 40 CFR 125.30 through 125.32, for any existing point source producing nickel sulfate, nickel chloride, nickel nitrate, or nickel fluorobate, the limits for total nickel are 0.0060 kg per 1,000 kg (kg/kkg) (1-day maximum) and 0.0020 kg/kkg (30-day avg.). For a source producing nickel carbonate, the limits for total nickel are 1.1 kg/kkg (1-day maximum) and 0.35 kg/kkg (30-day avg.).
40 CFR 415.473—Sec. 415.473 Effluent limitations guidelines representing the degree of effluent reduction attainable by the application of the best available technology economically achievable (BAT).	Except as provided in 40 CFR 125.30 through 125.32, for any existing point source producing nickel sulfate, nickel chloride, nickel nitrate, or nickel fluorobrate, the limits for total nickel are 0.00074 kg/kkg (1-day maximum) and 0.00024 kg/kkg (30-day avg.). For a source producing nickel carbonate, the limits for total nickel are 0.13 kg/kkg (1-day maximum) and 0.042 kg/kkg (30-day avg.).
40 CFR 415.474—Sec. 415.474 Pretreatment standards for existing sources (PSES).	Except as provided in 40 CFR 403.7 and 403.13, for any existing source producing nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, or nickel carbonate which introduces pollutants into a POTW, the limits for total nickel are 1.1 kg/kkg (1-day maximum) and 0.36 kg/kkg (30-day avg.). In cases where POTWs find it necessary to impose mass limitations, the limits for total nickel are the same as specified in 415.473.
40 CFR 415.475—Sec. 415.475 New source performance standards (NSPS).	For any new source subject to this subpart and producing nickel sulfate, nickel chloride, nickel nitrate, or nickel fluorobate, the limits for total nickel are 0.00074 kg/kkg (1-day maximum) and 0.00024 kg/kkg (30-day avg.). For any new source producing nickel carbonate, the limits for total nickel are 0.13 kg/kkg (1-day maximum) and 0.042 kg/kkg (30-day avg.).

Regulatory action	Effect of regulation and other comments
40 CFR 415.476—Sec. 415.476 Pretreatment standards for new sources (PSNS).	Except as provided in 40 CFR 403.7, for any new source subject to this subpart and producing nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, or nickel carbonate which introduces pollutants into a publicly owned treatment works (POTW), the limits for total nickel are the same as specified in 415. 474.
40 CFR 455—PART 455—PESTICIDE CHEMICALS. Promulgated: 43 FR 17776, 04/25/78. U.S. Code: 33 U.S.C. 1311, 1314, 1316, 1317, and 1361.	The appropriate pollution control technology for nickel sulfate hexahydrate is given in Table 10.
40 CFR 721—PART 721—SIGNIFICANT NEW USES OF CHEMICAL SUBSTANCES. Promulgated: 53 FR 28359, 07/21/88. U.S. Code: 15 U.S.C. 2604, 2607, and 2625(c). 40 CFR 721—Subpart E—Significant New Uses for Specific Chemical Substances.	
40 CFR 721.5330—Sec. 721.5330 Nickel salt of an organo compound containing nitrogen. Promulgated: 58 FR 51685, 11/04/93.	The chemical substance generically identified as nickel salt of an organo compound containing nitrogen is subject to reporting under this section for the following significant new uses: protection in the workplace; hazard communication program; industrial, commercial, and consumer activities; disposal; and release to water.

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 40 CFR, 1 July 1999.

Table 2-10. FDA Regulations

Regulatory action	Effect of regulation and other comments
21 CFR 73—PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION. Promulgated: 42 FR 15643, 03/22/77. U.S. Code: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, and 379e.	
21 CFR 73—Subpart B—Drugs.	
21 CFR 73.1015—Sec. 73.1015 Chromium-cobalt-aluminum oxide. Promulgated: 42 FR 15643, 03/22/77, as amended at 49 FR 10089, 03/19/84.	The color additive chromium-cobalt-aluminum oxide may contain small amounts (less than 1%) of nickel oxide.

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 21 CFR, 1 April 1 1999.

Table 2-11. OSHA Regulations

Regulatory action	Effect of regulation and other comments
29 CFR 1910—PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS. Promulgated: 39 FR 23502, 06/27/74.	
29 CFR 1910—Subpart H—Hazardous Materials. U.S. Code: 29 U.S.C. 653, 655, 657.	

Regulatory action	Effect of regulation and other comments
29 CFR 1910.119—Sec. 1910.119 Process safety management of highly hazardous chemicals.	Nickel carbonyl is listed as a toxic and highly reactive hazardous chemical which presents a potential for a catastrophic event at or above the threshold quantity.
29 CFR 1910—Subpart Z—Toxic and Hazardous Substances. Promulgated: 39 FR 23502, 07/27/74. Redesignated: 40 FR 23072, 05/28/75. U.S. Code: 29 U.S.C. 653, 655, and 657.	Regulation provides for protective clothing and hygiene requirements for workers, restricted open vessel operations, engineering requirements, respirators, medical surveillance requirements for workers, exhaust fan requirements, sign requirements for regulated areas, and labeling requirements for containers.
29 CFR 1910.1000—Sec. 1910.1000 Air contaminants. Promulgated: 58 FR 35340, 06/30/93 through 62 FR 1600, 01/10/97.	The PEL for nickel carbonyl (as Ni) is $\leq$ 0.007 mg/m^3, as an 8-h TWA. The PEL for nickel insoluble and soluble compounds (as Ni) is $\leq$ 1 mg/m^3, as an 8-h TWA.
29 CFR 1910.1200—Sec. 1910.1200. Hazard Communication. Promulgated: 61 FR 9245, 03/07/96. U.S. Code: also includes 5 U.S.C. 553.	Chemical manufacturers and importers and all employers are required to assess chemical hazards and to provide information to employees. The Hazard Communication Program is to include labels, materials safety data sheets, and worker training.
29 CFR 1910.1450—Sec 1910.1450. Occupational exposure to hazardous chemicals in laboratories. Promulgated: 55 FR 3327, 01/31/90 through 55 FR 12111, 03/30/90.	As select carcinogens (IARC Group 1 and NTP known carcinogens), nickel compounds are included as a chemical hazard in laboratories. Employers are required to provide employee information and training and a Chemical Hygiene Plan.
29 CFR 1915—PART 1915—OCCUPATIONAL SAFETY AND HEALTH STANDARDS FOR SHIPYARD EMPLOYMENT. Promulgated: 47 FR 16986, 04/20/82. U.S. Code: 29 U.S.C. 653, 655, and 657.	
29 CFR 1915—Subpart Z—Toxic and Hazardous Substances. Promulgated: 58 FR 35514, 07/01/93.	
29 CFR 1915.1000—Sec. 1915.1000 Air contaminants. Promulgated: 61 FR 31430, 06/20/96. 29 CFR 1926—PART 1926—SAFETY AND HEALTH REGULATIONS FOR CONSTRUCTION. Promulgated: 44 FR 8577, 02/09/79; 44 FR 20940, 04/06/79.	The requirements applicable to shipyard employment under this section are identical to those set forth in section 1910.1000.
29 CFR 1926—Subpart D—Occupational Health and Environmental Controls.	
29 CFR 1926.55—Sec. 1926.55 Gases, vapors, fumes, dusts, and mists. Promulgated: 39 FR 22801, 06/24/74 through 62 FR 1619, 01/10/97.	The requirements applicable to construction employment under this section are identical to those set forth in section 1910.1000.

Source: The regulations in this table have been updated through the 1999 Code of Federal Regulations 29 CFR, 1 July 1999.

3 Human Cancer Studies

Relatively little epidemiologic evidence pertains specifically to metallic nickel or nickel alloys. Therefore, in addition to describing this evidence, related evidence for carcinogenicity of nickel compounds and metal prostheses will be summarized briefly.

3.1 Metallic nickel and nickel alloys

IARC (1990) found *inadequate evidence* of carcinogenicity in humans for metallic nickel and nickel alloys, and concluded that metallic nickel is *possibly carcinogenic to humans* (Group 2B), on the basis of evidence in experimental animals. Overall, the epidemiologic studies evaluated by IARC (1990) involved either low levels of exposure to metallic nickel or nickel alloys or relatively few exposed workers. Moreover, exposure to metallic nickel was considered to be accompanied by exposure to other forms of nickel, including oxidic, sulfidic, and soluble nickel, or to other potential carcinogens, such as cadmium in the case of welders (see also the report of the International Committee on Nickel Carcinogenesis in Man [ICNCM 1990]). No study of nickel workers published since the IARC (1990) monograph includes workers exposed exclusively or even predominantly to metallic nickel or nickel alloys (see Section 3.2 for a review of these studies). Therefore, there are no epidemiological studies of exposed workers adequate for an evaluation of the carcinogenicity of metallic nickel or nickel alloys.

3.2 Nickel compounds

IARC (1990) found *sufficient evidence* of carcinogenicity in humans for nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel refining industry, and listed nickel compounds as *carcinogenic to humans* (Group 1). This evaluation was based on results of nine cohort studies and one case-control study of nickel workers, which were updated in the report of the ICNCM (1990). Elevated risks of lung and nasal cancer were associated with exposure to oxidic, sulfidic, and soluble nickel, particularly among workers with greater exposure or longer latency.

Subsequently, 12 additional cohort studies of nickel workers were published. Three studies of welders and one of battery workers are not considered, because these workers are exposed to other known or suspected carcinogens (e.g., chromate and cadmium). Two of the remaining eight studies are uninformative because of their small size (< 300 workers), and one was superceded by a subsequent study. Lung and nasal cancer results of the other five studies are briefly described below; two of these (Shannon *et al.* 1991 and Andersen *et al.* 1996) are updates of cohorts previously considered by IARC (1990). Risks are given as standardized mortality or incidence ratios (SMRs or SIRs, respectively) with 95% confidence intervals and number of exposed cases.

Moulin *et al.* (1990) studied 2,269 workers in a French plant producing ferrochromium and stainless steel. SMRs were based on national rates. A nonsignificant elevation in lung cancer risk was seen in the cohort as a whole (1.40, 0.72 - 2.45, n = 12). Greater risk was observed in exposed workers (2.04, 1.02 - 3.64, n = 11) than in unexposed workers (0.32, 0.01 - 1.77, n = 1), but this may have been due to confounding by exposure to polyaromatic hydrocarbons.

Shannon *et al*. (1991) studied 11,567 Canadian workers employed in mining, milling, and smelting. SMRs were calculated in comparison with Ontario rates. Risk of lung cancer was elevated in the cohort as a whole (1.28, 1.04 - 1.56, n = 98) and particularly among miners (1.53, 1.18 - 1.96, n = 63). No trends were observed for duration of mining or cumulative exposure to nickel. Risk of nasal cancer, based on one case, also was elevated (1.66).

Andersen *et al.* (1996) studied 4,764 workers employed for at least one year in a Norwegian nickel refinery. SIRs were calculated in comparison with the Norwegian population. Risk of lung cancer was elevated in the cohort as a whole (3.0, 2.6 - 3.4, n = 203), as was risk of nasal cancer (18.0, 12.3 - 25.4, n = 203). The risk of lung cancer increased with increasing cumulative exposure to soluble nickel after adjustment for smoking and other confounders. There was a multiplicative interaction between smoking and nickel exposure in their effects on risk of lung cancer.

Anttila *et al*. (1998) studied 1,388 workers employed for at least three months at a copper/nickel smelter and nickel refinery in Finland, 1,155 of whom were presumed to have exposure to nickel. SIRs were calculated in comparison with region-specific rates. Risk of lung cancer was elevated in the cohort as a whole (1.39, 0.86 - 2.13, n = 21) and further elevated among those with > 20 years latency (2.12, 1.29 - 3.27, n = 20). Risk of nasal cancer was elevated in the cohort as a whole (41.1, 4.97 - 148, n = 2), among those with > 20 years latency (67.1, 8.12 - 242, n = 2), and among those with > 5 years exposure (75.2, 9.10 - 271, n = 2).

Arena *et al*. (1999) studied 2,877 female production and fabrication high-nickel alloy workers in the United States. SMRs were calculated in comparison with the U.S. female population. Risk of lung cancer was elevated (1.34, 0.98 - 1.03, n = 200). Because female workers were assigned to different jobs than males, they may have had less exposure.

Three case-control studies have also been published since the IARC (1990) monograph. Risks for these studies are expressed as odds ratios, with 95% confidence intervals and number of exposed cases, when available.

Wortley *et al*. (1992) compared 235 cases of laryngeal cancer with 547 population controls in Washington state. Self-reported occupational histories and a job-exposure matrix were used to evaluate exposure. Risk was elevated among those with high exposure scores (1.6, 0.4 - 6.7, n = 7) and increased with increasing duration of exposure, but the study was limited by the small number of exposed cases.

Goldberg *et al.* (1994) studied 80 lung cancer cases nested within a cohort of nickel workers engaged in mining and refining in New Caledonia. Controls were selected from both the general population and the nickel cohort. Plant records and a job-exposure matrix were used to evaluate exposure. No excess risk was observed for exposure to total nickel (0.7, 0.4 - 1.3, n = 80) or to any type of nickel.

Horn-Ross *et al.* (1997) compared 141 cases of salivary gland cancer to 191 population controls in San Francisco, California. Self-reported occupational histories and a job-exposure matrix were used to evaluate exposure. Risk was elevated among those ever exposed to nickel compounds or

alloys (6.0, 1.6 - 22.0, n = 12), but risk was greater among those with < 3,000 hours exposure (9.0) than among those with > 3,000 hours exposure (3.7).

In summary, these results reinforce the finding of IARC (1990) that exposure to nickel compounds is associated with increased risks for lung and nasal cancer. On the basis of this evidence, NTP has concluded that nickel compounds are *known to be human carcinogens* (NTP 2000).

3.3 Prostheses and implants

The potential for carcinogenicity of prostheses and implants is of interest because these implants may be made of metal alloys containing up to 35% nickel (see Section 2.6), and numerous studies have demonstrated release of metal debris into the body from such implants (see Section 6). IARC (1999) found that there was *inadequate evidence* of carcinogenicity in humans for metallic implants and metallic foreign bodies and also for orthopedic implants of complex composition (metal with bone cement with or without polyethylene), and concluded that orthopedic implants of complex composition are *not classifiable as to their carcinogenicity to humans* (Group 3) (IARC 1999). This evaluation was based on both case reports and analytic studies; results are summarized below.

Case reports have described neoplasms originating from bone or soft connective tissue in the region of metal implants (16 cases) or orthopedic implants of complex composition (35 cases). In addition, 23 cases of sarcomas, 23 cases of carcinomas, and seven cases of brain tumors have been reported at the site of metallic foreign bodies, mainly bullets and shrapnel fragments. In some of these case reports, there is evidence of corrosion of the implant, due to contact between alloys of dissimilar composition. This would result in high local concentrations of metal and could account for the local tumors (IARC 1999).

Nine studies have evaluated cancer incidence in 14 cohorts of individuals with orthopedic implants (Gillespie *et al.* 1988, Mathiesen *et al.* 1995, Nyren *et al.* 1995, Lewold *et al.* 1996, Visuri *et al.* 1996, Gillespie *et al.* 1996, Paavolainen *et al.* 1999, Fryzek *et al.* 1999, Olsen *et al.* 1999). Two pairs of studies were partially overlapping. All but one cohort showed evidence of lower total cancer incidence, often accompanied by lower rates at specific sites, notably lung, stomach, colon, and breast. These results are most likely due to a “healthy patient” effect: patients selected for knee or hip replacement generally are healthier than members of the general population of similar age and also are often advised to stop smoking. An early study (Gillespie *et al*. 1988) of hip replacements found excess risk of all lymphohematopoietic cancers combined. In subsequent studies, some corroborating evidence was found for excess risk for total lymphohematopoietic cancers (one cohort) or for specific sites (lymphoma, one cohort; Hodgkin’s disease, one cohort; leukemia, two cohorts), but most results were negative. No other site was remarkable in more than one or two cohorts.

Several issues need to be considered in interpreting these studies. First, all but one study (Gillespie *et al.* 1996) compared cohort members with the general population. Because of the “healthy patient” effect, this could underestimate risk of cancer within the cohort. However, no excess risk of lymphoma or leukemia was seen by Gillespie *et al.* (1996) comparing cases to controls drawn from the same database. Second, some cohorts had few cases for some sites of

interest, such as lymphohematopoietic cancers, and so had little power to evaluate risk at these sites. Third, follow-up in most studies may have been too short to evaluate cancers with long latencies; even in studies with longer overall follow-up, the numbers of long-term survivors were low. Fourth, only one study (Visuri *et al*. 1996) evaluated metal-on-metal implants separately from metal-on-polyethylene implants. Excess risk of leukemia was confined to the former; thus, a greater risk of leukemia was found in recipients of metal-on-metal implants than in recipients of metal-on-polyethylene implants (3.77, 95% CI = 0.96 to 17.6). Most other studies had relatively few or even no patients with metal-on-metal implants, which have not been used since the 1970s in most countries. Although some metal debris is released from metal-on-polyethylene implants, more is released from metal-on-metal implants (see Section 6). Combining the two may therefore lead to misclassification of exposure, which would in general bias results. All the foregoing problems would tend to make it more difficult to observe an effect, particularly for rare cancers. In contrast, most studies included patients with rheumatoid arthritis, which is itself a risk factor for lymphohematopoietic cancers. In one study (Lewold *et al*. 1996), which evaluated cohorts with osteoarthritis and rheumatoid arthritis separately, excess risk of lymphoma was confined to the latter cohort. Thus, inclusion of these patients in other cohorts could create the appearance of an association of implants with lymphohematopoietic cancers in the absence of a true effect.

In summary, these studies are difficult to interpret, but generally suggest that there is little excess risk associated with orthopedic implants. However, it is worth noting a recent study that compared bone marrow samples from patients undergoing replacement of a worn prosthesis with samples from patients receiving a primary implant; a higher rate of chromosomal aberrations was found in the former group (Case *et al*. 1996) (see Section 5.2.2.3). Moreover, since exposure was not well quantified in these studies, they cannot be considered to rule out the possibility that metallic nickel or nickel alloys are carcinogenic to humans.

4 Studies of Cancer in Experimental Animals

4.1 Metallic nickel

IARC reviewed carcinogenicity studies of metallic nickel in experimental animals (IARC 1990, 1999; Appendix A and C, respectively). In these studies, metallic nickel was administered by inhalation (mice, rats, and guinea pigs), by intratracheal instillation (rats and hamsters), by intravenous (i.v.) injection (mice, rats, and hamsters), and by intramuscular (i.m.) injection (rats and hamsters). Additional studies in rats with metallic nickel used intrapleural, subcutaneous (s.c.), intraperitoneal (i.p.), intrarenal, subperiosteal, and intramedullary injections. No new studies with metallic nickel were located.

4.1.1 Inhalation studies in rats, mice, and guinea pigs

Groups of Wistar rats (50 per sex) and Bethesda black rats (60 females), two to three months old, were exposed to metallic nickel powder (> 99% pure nickel; particle diameter, ″ 4 ∝m) at a concentration of 15 mg/m^3 for six hours per day on four or five days per week for 21 months. Histological examinations of the lungs of the nickel-exposed rats revealed benign neoplasms (multicentric adenomatoid alveolar lesions and bronchial proliferations). Controls were not used in the study (Hueper 1958).

In another study, groups of Bethesda black rats (120) of unspecified sex were exposed to an unspecified concentration of metallic nickel powder (> 99.95% pure nickel; particle diameter, ″ 1 to 3 ∝m) combined with 20 to 35 ppm (50 to 90 mg/m^3) sulfur dioxide (as a mucosal irritant) and powdered chalk (to prevent clumping). The rats were exposed for five to six hours per day for an unspecified number of days per week over an unspecified period. Although several rats developed squamous metaplasia and peribronchial adenomatoses, no lung tumors were observed in the nickel-exposed rats (Hueper and Payne 1962).

No lung tumors were observed in a group of C57B1 mice (20 females, two months old) exposed by inhalation to metallic nickel powder (> 99% pure nickel; particle diameter, ″ 4 ∝m) at a concentration of 15 mg/m^3 for six hours per day on four or five days per week for 21 months. None of the mice survived the study (Hueper 1958).

Almost all strain 13 guinea pigs (32 male and 10 female, about three months old), developed adenomatoid alveolar lesions and terminal bronchial proliferations after exposure to metallic nickel powder (> 99% pure nickel; particle diameter not stated) at a concentration of 15 mg/m^3 for six hours per day on four or five days per week for 21 months. Mortality was high. One nickel-exposed guinea pig had an anaplastic intra-alveolar carcinoma, and another had an apparent adenocarcinoma metastasis in an adrenal node, although no primary tumor was identified. None of the nine controls had any of these neoplasms (Hueper 1958).

4.1.2 Intratracheal instillation studies in rats and hamsters

Female Wistar rats (11 weeks old) were given either 10 weekly intratracheal instillations of 0.9 mg of metallic nickel powder (32 rats) (total dose, 9 mg) or 20 weekly instillations of 0.3 mg of metallic nickel powder in 0.3 mL saline (39 rats) (total dose, 6 mg) and observed for almost

two and a half years. Exposed rats developed lung tumors, including carcinomas (incidence, 7/32) and a mixed tumor (incidence, 1/32) in the 0.9-mg dose group and carcinomas (incidence, 9/39) and adenomas (incidence, 1/39) in the 0.3-mg dose group. Pathologic classification of the tumors, in the two groups combined, revealed one adenoma, four carcinomas, 12 squamous cell carcinomas, and onr mixed tumor. Tumors were not found in the lungs of 40 control rats (Pott *et al.* 1987).

Groups of 100 Syrian golden hamsters were given single intratracheal instillations of 10, 20, or 40 mg of metallic nickel powder (particle diameter, 3 to 8 ∝m). The incidence of malignant neoplasms (fibrosarcomas, mesotheliomas, and rhabdomyosarcomas) in the hamsters was about 10%. Tumors were not observed in controls. This study was reported as an abstract (Ivankovic *et al.* 1987).

Syrian golden hamsters (strain Cpb-ShGa 51, about 60 per sex, 10 to 12 weeks old) were given 12 intratracheal instillations of 0.8 mg of metallic nickel powder (99.9% nickel; mass median diameter, 3.1 ∝m) in 0.15 mL of saline at two-week intervals (total dose, 9.6 mg). An adenocarcinoma of the lung was found in one of the exposed hamsters, but no tumors were found in the control animals or in the positive control group (Muhle *et al.* 1990).

4.1.3 Intrapleural administration studies in rats

A 12.5% suspension of 6.25 mg of metallic nickel powder in 0.05 mL of lanolin was injected into the right pleural cavity of 25 six-month-old female Osborne-Mendel rats, once a month for five months. Round-cell and spindle-cell sarcomas were found in the injection sites of four of the 25 rats, 12 of which were examined histopathologically. None of 70 vehicle-only control rats developed these neoplasms (Hueper 1952). In another study, two rats developed mesotheliomas following metallic nickel exposure. Fisher 344 rats (five per sex, 14 weeks of age) received five monthly intrapleural injections of metallic nickel powder (5 mg) suspended in 0.2 mL of saline. No tumors were found in controls (Furst *et al.* 1973).

4.1.4 Subcutaneous administration studies in rats

Local sarcomas (fibrosarcoma and rhabdosarcoma) were found in five of 10 Wistar rats (five per sex, four to five weeks old) exposed to metallic nickel in the form of four s.c. pellet implants (approximately 2 x 2 mm). The rats were observed for 27 months. No tumors were found in control rats that received similar implants of other dental materials (Mitchell *et al.* 1960).

4.1.5 Intramuscular administration studies in rats and hamsters

In an early study, 10 female hooded rats (two to three months old) were injected in the thigh muscle with 28.3 mg of metallic nickel powder in 0.4 mL of fowl serum. All rats injected with metallic nickel developed rhabdomyosarcomas at the injection site within 41 weeks. No local tumors had been observed in historical control rats dosed with fowl serum only (Heath and Daniel 1964).

In a study with F344 rats (25 per sex, of unspecified age) five monthly i.m. injections of 5 mg of metallic nickel powder in 0.2 mL of trioctanoin resulted in the development of fibrosarcomas in

38 of the 50 animals. No fibrosarcomas were detected in male or female vehicle-only control rats (25 per sex) (Furst and Schlauder 1971).

Two groups of 10 F344 male rats (three months old) were administered single i.m. doses (3.6 or 14.4 mg per rat) of metallic nickel powder in 0.5 mL of penicillin G procaine. Injection-site sarcomas were found in 0/10 rats in the 3.6-mg group and in 2/9 rats in the 14.4-mg group. No sarcomas were found in vehicle control rats (Sunderman and Maenza 1976).

Injection-site sarcomas were found in 17 of 20 WAG rats of unspecified age and sex given a single i.m. injection of 20 mg of metallic nickel powder in an oil vehicle of unspecified type. Vehicle-only controls (56 rats) did not develop sarcomas (Berry *et al.* 1984).

A group of 20 male F344 rats (two to three months old) were given a single i.m. injection of 14 mg of metallic nickel powder (99.5% pure) in 0.3 to 0.5 mL of penicillin G vehicle in the thigh. Injection-site tumors were found in 13 rats. The tumors were mainly rhabdomyosarcomas, with an average latency period of 34 weeks. None of the control rats (44 given penicillin G or 40 given glycerol) developed tumors (Sunderman 1984).

Rhabdomyosarcomas also occurred in 14 of 30 rats examined from a group of 40 male inbred WAG rats (10 to 15 weeks of age) given single i.m. injections of 20 mg of metallic nickel in paraffin oil. Metallic nickel also depressed natural killer cell activity, a response that correlated with rhabdomyosarcoma development in the rats. In another group given i.m. injections of interferon at 5×10^4 U per rat twice a week beginning in the tenth week after nickel treatment, five of 10 rats also developed rhabdomyosarcomas (Judde *et al.* 1987).

In male Syrian hamsters, two fibrosarcomas occurred in a group (25 per sex, three to four weeks old) given five monthly i.m. injections of 5 mg of metallic nickel powder in 0.2 mL of trioctanoin. No tumors occurred in vehicle controls (25 per sex) (Furst and Schlauder 1971).

4.1.6 Intraperitoneal administration studies in rats

An unspecified number of F344 rats (weighing 80 to 100 g) were administered 5 mg of metallic nickel powder in 0.3 mL of corn oil by i.p. injection twice a month for eight months. Following exposure, 30% to 50% of the rats developed intraperitoneal tumors. No tumor incidences were reported for control rats given only corn oil (Furst and Cassetta 1973).

A group of 50 female Wistar rats (12 weeks of age) received 10 weekly i.p. injections of 7.5 mg of metallic nickel powder of unspecified purity. Abdominal tumors (sarcomas, mesotheliomas, and carcinomas) were found in 46 of 48 rats. The average tumor latency was approximately eight months. The incidence of abdominal tumors in non-concurrent saline control Wistar rats ranged from 0% to 6% (Pott *et al.* 1987).

Other groups of female Wistar rats (18 weeks of age) developed tumors after being given single or repeated i.p. injections of metallic nickel powder (100% pure in 1 mL saline) once or twice a week, for a total dose of 6 to 25 mg of nickel (Pott *et al.* 1989, 1990, 1992). The dosages, incidences of mesotheliomas and sarcomas observed in 24 months, and total incidences of tumors at 30 months are shown in Table 4-1.

Table 4-1. Incidence of mesotheliomas and sarcomas in rats 24 months and 30 months after intraperitoneal injection of metallic nickel powder

Compound	Total dose (mg, as Ni)	No. of injections and dose	Incidence in 24 months		Incidence at 30 months (no. with tumor/no. examined)
			Sarcomas	Mesotheliomas	
Metallic nickel	6	1 x 6 mg	1	7	8/35*
	12	2 x 6 mg	3	11	13/35*
	25	25 x 1 mg	1	1	2/33
Saline control	0	3 x 1 mL	0	1	1/33
	0	50 x 1 mL	0	0	0/34

Source: Pott *et al*. 1989, 1990, 1992

*$P < 0.05$; significant different from vehicle control

4.1.7 Intravenous administration studies in rats, mice, and hamsters

A group of 25 Wistar rats of unspecified sex (24 weeks of age) received i.v. injections of metallic nickel powder as a 0.5% suspension in saline at a dose of 0.5 mL/kg body weight (b.w.) once a week for six weeks. Seven rats developed sarcomas in the groin region along the saphenous vein path of injection. No controls were used (Hueper 1955).

No tumors were observed in a group of 25 male C57B1 mice (six weeks old) given two i.v. injections in the tail vein of 0.05 mL of a 0.005% suspension of metallic nickel powder in 2.5% gelatin. The mice were observed up to 60 weeks after dosing; 19 survived more than 52 weeks, but only six were alive at the end of 60 weeks. No controls were used in the study (Hueper 1955).

4.1.8 Intrarenal administration studies in rats

During a 12-month observation period, tumors were not observed in a group of 20 female Sprague-Dawley rats of unspecified age given a single injection of 5 mg of metallic nickel in 0.05 mL of glycerin in each pole of the right kidney (Jasmin and Riopelle 1976).

In 18 F344 rats (two months old), intrarenal injection of 7 mg of metallic nickel powder in 0.1 or 0.2 mL of saline solution into each pole of the right kidney did not result in kidney tumors. Median survival was 100 weeks, compared with 91 weeks for controls. No tumors were observed in vehicle controls (Sunderman *et al*. 1984).

4.1.9 Subperiosteal injection studies in rats

Injection-site tumors were found in 11 of 20 WAG rats of unspecified age and sex each given a single subperiosteal injection of 20 mg of metallic nickel powder. No control information was reported (Berry *et al*. 1984). In its review of this study, the IARC Working Group noted the inadequate reporting of the study (IARC 1990).

4.1.10 Intramedullary injection studies in rats

Injection-site tumors were found in 9 of 20 WAG rats of unspecified age and sex each given a single intramedullary injection of 20 mg of metallic nickel powder. No control information was reported (Berry *et al*. 1984). In its review of this study, the IARC Working Group noted the inadequate reporting of the study (IARC 1990).

The carcinogenicity studies conducted with metallic nickel evaluated by IARC (1990) are summarized in Table 4-2.

Table 4-2. Summary of metallic nickel carcinogenicity studies in experimental animals

Route	Species (number)	Exposure (mg)	Tumor type and incidence (no. with tumors/no. examined)	Controls (no. with tumors/ no. examined)	Reference
Inhalation	rat (160)	not given	not given, benign lung neoplasms	no specific controls	Hueper 1958
Inhalation (plus sulfur dioxide)	rat (120)	15 (mg/m^3)	0/46 no lung tumors	no control data provided	Hueper and Payne 1962
Inhalation	mouse (20)	15 (mg/m^3)	0/20	no controls used	Hueper 1958
Inhalation	guinea pig (42)	15 (mg/m^3)	1/23 intraalveolar carcinoma 1/23 metastasis of adenocarcinoma	0/9	Hueper 1958
Intratracheal	rat (80)	0.9 (10 doses)	8/32* lung tumors (mostly carcinomas)	0/40	Pott *et al*. 1987
		0.3 (20 doses)	10/39* lung tumors (mostly carcinomas)	0/40	
Intratracheal	hamster (100)	10	1/100 local malignant tumors	no tumors	Ivankovic *et al.* 1987
		20	8/100 local malignant tumors	no tumors[a]	
		40	12/100 local malignant tumors	no tumors[a]	
		20 (4 doses)	10/100 local tumors	no tumors[a]	
Intratracheal	hamster (60)	0.8 (12 doses)	1/56 lung tumors	no tumors[a]	Muhle *et al.* 1990
Intratracheal	rat (85)	20 mg[b]	2/85; lung adenomas	number tumors not given[c]	Stettler *et al.* 1988[d]
Intrapleural	rat (25)	6.25	4/12* local sarcomas	0/70	Hueper 1952
Intrapleural	rat (10)	5	2/10 mesotheliomas	0/20	Furst *et al.* 1973
Subcutaneous	rat (10)	not given	5/10 local sarcomas	0/10	Mitchell *et al.* 1960
Intramuscular	rat (10)	28.3	10/10 local sarcomas	no tumors	Heath and Daniel 1964
Intramuscular	rat (50)	5	38/50 local sarcomas	0/50	Furst and Schlauder 1971
Intramuscular	rat (20)	3.6	0/10 local tumors	0/20	Sunderman and Maenza 1976
		14.4	2/9 local tumors	0/20	
Intramuscular	rat (20)	20	17/20 local tumors	0/56	Berry *et al.* 1984
Intramuscular	rat (20)	14	13/20 local tumors	0/44 (penicillin G)	Sunderman 1984

Route	Species (number)	Exposure (mg)	Tumor type and incidence (no. with tumors/no. examined)	Controls (no. with tumors/ no. examined)	Reference
Intramuscular	rat (40)	20	14/30 local tumors	no control data provided	Judde *et al.* 1987
Intramuscular	hamster (50)	5 (5 doses)	2/50 local fibrosarcomas	0/50	Furst and Schlauder 1971
Intraperitoneal	rat	5 (16 doses)	30%–50% local tumors	no control incidence reported	Furst and Cassetta 1973
Intraperitoneal	rat (50)	7.5 (10 doses)	46/48 abdominal tumors	0–6%[e]	Pott *et al.* 1987
Intraperitoneal	rat	6	4/34 local tumors (sarcomas or mesotheliomas)	1/67 (sarcoma)	Pott *et al.* 1989, 1990
		6 (2 doses)	5/34 local tumors (sarcomas or mesotheliomas)		
		1 (25 doses)	25/35 local tumors (sarcomas or mesotheliomas)		
Intravenous	rat (25)	0.5 mL/kg of 0.5% in saline	7/25, local tumors	no controls used	Hueper 1955
Intravenous	mice	0.5 mL of 0.005% in 2.5% gelatin	no tumors	no controls used	Hueper 1955
Intrarenal	rat (20)	5	no tumors	no control data provided	Jasmin and Riopelle 1976
Intrarenal	rat (18)	7	no tumors	no tumors	Sunderman *et al.* 1984
Subperiosteal	rat (20)	20	11/20 local tumors	no controls used	Berry *et al.* 1984
Intramedullary	rat (20)	20	9/20 local tumors	no controls used	Berry *et al.* 1984

Source: IARC 1990, 1999

*$P < 0.05$; significantly different from controls.

[a]Number of control animals not provided.

[b]Nickel slag containing approximately 20% nickel and 53% chromium.

[c]Author stated that the tumor incidence in treated animals was not significantly different from the control incidence.

[d]Not cited in IARC 1990.

[e]Abdominal tumors, in non-concurrent saline controls.

4.2 Nickel alloys

IARC also reviewed studies of the carcinogenic action of nickel alloys in experimental animals (IARC 1990, 1999; Appendix A and C, respectively). In these studies, nickel alloy powders were administered to hamsters by intratracheal instillation and to rats by s.c., i.m., i.p., and intrarenal injection and by piercing of the ear pinna with metallic identification tags containing nickel.

4.2.1 Intratracheal instillation studies in hamsters and rats

Groups of 100 Syrian golden hamsters were given single doses of 10, 20, or 40 mg of one of two nickel alloys in powdered form (particle diameter, 0.5 to 2.5 ∝m; alloy I: 26.8% nickel, 16.2% chromium, 39.2% iron, 0.04% cobalt; alloy II: 66.5% nickel, 12.8% chromium, 6.5% iron, 0.2% cobalt) or four-20 mg intratracheal instillations of one of the alloys every six months (total dose, 80 mg). In the hamsters given a single instillation of alloy II, malignant intrathoracic tumors were reported at frequencies of 1%, 8%, and 12% for the 10-, 20-, and 40-mg groups, respectively. In the hamsters given multiple instillations of alloy II, the incidence of malignant neoplasms (fibrosarcomas, mesotheliomas, and rhabdomyosarcomas) was 10%. Tumors were not observed in animals given alloy I or in controls (Ivankovic *et al.* 1987).

Syrian golden hamsters (strain Cpb-ShGa 51, 10 to 12 weeks old, approximately 60 per sex) were given 12 intratracheal instillations of 3 mg of pentlandite (containing 34.3% nickel; total dose, 36 mg), 3 or 9 mg of chromium/nickel stainless steel dust (containing 6.79% nickel; total doses, 36 or 108 mg), or 9 mg of chromium stainless steel dust (containing 0.5% nickel; total dose, 108 mg). Median survival was 90 to 130 weeks in the different groups. An adenoma of the lung was found in the pentlandite-treated group. No tumors were found in the stainless steel–treated animals, in the control animals (Muhle *et al.* 1990), or in the positive control group (IARC 1990).

The carcinogenic potential of nickel slag (containing approximately 20% nickel and 53% chromium) was tested in rats. In the study, 85 male F344 rats of unspecified age were given single 20-mg intratracheal instillations of nickel slag in deionized water and observed for 22 months. A separate group of 85 rats were given intratracheal instillations of deionized water and served as controls. Only two nickel slag–treated rats developed primary lung tumors (adenoma). The lung of one rat sacrificed at 18 months had multiple adenomas, and a rat that died between 12 and 18 months had a single adenoma. The tumor incidence was not significantly greater in nickel-treated rats than in the control group (Stettler *et al*. 1988).

4.2.2 Subcutaneous administration studies in rats

Local sarcomas (fibrosarcoma and rhabdosarcoma) were found in nine of 10 Wistar rats (five per sex, four to six weeks old) exposed to a nickel-gallium alloy (60% nickel) used for dental prostheses, as four s.c. pellet implants (approximately 2 x 2 mm). The rats were observed for 27 months. No tumors were found in control rats that received similar implants of other dental materials (Mitchell *et al.* 1960).

4.2.3 Intramuscular injection studies in rats

A group of 16 male F344 rats (two to three months old) were given single i.m. injections into the thigh of 14 mg (of the nickel component) of a ferronickel alloy ($NiFe_{16}$, Fe62Ni38) in 0.3 to 0.5 mL of penicillin G vehicle. The average latency period was 34 weeks. No tumors were observed in the exposed rats, in the 44 vehicle control rats given only penicillin G, or in 40 control rats given only glycerol (Sunderman 1984).

4.2.4 Intraperitoneal administration studies in rats

Groups of female Wistar rats (18 weeks of age) were given single or repeated i.p. injections of one of three nickel alloys (50% nickel, 29% nickel, 66% nickel) in 1 mL of saline once or twice a week and observed for 24 months. The dosing schedule and number of sarcomas and mesotheliomas observed in the rats are shown in Table 4-3 (Pott *et al*. 1989, 1990).

Table 4-3. Incidence of peritoneal mesotheliomas and sarcomas in rats 24 and 30 months after i.p. injection of nickel alloys

Compound	Total dose (mg, as Ni)	Injection schedule	Tumor incidence at 24 months		Incidence in 30 months (no. with tumors/ no. examined)
			Sarcomas	Mesotheliomas	
Alloy (29% Ni)[a]	50	1 x 50 mg	1	1	2/33
	100	2 x 50 mg	0	1	1/36
Alloy (52% Ni)	50	1 x 50 mg	1	7	8/35*
	150	3 x 50 mg	3	11	13/35*
Alloy (66% Ni)[b]	50	1 x 50 mg	0	12	12/35*
	150	3 x 50 mg	5	19	22/33*[c]
Saline control	0	3 x 1 mL	0	1	1/33
	0	50 x 1 mL	0	0	0/34

Source: Pott *et al*. 1989, 1990, 1992

*$P < 0.05$; significantly different from controls.

[a]Before milling: 32% Ni, 21% Cr, 0.8% Mn, 55% Fe.

[b]Before milling: 74% Ni, 16% Cr, 7% Fe.

[c]Two animals had both mesothelioma and sarcoma.

4.2.5 Intrarenal administration studies in rats

Two-month-old male F344 rats received an intrarenal injection of 7 mg of a ferronickel alloy ($NiFe_{16}$; 7 mg of Ni per rat) in 0.1 or 0.2 mL of saline solution into each pole of the right kidney A renal tumor (nephroblastoma) was observed in one of 14 rats examined. The rats were observed for two years. No tumors were observed in vehicle controls (Sunderman *et al*. 1984).

4.2.6 Tissue implantation/insertion studies in rats

In an assessment of the carcinogenicity of cadmium chloride, tumors were found in male Wistar rats (six weeks of age) at the sites of insertion of nickel-copper alloy ear tags (65% nickel, 32% copper, 1% iron, 1% manganese) (Waalkes *et al*. 1987). The tags were inserted through the cartilaginous portion of the ear pinna. In this study, 16 tumors developed in the 361 rats within 104 weeks of placement of the ear tags. The tumors were mostly osteosarcomas at the site of attachment. Many other rats showed preneoplastic connective tissue lesions. No tumors developed in the contralateral, non-tagged ear pinna. A concomitant early infection at the implant site appeared to have played a role in the development of tumors, as tumors developed at a much lower rate at ear-tag sites without early infection. The authors suggested that the early infection may have helped mobilize nickel from the tag.

In a study of tumors induced by the tumor initiator 1,2-dimethylhydrazine (1,2-DMH) in the cecum of rats, it was concluded that tumor development may have been promoted by stapling with a ferronickel alloy (Buhr *et al*. 1990). In 25 BD9 rats (three months old, of unspecified sex), the cecum had been sutured with ferronickel alloy staples (iron 70%, chromium 15%, nickel 12%, other materials 3%). After a recovery period of three weeks, the rats were given weekly s.c. injections (21 mg/kg) of the known carcinogen 1,2-DMH for one year. Nickel control animals (18 rats) had the cecum sutured with the ferronickel alloy but were not given 1,2-DMH. Positive control animals (25 rats) were laparotomized without sutures and given 1,2-DMH. Negative control animals were laparotomized without sutures and were not given 1,2-DMH. Suture controls (25 rats) had the cecum sutured with absorbable vicryl sutures (3-0, Ethicon) and were given 1,2-DMH. The results of the study suggest that the ferronickel staples significantly ($P < 0.05$) increased the incidence of 1,2-DMH-induced gastrointestinal tumors, compared with 1,2-DMH treatment alone. Gastrointestinal tumor incidences related to these treatments are shown in Table 4-4 .

Table 4-4. Promotional effect of ferronickel staples on the incidence of 1,2-DMH-induced gastrointestinal tumors

Observation	Number of tumors			
	Staples + 1,2 DMH (n = 25)	Staples only control (n = 18)	Vicryl + 1,2-DMH (n = 25)	1,2-DMH control (n = 25)
Tumor site				
Stomach	1	0	0	1
Small bowel	4	0	2	2
Cecum	9	0	11	6
Cecum ascendens	6	0	5	6
Cecum transcendens	3	0	2	2
Cecum descendens	26	0	20	19
Rectum	4	0	1	0
Total no. of gastrointestinal tumors	53	0	41	36
Number of tumor-bearing animals	23	0	19	20

Source: Buhr *et al.* 1990

The carcinogenic potential of nickel orthopedic prosthetic bone implants (composition ranging from 0.1% to 35.4% nickel by weight) was studied in groups of 10 to 17 male and 13 to 15 female Sprague-Dawley rats (total number, 409; 30 to 43 days old) and evaluated by complete autopsy examination performed at the time of death or at the end of the 30-month experimental period (Memoli *et al*. 1986). A total of 77 rats (groups of 12 or 13 males) were used as 24- and 30-month untreated or sham-operated controls. The following nickel alloys used:

solid 316L: 13.77% nickel, 65.2% iron, 17.2% chromium, 2.46% molybdenum, 0.47% manganese, 0.46% silicon, 0.24% copper, 0.11% cobalt, 0.10% phosphorus, 0.03% sulfur, 0.02% carbon

powdered 316L: 13.4% nickel, 67.8% iron, 16.1% chromium, 2.42% molybdenum, 0.11% manganese, 0.11% cobalt, 0.07% copper, 0.064% N, 0.024% carbon, 0.015% sulfur

solid CoCrWNi: 12.44% nickel, 46.8% cobalt, 19.63% chromium, 13.76% tungsten, 3.78% iron, 2.21% magnesium, 1.39% silicon

CoCrWNi wire: 10.36% nickel, 51% cobalt, 19.79% chromium, 14.47% tungsten, 2.35% iron, 1.67% manganese, 0.27% silicon, 0.09% carbon, 0.02% sulfur, 0.013 phosphorus

solid $MP_{35}N$: 36.1% nickel, 32.5% cobalt, 20.0% chromium, 9.4% molybdenum, 1.5% iron, 0.74% titanium, 0.12% carbon, 0.09% silicon, 0.03% manganese

powdered $MP_{35}N$: 35.4% nickel, 33.0% cobalt, 21.8% chromium, 8.7% molybdenum, 0.7% titanium, 0.4% iron

Implant site–associated malignancies found in the rats administered the CoCrWNi alloy included malignant fibrous histiocytoma (two rats) and undifferentiated sarcoma (one rat). Rats administered the $MP_{35}N$ alloy bore rhabdomyosarcoma (three rats). Spontaneous, non-implant site malignancies were found in most of the aging rats (66 rats); these included medullary and papillary carcinomas of the thyroid and squamous cell carcinoma of the skin and lungs, soft tissue fibrosarcoma, leiomyosarcoma of the uterus, mammary carcinomas, and basal cell carcinomas of the skin. The incidence of sarcoma was significantly higher in animals bearing nickel alloy implants than in control and sham-operated animals.

The carcinogenicity of a nickel alloy (96.3% nickel, 2.52% tungsten, 0.66% aluminum, 0.34% manganese, 0.11% silicon, 0.11% iron, 0.01% carbon, 0.01% copper, 0.001% sulfur) was evaluated by implantation of solid rods of the alloy in the thigh muscle of C57BL/6N mice (23 per sex) for 24 months (Takamura *et al*. 1994). The incidence of tumor-caused mortality among the mice at the end of 24 months was 87% for both sexes combined. Tumor incidence was 91.3% for both sexes combined. Days to tumor appearance were 424.3 ± 82.7 in male mice and 343.2 ± 57.6 in female mice. Tumors found at the implantation site included malignant fibrous histiocytoma or fibrosarcoma (21 each in males and females). Although the incidences of non-implantation site spontaneous tumors were high in all groups of mice in the study, no evidence of substance-induced carcinogenicity was seen in sham-operated controls or in animals receiving non-nickel implants (stainless steel alloy, titanium alloy, alumina, or zirconia).

The carcinogenicity studies of nickel alloys evaluated by IARC (1990) are summarized in Table 4-5.

Table 4-5. Studies of the carcinogenicity of nickel alloys in experimental animals evaluated by IARC

Alloy	Route	Species (number)	Exposure (mg)	Tumor type and incidence (no. with tumors/ no. examined)	Controls (no. with tumors/ no. examined)	Reference
Nickel alloy: 26.8% Ni, 16.2% Cr, 39.2% Fe, 0.04% Co	intratracheal	hamster (100)	10	no local tumors	no tumors[a]	Ivankovic *et al.* 1987
			20	no local tumors		
			40	no local tumors		
			20 (4 doses)	no local tumors		
Nickel alloy: 66.5% Ni, 12.8% Cr, 6.5% Fe, 0.2% Co	intratracheal	hamster (100)	10	1/100, local tumors		
			20	8/100, local tumors		
			40	12/100, local tumors		
			20 (4 doses)	10/100, local tumors		
Nickel-gallium alloy (60% Ni)	s.c.	rat (10)	not given	9/10, local tumors	0/10	Mitchell *et al.* 1960
Nickel alloy (12.44% Ni)	intramuscular implantation	rat (32)	not given	3/32, local malignant fibrous histiocytoma and undifferentiated sarcoma	no local tumors	Memoli *et al.* 1986
Nickel alloy (35.4% Ni)	intramuscular implantation	rat (26)	not given	3/26, local rhabdosarcoma	no local tumors	Memoli *et al.* 1986
Nickel alloy (96.3% Ni)	intramuscular implantation	mouse	not given	male: 21/23, local tumors female: 21/23, local tumors	no local tumors	Takamura *et al.* 1994
Nickel-iron alloy ($NiFe_{1.6}$)	intramuscular implantation	rat (16)	14	0/16, local tumors	0/44	Sunderman 1984
Nickel-iron alloy ($NiFe_{1.6}$)	intrarenal	rat	7	1/14, renal cancers	0/46	Sunderman *et al.* 1984
Nickel alloy (29% Ni)	i.p.	rat	50	2/33, local tumors	1/67	Pott *et al.* 1989, 1990
			50 (2 doses)	1/36, local tumors		
Nickel alloy (50% Ni)	i.p.	rat	50	8/35, local tumors		
			50 (3 dose)	13/35, local tumors		
Nickel alloy (66% Ni)	i.p.	rat	50	12/35, local tumors		
			50 (3 doses)	22/33, local tumors		
Pentlandite	intratracheal	hamster (60)	3 (12 doses)	1/60, local tumors	no tumors[a]	Muhle *et al.* 1990
Nickel alloy (65% Ni)	unilateral ear pinna implantation	rat	not given	16/361; mainly osteosarcomas[b]	no local tumors in contralateral pinna	Waalkes *et al.* 1987

Source: IARC 1990, 1999

[a]Number of control animals not provided.

[b]Osteosarcoma, fibrosarcoma, histiocytoma, papilloma, giant cell tumor.

4.3 Other nickel compounds

IARC (1990) found *sufficient evidence* of carcinogenicity at various sites in rodents for nickel monoxides, nickel hydroxides, and crystalline nickel sulfides. IARC found *limited evidence* of carcinogenicity in rodents for nickel carbonyl, nickel arsenides, nickel antimonides, nickel selenides, and nickel telluride. There was *inadequate evidence* of carcinogenicity in experimental animals for nickel trioxide, amorphous nickel sulfide, and nickel titanate.

The NTP (1996a,b,c) conducted 104- or 105-week inhalation cancer bioassays studies with nickel oxide, nickel subsulfide, and sulfate hexahydrate in F344/N rats and $B6C3F_1$ mice of both sexes. The researchers concluded that for nickel oxide there was *some evidence of carcinogenic activity* in male and female rats and *no evidence of carcinogenic activity in male mice, and equivocal evidence of carcinogenicity* in female mice (NTP 1996a). There was *clear evidence of carcinogenic activity* in male and female rats, but not in male or female mice exposed to nickel subsulfide (NTP 1996b). Nickel sulfate hexahydrate was *not carcinogenic* in rats or mice (NTP 1996c). Tumor types observed in these studies included alveolar or bronchiolar adenomas and carcinomas.

Soluble nickel(II) acetate tetrahydrate, administered by a single i.p. injection to male F344/NCr rats (five weeks of age), was an effective initiator of renal cortical epithelial tumors at a dose of 90 ∝mol/kg b.w. (Diwan *et al*. 1992, Kasprzak *et al*. 1990). In a similar study, nickel(II) acetate administered by a single i.p. injection to pregnant female F344/NCr rats caused tumors in the offspring at a dose of 90 ∝mol/kg b.w. Nickel(II) acetate was found to be a transplacental initiator of epithelial tumors of the kidney and a complete transplacental carcinogen for rat pituitary, primarily inducing rare pituitary carcinomas (Diwan *et al*. 1992).

4.4 Summary

Metallic nickel and a variety of nickel alloys were carcinogenic to rodents in instillation, injection, and implantation studies, causing significantly increased tumor incidences in soft tissue and bone.

In studies with metallic nickel, no malignant tumors were observed when rats and guinea pigs were exposed by inhalation. One study, however, found intra-alveolar carcinoma and metastasis of adenocarcinoma in one of 23 male and female hamsters following inhalation of metallic nickel. Via other routes of exposure, significantly elevated incidences of local adenocarcinomas and squamous cell carcinomas were observed in lungs of rats. Adenocarcinomas, fibrosarcomas, mesotheliomas, and rhabdomyosarcomas were observed in hamsters following intratracheal instillation of metallic nickel powder. Round-cell and spindle-cell sarcomas of the lungs were found in the injection sites of rats exposed by the intrapleural route, whereas no tumors were found in control rats. Local tumors of an unspecified nature and injection-site rhabdomyosarcomas, fibrosarcomas, and sarcomas were found in rats subcutaneously exposed to metallic nickel, but not in unexposed control rats. Fibrosarcomas were found in hamsters following i.m. exposure. Significantly elevated incidences of injection-site tumors also were observed in rats following i.p., i.v., subperiosteal, and intrafemoral exposures to metallic nickel. Tumors were not found in rats given intrarenal doses of metallic nickel or in mice following i.v. exposure to metallic nickel powder.

In studies with nickel alloys, malignant local neoplasms (adenoma, fibrosarcomas, mesotheliomas, and rhabdomyosarcomas) were seen in rats and hamsters given intratracheal instillations. Rats exposed to nickel alloys via i.p. injections, intrarenal injections, or s.c., ear, muscle, or bone implants developed local sarcomas or osteosarcomas. No tumors were observed, however, in rats injected i.m. with a nickel alloy or in hamsters injected intratracheally with a nickel alloy containing only 26.8% nickel. Nickel alloy staples were observed to promote 1,2-DMH-induced gastrointestinal adenocarcinomas in rats. In general, alloys containing > 50% nickel were carcinogenic in implantation studies, and carcinogenicity showed a dose-response pattern, increasing with increasing nickel content.

The carcinogenicity of many soluble and insoluble nickel compounds is well established in experimental animals. Nickel monoxide, nickel hydroxide, crystalline nickel sulfide, nickel acetate, and nickel sulfate were carcinogenic in studies with experimental animals. Studies of nickel arsenides, nickel antimonides, nickel selenides, and nickel telluride, as well as nickel carbonyl and nickel salts, provided limited evidence of carcinogenicity in experimental animals. Studies of experimental animals exposed to nickel trioxide, amorphous nickel sulfide, and nickel titanate did not provide evidence of carcinogenicity.

5 Genotoxicity

IARC conducted an expansive review of the literature through 1990 on the genotoxicity of nickel and nickel compounds (IARC 1990). This section contains genotoxicity information from the IARC review and recent publications, with emphasis on nickel metal and nickel alloys.

Appendix B (adapted from IARC 1990 and updated) presents a concise comparative summary of genetic and related effects in terms of phylogenetic origin, type of nickel, test system applied, result (positive, negative, or conditional), and study references.

5.1 Prokaryotic systems

5.1.1 Gene mutation in Salmonella typhimurium

Wever *et al*. (1997) tested extracts of the nearly equiatomic nickel–titanium alloy (NiTi) with an interest in its safety for use in surgical procedures, including osteosynthesis staples, blood vessel filters, other blood vascular applications, and various permanent implants. The studies were carried out in compliance with International Organization of Standardization (ISO) standards for biological evaluation of medical devices, using validated procedures. AISI 316 LVM, a widely used stainless steel implant material (13% to 15% nickel) was employed in these studies as a negative control. Both alloys were extracted in physiological aqueous solution at 37ºC, with gentle shaking over a period of 72 hours.

S. typhimurium strains TA1535, TA100, TA1537, and TA98 were exposed to five concentrations of the extraction samples (from 20% to 100%) with and without metabolic activation provided by addition of rat liver S9 microsomal fraction to the reaction mix. Plates were scored for revertant colonies after a standard 48-hour, 37ºC incubation. The NiTi extract did not induce reverse mutations in any tester strain at any tested concentration, with or without S9.

5.2 Plants

5.2.1 Micronucleus formation in Tradescantia *and* Vicia

Intact *Tradescantia* plants (hybrid clone #4430) and germinated *Vicia* beans were directly planted in soils containing various amounts of nickel chloride and analyzed for induction of micronuclei according a standardized method (German leaching test DIN 38414-S4) (Knasmuller *et al*. 1998). *Tradescantia* specimens were exposed to doubling concentrations of nickel chloride from 1.25 to 10 mM. After a six-hour exposure period and a 24-hour tap-water recovery period, cuttings were histologically fixed, five slides were prepared for each exposure level, and 300 tetrads were scored per slide. *Vicia* bean roots were exposed to nickel chloride solutions in doubling concentrations from 1.25 mM to 40.0 mM for six hours, followed by a 24-hour recovery period. They were then fixed and acid hydrolyzed, and slides were prepared by squashing and staining of the cells. Three slides were prepared per exposure concentration, and 100 cells were scored per slide.

No acute toxic effects were observed in *Tradescantia* or *Vicia* at the exposure levels used. Dose-related increases in micronuclei were observed in the *Tradescantia* experiments and were said to be significant (*P* value not provided) at the two highest exposure concentrations. The *Vicia*

experiments did not result in micronucleus induction. The authors suggested their modification of the *Tradescantia* micronucleus assay may be useful for *in situ* soil monitoring for genotoxic metals.

5.3 Mammalian systems

5.3.1 In vitro assays

5.3.1.1 LacI mutation in transgenic rat embryonic fibroblasts

The Stratagene Big Blue Rat 2 transgenic embryonic fibroblast cell line, carrying the bacteriophage ∞-*lacI* shuttle vector, was tested (Mayer *et al*. 1998). Log-phase cells were exposed to nickel subsulfide for two hours at concentrations from 2.4 to 40.8 mg/L. They were then washed, passaged at 48 hours, and seeded for plating efficiency, and aliquots were grown to confluence, harvested, and frozen for DNA processing. Genomic DNA was extracted for packaging of the target genes into ∞phages, and single mutant *lacI* plaques were subjected to sequence analysis.

Nickel subsulfide exposure increased the frequency of the *lacI* mutation more than fourfold over the background level of 4.0×10^{-5} in a concentration-dependent manner (no *P* values provided). Plating efficiency decreased with higher nickel concentrations, and induction of mutations appeared to correlate strongly with toxicity. Sequencing showed that the majority of mutants from both exposed and control cells had simple base substitutions (78% and 89%, respectively). Transitions at G:C basepairs occurred at CpG sites in 83% of nickel-exposed cells but in only 33% of control cells. However, in 33% of the phenotypic mutants from the exposed group, no sequence change was detected, and the proportion of mutants with no sequence change increased when the background contribution was deducted.

5.3.1.2 Chromosomal aberrations in Chinese hamster fibroblasts

Induction of chromosomal aberrations was tested in Chinese hamster fibroblasts (cell line V79). The cells were exposed to extracts of nickel–titanium alloy prepared as described in section 5.1.1, with and without rat liver S9 metabolic activation (Wever *et al*. 1997). The exposure levels were 6%, 8%, and 10% NiTi extracts diluted with aqua bidest. Positive controls were ethylmethanesulfonate without metabolic activation and cyclophosphamide with metabolic activation. After a 20-hour incubation, cells were fixed and stained, and 200 metaphases per dose level were scored for breaks, fragments, deletions, exchanges, disintegrations, and gaps. No significant difference in the number of cells with chromosomal aberrations was observed under any of the exposure conditions.

5.3.1.3 DNA single-strand breaks in mouse lung and nasal mucosa cells (comet assay)

Lung and nasal mucosa cells from male CD2F1 mice were exposed to nickel subsulfide at 9.6 mg/L or 40.8 mg/L for 2 hours and assayed with the alkaline comet assay (single-cell gel electrophoresis) (Mayer *et al*. 1998). The treatment did not affect the viability of the cells. At the higher concentration, about 90% of both cell types sustained DNA damage. At the lower concentration, 60% of lung cells and 40% of nasal mucosa cells were observed to contain fragmented DNA. The authors stated that the damage was likely due to reactive oxygen species,

because it was completely inhibited by the addition of the peroxide scavenger catalase at 500 ∝g/mL.

5.3.1.4 Morphological transformation of hamster cells in culture

Costa *et al.* (1981) reported induction of dose-dependent morphological transformation in cultured SHE cells by nickel powder ground to a mean particle size of 4 to 5 ∝m and applied at concentrations of 5, 10, and 20 ∝g/mL. At the highest exposure level, the incidence of transformation was 3%.

Hansen and Stern (1984) reported that nickel powder transformed baby hamster kidney (BHK-21) cells in a soft agar proliferation system. The IARC Working Group did not consider the results of this study in its final evaluation, owing to associated technical and interpretative difficulties.

5.3.1.5 Inhibition of DNA synthesis in Chinese hamster ovary (CHO) cells

Powdered nickel blocked progression through S phase of the cell cycle (DNA replication) in cultured CHO cells in a flow cytometric assay (Costa *et al.* 1982).

5.3.1.6 Chromosomal aberrations in human peripheral blood lymphocytes

Human peripheral blood lymphocytes exposed to nickel powder under short-term culture conditions did not have chromosomal aberration frequencies above the background levels (Paton and Allison 1972).

5.3.1.7 DNA single-strand breaks in human peripheral blood lymphocytes

Assad *et al*. (1999) adapted an assay that combines *in situ* end-labeling, colloidal gold tagging, and electron microscopy to measure genotoxicity induced *in vitro* by biomaterials. This new method localizes and quantitates DNA breakage and repair. For these studies, nickel–titanium alloy and 316L stainless steel (each powdered to 250 ∝m < ø < 500 ∝m), commercially pure nickel (particles ″ 250 ∝m), and commercially pure titanium (particles < 150 ∝m) were extracted under simulated dynamic physiological conditions according to ISO standards. The extraction method was similar to that described in Section 5.1.1, except that incubation was for 24 hours, rather than 72 hours. For negative controls, culture tubes with media were processed under the same conditions, but without metal specimens added.

Human lymphocytes, in whole blood obtained from volunteers, were exposed to the metal extracts in complete medium under conditions typical for culturing and collecting cells for analyses of metaphases, and slides were prepared for scoring chromosome spreads. For visualization of the location of strand breaks, the chromosomes were digested with exonuclease III, which amplified lesions by releasing nucleotides at free 3∝hydroxyl ends from nicked double-stranded DNA. The single-stranded DNA was hybridized with short oligonucleotides of random sequences including biotinylated 2∝deoxyuridine-5∝triphosphate (dUTP). After random priming with *Escherichia coli* DNA polymerase I, incorporation of biotin-dUTP was detected by immunogold binding to the chromatin. Labeling was quantified through computerized image analysis of electron microscopic images and enumerated as mean number of immunogold

particles per square micrometer of chromatin. An electron microscopy *in situ* end-labeling assay was used in conjunction with AAS to quantitate metal ion diffusion and to measure presumed genotoxic effects. The results are summarized in Table 5-1.

Table 5-1. Induction of DNA single-strand breaks in human lymphocytes by powdered pure nickel, stainless steel, nickel–titanium alloy, and pure titanium

	Mean solubility (released ions, µg/L)	Mean immunogold binding (particles/µm^2)	
		Interphase	Metaphase
Pure nickel	2,600	430.7[a]	459.0[a]
Stainless steel	86.7	429.3[a]	570.0[b]
Nickel–titanium alloy	23.7	166.1	198.1
Pure titanium	20.5	159.1	163.4
Negative control	< 0.6	145.5	155.2

Source: Assad *et al*. 1999

[a]$P \leq 0.001$; significantly different from NiTi, titanium, and negative control (one-way analysis of variance).

[b]$P \leq 0.001$; significantly different from nickel, NiTi, titanium, and negative control (one-way analysis of variance).

The authors noted that the high concentrations of nickel ions in the pure nickel extracts were strongly cytotoxic to lymphocytes, causing cell-cycle arrest at interphase, with signs of apoptosis or necrosis. The authors stated that only a few mitoses could be harvested from cultures containing pure nickel extracts owing to toxicity (no data provided).

Significant differences were found in the potency of the various metal extracts to induce single-strand DNA breaks. As shown in Table 5-1, the effects were greatest in pure nickel and stainless steel, in both interphase and metaphase. Two-way analysis of variance indicated that single-strand breaks were more frequent in metaphase than interphase. The authors suggested that the observed differences between metaphase and interphase DNA vulnerability to attack by nickel (and other ions) resulted from different relative levels of chromatin compaction. They also speculated that the potency of the stainless steel might be due to interaction of chromium and other elements not measured, in addition to free nickel ion (Assad *et al*. 1999).

5.3.2 In vivo *assays*

5.3.2.1 LacZ *and* lacI *mutations in transgenic rodents*

Muta Mouse transgenic male mice carrying the bacterial gene *lacZ* and Big Blue transgenic male rats (Fischer 344) carrying the bacterial gene *lacI* were exposed to nickel subsulfide by inhalation for two hours at concentrations calculated to yield doses of 4, 7, and 13 mg/kg b.w. (Mayer *et al*. 1998). The distribution of inhaled particles deposited in the lungs and nasal mucosa was determined by AAS. The mean nickel content in rat lung was about 540 ∝g/g (compared with a background level of about 1.0 ∝g/g), and the mean nickel content in rat nasal mucosa was 70 ∝g/g (compared with a background level of 2.0 ∝g/g). After a two-week expression period,

nasal mucosa and lung tissues were removed and stored in liquid nitrogen before further processing. Histological examination at the time of harvest revealed marked hyperemia of the lung. Nevertheless, the mutation assays, performed as described in Section 5.3.1.1 for *lacI* transgenic rats and in Dean and Myhr (1994, cited in Mayer *et al.* 1998) for *lacZ* transgenic mice, showed no significant increases in mutation frequencies.

5.3.2.2 DNA single-strand breaks in rodent lung and nasal mucosa

Transgenic and non-transgenic CD2F1 mice and F344 rats were exposed to nickel subsulfide by nose-only inhalation for two hour at concentrations calculated to yield doses of 4, 7, and 13 mg/kg b.w. (Mayer *et al*. 1998). The distribution of inhaled particles was determined by AAS. The comet assay was applied to cells freshly isolated from nasal mucosa and lung tissue. Nickel uptake totals in transgenic animals (*lacZ* mice and *lacI* rats) used in mutation analyses were similar to those determined in the non-transgenic animals used in the *in vivo* comet assay studies. DNA strand breaks in non-transgenic mice was observed as about 25% in the lung and 60% in nasal mucosa at 4 mg/kg. DNA damage in non-transgenic rats was about 10% in the lung (7 mg/kg) and 40% in nasal mucosa (13 mg/kg). Transgenic rats and mice did not show a significant increase in mutation frequencies compared to negative controls.

5.3.2.3 Chromosomal aberrations in human bone marrow cells

Bone marrow samples from 71 patients undergoing revision arthroplasty of a loose or worn prosthesis and 30 patients undergoing primary arthroplasty (controls) were examined for chromosomal damage (Case *et al.* 1996). Bone marrow cells adjacent to the prosthesis at revision surgery had more chromosomal aberrations than either iliac crest marrow cells from the same patients or femoral bone marrow cells from the control patients. Chromosomal aberrations included gaps, chromatid breaks and exchanges, and chromosome breaks and exchanges. However, tissue metal concentrations were not compared with the aberration rates, nor were the affected cell types recorded.

5.3.2.4 Sister chromatid exchange (SCE) in human peripheral blood lymphocytes

Urinary excretion of metals and frequency of SCEs in circulating lymphocytes were compared between 26 male workers occupationally exposed to dusts of cobalt, chromium, and nickel and 25 male controls matched by age and smoking habits (Gennart *et al*. 1993). Excretion of metals and SCE frequencies both were significantly greater in exposed workers than in controls. Tobacco smoking increased SCE frequency in both groups, independently of increases associated with metal dust exposure. The authors concluded (perhaps erroneously) that since cobalt is thought to be only weakly mutagenic, their results suggested that the small amounts of chromium and nickel absorbed into the blood may have been sufficient to induce SCEs. Evidence was not presented to allow determination of the relative genotoxic influences of chromium and nickel.

Werfel *et al*. (1998) conducted a study on 39 metal-arc welders in Essen, Germany, occupationally exposed fumes containing nickel and chromium. The control group consisted of 39 non-welders matched according to age and smoking and alcohol consumption habits and known not to be substantially exposed to occupational or environmental carcinogens. Blood samples were assayed for sister chromatid exchanges, chromium levels in the erythrocyte

fraction and nickel levels in whole blood (by AAS), and concentrations of serum glutamate-oxalacetatetranspeptidase (SGOT), glutamate-pyruvatetranspeptidase (SGPT), and gamma-glutamyltranspeptidase (SGGT).

Chromium and nickel concentrations for the welders were 4.3 and 4.6 ∝g/L, respectively (values for controls were not reported). Workplace atmospheric measurements were not taken, but the authors estimated that these values may correspond to air concentrations of approximately 100 ∝g CrO_3/m^3 and 300 ∝g Ni/m^3.

The SCE assay was conducted according to the procedure of Perry and Wolff (1974, cited in Werfel *et al.* 1998). SCE were enumerated by scoring 25 complete second division metaphases per subject. The individual SCE frequencies were calculated as the average SCE frequency per metaphase spread. The mean SCE frequency for the welders (6.22) was significantly higher than that of the controls (5.87) ($P = 0.04$). Age and observed SCE frequency for all subjects were significantly correlated, but age was not seen as a factor when comparing the worker and control groups. The SCE frequency was significantly higher among welders who drank alcohol (n = 33) than among welders who were non-drinkers (n = 6) (6.38 versus 5.34, $P = 0.016$). In the control group, the SCE frequency also was significantly higher among alcohol drinkers (n = 28) than among non-drinkers (n = 11) (6.37 versus 5.69, $P = 0.034$). Welders with an SGGT activity above the threshold level of 25 U/L (n = 7) also had higher SCE frequencies than did welders with normal GGT activity (6.94 versus 6.04, $P = 0.023$).

5.3.2.5 DNA single-strand breaks in human peripheral bolld lymphocytes

The study of welders by Werfel *et al*. (1998) (described above) also included an evaluation of alkaline filter elution rates, to measure DNA single-strand breakage in peripheral blood lymphocytes, employing a slight modification of the method of Doerjer *et al*. (1988, cited in Werfel *et al.* 1998). The elutions were performed with both polycarbonate and polyvinylidene fluoride (HVLP) filters, with and without proteinase K.

When polycarbonate filters were used with proteinase K, the mean relative DNA elution rate was significantly higher for the welders (n = 39) and than for the controls (n = 39) (1.40 vs. 0.82; $P = 0.0001$). No significant differences in relative DNA elution rates were observed with polycarbonate filters without proteinase K or with HVLP filters.

The authors interpreted the results to indicate significantly elevated DNA single-strand breakage frequency along with DNA-protein crosslinks in welders. Further, welders who spent more than 50% of their shifts metal-arc welding had higher DNA elution rates with both filter types. Age was not significantly correlated with relative DNA elution rates for either filter type. The biomonitoring results did not differ between smokers and non-smokers. However, elution rates were significantly lower for welders who were alcohol drinkers, both with PC filters with proteinase K (1.23 versus 2.30, $P = 0.002$) and with HVLP filters (2.60 versus 4.22, $P = 0.031$). SGGT activity did not seem to influence DNA elution rates in any case.

Werfel *et al*. (1998) stated that their results were not specific for exposure to either chromium or nickel, and that there were no significant correlations between biomonitoring data, SCE frequencies, and DNA elution rates. However, they believed their methods were sufficiently

sensitive to demonstrate DNA damage in welders, as a group, receiving exposures within the occupational limits (threshold limit values, maximum workplace concentrations, and technically achievable workplace concentrations).

5.4 Summary

In assays with plants, nickel chloride induced micronucleus formation in *Tradescantia* at concentrations of 20.0 and 40.0 mM, but not in *Vicia*.

Equiatomic nickel–titanium alloy, a surgical implant material, did not induce reverse mutations in the *S. typhimurium* or chromosomal aberrations in Chinese hamster fibroblasts.

Nickel powder induced dose-dependent morphological transformations in cultured SHE cells, with a 3% incidence at the highest exposure level. Finely ground nickel also transformed BHK-21 cells in a soft agar proliferation system. Nickel powder interfered with DNA synthesis, blocking proliferation of CHO cells at S phase, in a flow cytometric assay.

Nickel subsulfide induced a 4.5-fold increase in mutation frequency in a rat *lacI* transgenic embryonic fibroblast line. The DNA-damaging effects of nickel subsulfide also were examined in the comet assay and transgenic rodent mutation assays to measure effects in cells thought to be targets of nickel-induced carcinogenesis. Freshly isolated primary cells from lung and nasal mucosal tissues were affected in a concentration-dependent fashion after *in vitro* exposures. Analogous results were not observed in the same cell types following inhalation exposures of mice and rats, although a high degree of DNA damage was observed in mouse nasal mucosa. Nickel subsulfide exposures by inhalation failed to induce mutations in transgenic *lacZ* mice and *lacI* rats. The authors suggested that the results might support a proposed nongenotoxic model of nickel carcinogenesis based on gene silencing after methylation of DNA and condensation of the affected chromatin. This model may also explain the *in vitro* findings that phenotypic *lacI* mutation frequencies can be increased without any alteration of DNA sequence in the coding region of *lacI*.

A proposed genotoxicity test that combines *in situ* end-labeling, colloidal gold tagging, and electron microscopy was used to assess effects of nickel–titanium alloy, stainless steel, pure nickel, and pure titanium extracts on human lymphocytes in culture. After exposures to pure nickel and stainless steel, both interphase and metaphase chromatins contained significant increases in single-strand DNA breaks.

Nickel powder did not cause chromosome aberrations in human peripheral blood lymphocytes exposed and tested *in vitro* under short-term culture conditions.

In the welding fume studies described here, nickel quality and quantity are not well characterized. The amount of elemental nickel in the cells following *in vivo* exposures was measurable by AAS, but the exact form of nickel upon entry into the body was not known. The results were further confounded by the presence of chromium and probable interactions between biological effects of the metals. The welder-exposure study revealed no significant correlations between biomonitoring results, SCE frequencies, and DNA elution rates. Slight significant

increases in SCE frequencies and incidences of single-strand DNA breakage were observed in lymphocytes from steel welders occupationally exposed to nickel-containing fumes.

6 Other Relevant Data

6.1 Absorption, distribution, and excretion

The ability of divalent nickel ions, Ni(II) or Ni^{2+}, to interact with nucleoproteins appears to be the major determinant of the carcinogenic effect of nickel (Sunderman 1989a). The release of Ni^{2+} from inhaled metallic nickel or nickel alloy particles depends on oxidization of the elemental nickel by endogenous oxidants rather than on the solubility of the elemental nickel. The smaller the particle size, the faster the clearance from the lungs and the higher the release of nickel ions from inhaled metallic nickel or nickel alloys (NiPERA 1998).

6.1.1 Metallic nickel

When finely powdered metallic nickel was injected into rat muscle, it slowly dissolved and diffused from the injection site into the surrounding cells. Upon further examination, nickel was found in the nuclear fraction (bound to nucleoli) and mitochondria of the local rhabdomyosarcoma that developed in the rats. The microsomes contained little or no nickel (Heath and Webb 1967, Webb *et al.* 1972). In another study, metallic nickel powder slowly dissolved when incubated at 37°C in Tyrode's solution with horse serum or sterile homogenates of rat muscle, liver, heart, or kidney. In tissue homogenates, nickel was bound to the diffusible components identified, in descending order of magnitude, as histidine, nucleotides, nucleosides, and free bases (Weinzierl and Webb 1972).

In a study using human gingival fibroblast cell cultures to evaluate the cellular response to nickel–chromium dental alloys, metallic nickel (the positive control) released more nickel ion than did the nickel alloys being tested. At the end of a 24- to 72-hour monitoring period, metallic nickel released nickel ions into the culture medium at a concentration greater than 324.1 ppm, 1,000 times the concentrations of ions released from the nickel alloys (Bumgardner and Lucas 1995).

Endocytosis and oxidation of metallic nickel and transport of Ni^{2+} via calcium channels are possible mechanisms for the cellular uptake of nickel. Although endocytosis accounts for most of the intracellular Ni^{2+}, several studies have demonstrated that Ni^{2+} crosses cell membranes via calcium channels, thus competing with calcium ions for specific receptors in the process (NiPERA 1998, Sunderman 1989a).

6.1.2 Nickel alloys

In a study using human gingival fibroblast cell cultures to evaluate the cellular response to nickel–chromium dental alloys, significant amounts of nickel ions were released from the nickel-chromium alloys (Bumgardner and Lucas 1995). The following alloys were used:

> Neptune: 63.36% nickel, 20.95% chromium, 8.40% molybdenum, 1.73% iron, 1% other (niobium, aluminum, silicon, manganese, titanium)
>
> Rexalloy: 67.21% nickel, 12.88% chromium, 6.76% molybdenum, 5.18% iron, 7.04% other (gallium, silicon, manganese, cobalt)

Regalloy: 71.20% nickel, 15.89% chromium, 4.50 molybdenum, 0.10% iron, 0.57% beryllium, 7.59% other (3.31% aluminum and silicon, 4.28% manganese)

Vera Bond: 77.36% nickel, 12.27% chromium, 4.84% molybdenum, 0.14% iron, 1.67% beryllium, 2.76% other (aluminum, cobalt, titanium, silicon)

The alloys were induction-cast into discs measuring approximately 15 mm in diameter and 3 mm thick. At the 24-, 48-, and 72-hour test intervals, all nickel-chromium alloys had released significantly more nickel ions than ions of other metals. Metal ion release was not proportional to composition, but was correlated with corrosivity. Hence, the low-chromium and corrosion-susceptible Rexalloy specimen released more ions than the high-chromium, corrosion-resistant Neptune alloy over the same period. In experiments with the corrosion-susceptible beryllium-containing alloys, Regalloy T and Vera Bond, nickel and beryllium ions were released preferentially to ions of other metals in the alloy. The results are summarized in Table 6-1.

Table 6-1. Concentrations of ionic nickel from nickel-chromium dental casting alloys in culture medium after incubation for 24 to 72 hours

Alloy	Nickel content of alloy (%)	Nickel ion concentration (ppb)		
		24 hours	48 hours	72 hours
Neptune	63.36	101	146	193
Rexalloy	67.21	253	294	343
Regalloy	71.20	202	228	294
Vera Bond	77.36	227	270	314

Source: Bumgardner and Lucas 1995

Nickel alloys implanted in tissues (e.g., prostheses) slowly corrode or dissolve in body fluids, liberating nickel particles and ions that gradually accumulate in the surrounding tissue. A review of this process (Sunderman 1989b) is summarized in Table 6-2. Concern has been expressed that the release of metal debris from prosthetic devices could lead to systemic toxicity, allergic reactions, and cancer (Sunderman *et al.* 1989b, Case *et al.* 1996, Paavolainen *et al.* 1999). Metal particles may accumulate in tissues surrounding the implant site and cause chronic inflammatory reactions (Case *et al.* 1994). Consequently, many studies have investigated the release and distribution of metal particles and ions from knee and hip prostheses (Sunderman *et al.* 1989a, Betts *et al.* 1992, Langkamer *et al.* 1992, Case *et al.* 1994, Urban *et al.* 2000). Increased concentrations of nickel, cobalt, chromium, and manganese in serum and urine from patients with various types of implants have been reported. Several factors (e.g., type of alloy, porosity of surfaces, and instability of the prosthetic head) may affect the amount of metal debris released from the prosthesis (Sunderman *et al.* 1989a, Urban *et al.* 2000). Some of these studies also indicate greater metal release from metal-to-metal articular surfaces than from metal-to-polyethylene surfaces (Dobbs and Minski 1980, Black *et al.* 1983, both cited in Sunderman 1989b, Paavolainen *et al.* 1999).

Table 6-2. Detection of nickel in body fluids of hip arthroplasty patients

Alloy and type of implant[a]	No. of patients	Period of observation	Observation	Reference
Hip, stainless steel (c, np, pe)	20	10 to 13 years	elevated nickel concentration in plasma, blood, and urine	Pazzaglia *et al.* 1983
Hip, CoCrMo (c, np, pe)	15	1 day to 6 months	elevated nickel concentration in serum (peak at 6 months)	Black *et al.* 1983
Hip, stainless steel (c, np, pe)	13	9 to 15 years	elevated serum nickel concentration in only 1 patient[b]	Linden *et al.* 1985
Hip, CoCrMo (nc, pc, pe)	not reported	1 week to 1 year	elevated urinary nickel concentration in 2 patients at 6 months, elevated nickel concentration in urine in 3 of 4 patients at 1 year	Jones and Hungerford 1987

Source: Sunderman 1989b

[a]c = cemented; nc = non-cemented; pc = porous-coated; np = nonporous-coated; pe = polyethylene articular component.

[b]Renal insufficiency may also have been a contributing factor.

Metal debris associated with prosthetic devices is not found just in tissues surrounding the implant. Particles have been found in regional and distant lymph nodes, the spleen, and the liver (Langkamer *et al.* 1992, Case *et al.* 1994, Urban *et al.* 2000). These studies indicate that metal debris is not biologically inert and can be disseminated in relatively large quantities following prosthetic joint replacement, particularly in patients who have had a failed hip arthroplasty. Betts *et al.* (1992) reported that tissue metal content did not correlate with the histologic findings or the duration of implantation in 22 patients who had total hip revision arthroplasties. Their data suggested that the metal debris was composed primarily of wear particles, rather than ionic corrosion products, and that the cement or polyethylene particles may have been more important than the metals in producing inflammatory reactions and loosening.

Circulating nickel from dissolved nickel alloys in the body can be further degraded by endogenous oxidizing agents and taken into the cells by transport of Ni^{2+} via calcium channels. Another likely mechanism for the cellular uptake of particulate nickel is endocytosis. Particle size, surface properties, and chemical composition affect the endocytosis of nickel-containing particulates. A portion of the absorbed nickel enters the nucleus, in either ionic or particulate form, and a portion of the nickel (assumed to be Ni^{2+}) becomes bound to nucleoproteins (NiPERA 1998, Sunderman 1989a).

6.1.3 Other nickel compounds

The absorption, distribution, and elimination of nickel compounds depend upon solubility, concentration, and, in inhalation exposures, the particle sizes of various nickel compounds (NiDI 1997).

In humans, almost 35% of inhaled nickel is absorbed into the blood from the respiratory tract (Bennett 1984, Grandjean 1984, Sunderman and Oskarsson 1991, all cited in NTP 1996a,b,c). Human volunteers absorbed 25% of an oral dose of nickel sulfate administered in water, but only

1% of the dose ingested as a food additive (NiDI 1997). In mice, rats, and dogs orally administered nickel sulfate, nickel subsulfide, and nickel oxide, 1% to 10% of the dose was absorbed. An absorption rate of 1% (in 24 hours) through guinea pig skin was reported (Nielson *et al.* 1993; cited in NTP 1996a,b,c, ATSDR 1997).

In humans, absorbed nickel is widely distributed in the body. Post-mortem studies of nickel workers showed the highest levels of nickel disposition in the lungs, thyroid, and adrenal glands, with lesser concentrations in the kidney, liver, heart, spleen, and other tissues (NiDI 1997).

Systemically absorbed nickel is mainly excreted in urine. In human volunteers exposed orally to soluble nickel sulfate hexahydrate, the half-life of nickel averaged 11 hours. In this study, 100% of the nickel was recovered either in urine or as unabsorbed nickel in the stool within four days of exposure (Christensen and Lagesson 1981). Nickel also may be eliminated via sweat, the hair, or human breast milk (NiDI 1997). In experimental animals, ingested nickel compounds were excreted in the urine and feces (English *et al.* 1981, Carvalho and Zeimer 1982). The pulmonary half-life of nickel compounds depends upon solubility and particle size (NiDI 1997). In a study of workers exposed to insoluble nickel particles of small diameter, nickel had a half-life in urine ranging from 30 to 53 hours (Raithel *et al.* 1982). Studies have suggested that nickel has a longer half-life, ranging from months to years, in workers exposed to insoluble particles of increasing size (Torjussen and Andersen 1979, Boysen *et al.* 1984, Morgan and Rouge 1984). In chronic exposure studies with rats and mice, nickel sulfate had the shortest half-life (1 to 3 days), followed by nickel subsulfide (five days), and nickel oxide (100 days) (Benson *et al.* 1987, Dunnick *et al.* 1989, both cited in NTP 1996a,b,c). A biphasic pulmonary clearance (one to two hours for the first, and 120 to 300 hours for the second) was reported after intratracheal instillation of nickel subsulfide in mice (Valentine and Fisher 1984, Finch *et al.* 1987).

6.2 Formation of protein and DNA adducts

Although covalent nickel:DNA adducts (nickel:DNA base binding) have not been found (Savolainen 1996), Ni^{2+} binds to DNA at its high- and low-affinity phosphate sites *in vitro*. Such binding produces conformational changes in DNA molecules studied in aqueous solution. Other studies have demonstrated that nickel forms a stable mixed-ligand complex with the amino acids glycine, glutamine, histidine, arginine, cysteine, alanine, and lysine (Jones *et al.* 1980, cited in Kasprzak *et al.* 1986). Thus, DNA adduct formation is not a likely factor in nickel carcinogenicity.

6.3 Lipid peroxidation and oxidative DNA damage

The carcinogenic effect of nickel may be related to its lipid peroxidation properties which induce DNA-strand gaps and breaks and DNA-protein crosslinks (Savolainen 1996, Sunderman 1989a). Although the mechanism of nickel lipid peroxidation *in vivo* has not been established, proposed mechanisms suggest that this reaction may be indirectly mediated by Ni^{2+} displacement of iron or copper ions (Fe^{2+} or Cu^{2+}) from their intracellular binding sites producing the lipid peroxidating redox couples Fe^{2+}/Fe^{3+} or Cu^{+}/Cu^{2+}. Several other hypotheses have been proposed for direct and indirect nickel lipid peroxidation. Proposed direct mechanisms suggest that free oxygen radicals (reactive oxygen species) are generated by Ni^{2+}/Ni^{3+}. This is thought to occur in single-electron transfer reactions that accelerate the degradation of lipid hydroperoxides to form

lipid-O· radicals by Ni^{2+} propagation (rather than initiation) of autocatalytic peroxidative reactions. Proposed indirect mechanisms include impairment of cellular defenses against peroxidation by depletion of free radical scavengers such as glutathione, or by inhibition of catalase, superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, or other enzymes that protect against free-radical injury (Sunderman 1989a).

In an assay to evaluate the lipid peroxidating potential of nickel, the level of lipid peroxidation was measured in nickel-treated CHO cells by means of barbituric acid reactions to quantify lipid peroxidation. Nickel sulfide, nickel subsulfide, nickel oxide (black and green), and nickel chloride were shown to increase oxidation of 2',7'-dichlorofluorescein-diacetate to the fluorescent 2',7'-dichlorofluorescein, suggesting that nickel compounds increased the concentration of oxidants in CHO cells. The results of the study indicated that Ni^{2+} causes an increase in reactive oxygen species that may have the ability to convert Ni^{2+} to Ni^{3+} or damage DNA bases and induce DNA-protein crosslinks (Huang *et al*. 1994).

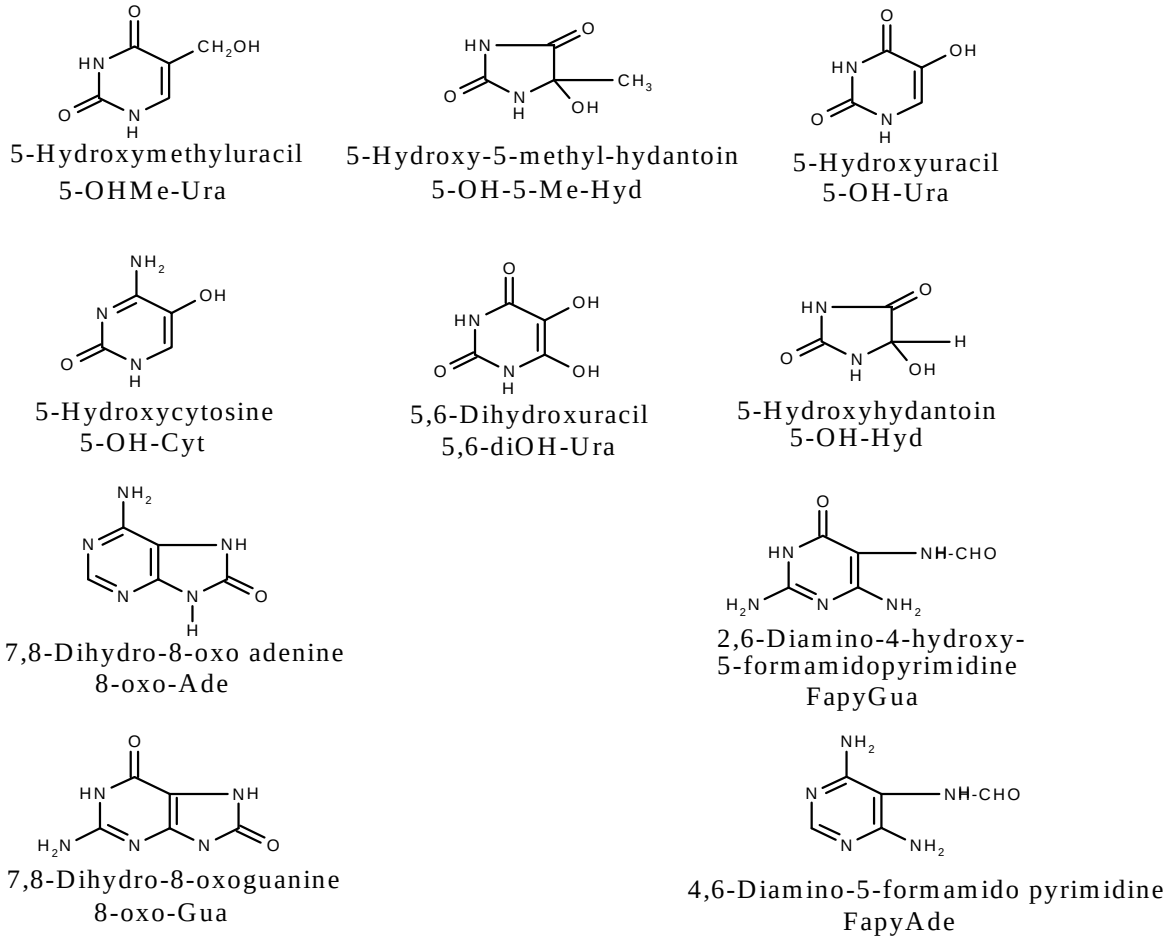
DNA base damage was significantly increased in the tissues of five-week-old male F344/NCr rats receiving a single i.p. injection of 90 µmol/kg of nickel(II)acetate. DNA damage was assayed via GC/mass spectroscopy with selected ion monitoring in renal and hepatic chromatin of the male rats, up to 14 days after nickel administration (Kasprzak *et al.* 1997). The ten damaged bases found are shown in Figure 6-1.

6.4 Summary

Metallic nickel and nickel alloys are converted to Ni^{2+} in target cells, and the ions may then enter the nucleus and bind to nucleoproteins. This process is a major determinant of the carcinogenic effect of nickel. Although no covalent nickel adducts (binding to bases) have been found in DNA, *in vitro* studies show that Ni^{2+} from metallic nickel and nickel alloys loosely binds to DNA at its high- and low-affinity phosphate sites.

Nickel lipid peroxidation, an effect related to DNA base damage and the carcinogenic effect of nickel, has been demonstrated, but the mechanism(s) of this effect has not been established. Proposed mechanisms include indirect production of active peroxidating redox couples by Ni^{2+}, depletion of the free radical scavengers by Ni^{2+}, and the direct generation of reactive oxygen species by Ni^{2+}. The reactive oxygen species are known to accelerate the degradation of lipid hydroperoxides, forming lipid-O· radicals.

Absorption, distribution, and excretion of nickel compounds depend upon solubility, concentration, and surface area. Once absorbed, the ionic form of nickel acts as the ultimate carcinogenic species, with a variety of biokinetic factors dictating the carcinogenic potential of the soluble or insoluble nickel compounds.



Source: Kasprzak *et al.* 1997

Figure 6-1. Nickel(II)-damaged oxidative DNA products

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Appendix D: Profile for Nickel and Certain Nickel Compounds. Report on Carcinogens, Ninth Edition (2000)

Appendix A: IARC. (1990). Chromium, Nickel, and Welding. Monographs on the Evaluation of Carcinogenic Risks to Humans. Nickel. World Health Organization. Lyon, France. Vol. 49. PP. 257-445.

Appendix B: IARC. (1990). Chromium, Nickel, and Welding. Monographs on the Evaluation of Carcinogenic Risks to Humans. Nickel (Tables for Genotoxicity). World Health Organization. Lyon, France. Vol. 49. PP. B-1 – B-9

Appendix C: IARC. (1999). Surgical Implants and Other Foreign Bodies. Monographs on the Evaluation of Carcinogenic Risks to Humans. World Health Organization. Lyon, France. Vol. 74. PP. C-1 – C-125.

Appendix D: Profile for Nickel and Certain Nickel Compounds. Report on Carcinogens, Ninth Edition (2000)

NICKEL AND CERTAIN NICKEL COMPOUNDS

First Listed in the *First Annual Report on Carcinogens*

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of nickel (CAS No. 7440-02-0) and the following nickel compounds in experimental animals: nickel acetate (373-02-4), nickel carbonate (3333-67-3), nickel carbonyl (13463-39-3), nickel hydroxide (12054-48-7 or 11113-74-9), nickelocene (1271-28-9), nickel oxide (1313-99-1), and nickel subsulfide (12035-72-2) (IARC V.2, 1973; IARC V.11, 1976; IARC S.4, 1982; IARC S.7, 1987). When injected intramuscularly, nickel induced incidences of fibrosarcomas in rats and hamsters of both sexes, local sarcomas in rats of both sexes, and local tumors with some metastases to pre-vertebral lymph nodes in female rats. When injected intrapleurally, nickel powder induced round cell and spindle cell tumors at the injection site in female rats. When administered by inhalation, nickel induced lymphosarcomas in female mice and anaplastic intraalveolar carcinomas, including one with extensive pulmonary adenomatosis, in male and female guinea pigs. Subdermal implantation of nickel pellets induced sarcomas surrounding the pellet in female and male rats. When injected intramedullarly into the femur, rats developed neoplasms at or near the site, including fibrosarcomas (neurogenic in origin), and one reticulum cell sarcoma with metastases. The same route of administration induced one metastasizing endothelial fibrosarcoma in a rabbit (IARC V.11, 1976; IARC V.2, 1973). When administered intraperitoneally, nickel acetate induced an excess of lung adenomas and carcinomas in mice (IARC S.4, 1982). When implanted intramuscularly, nickel carbonate induced sarcomas at the site of the implanted pellet. When administered nickel carbonyl through inhalation, male rats developed one pulmonary adenocarcinoma with metastases, extensive squamous metaplasms of the epithelium, neoplasms of the lung, one mixed adenocarcinoma and squamous cell carcinoma with metastases to the kidney and mediastinum, and papillary bronchiolar adenomas. Injection of nickel carbonyl into the tail vein of rats of both sexes induced malignant tumors including undifferentiated leukemia, pulmonary lymphomas, and individual incidences of liver, kidney, and mammary carcinomas. When millipore diffusion chambers containing nickel hydroxide were implanted in rats, local tumors were induced. When administered by intramuscular injection, nickelocene induced fibrosarcomas in rats and hamsters of both sexes. When administered by intramuscular injection, nickel oxide induced injection site sarcomas in mice and rats; administration by intramuscular implantation induced rhabdomyosarcomas and fibrosarcomas in mice and implantation site sarcomas in rats. When administered by intramuscular implantation, nickel subsulfide induced rhabdomyosarcomas and fibrosarcomas in mice and rats, rhabdomyosarcomas with distant metastases and implantation site sarcomas in rats, and tumors in mice. Palpable local tumors arose at implantation sites after nickel subsulfide pellets were removed from rats at various times. Intratracheal injection of nickel subsulfide induced malignant neoplasms of the lungs, adenocarcinomas, and squamous cell carcinomas, in rats of both sexes. Intramuscular injection of nickel subsulfide induced injection site sarcomas and rhabdomyosarcomas in rats and mice and fibrosarcomas and undifferentiated sarcomas in male rats; in addition, the sarcomas metastasized to distant sites, e.g., lungs, liver, heart, spleen, mediastinum, and mesentery and para-aortic lymph nodes (IARC V.2, 1973; IARC V.11, 1976). Nickel subsulfide induced malignant tumors in rats after insertion into heterotransplanted tracheas and after intrarenal, intratesticular, and intraocular administration (IARC S.4, 1982).

An IARC Working Group determined that there is limited evidence for the carcinogenicity of nickel and certain nickel compounds, and sufficient evidence for the carcinogenicity of nickel refining in humans (IARC S.4, 1982). A subsequent IARC Working Group determined that there is sufficient evidence for the carcinogenicity of the group of nickel

compounds in humans. However, the specific carcinogenic substance(s) could not be identified (IARC S.7, 1987). Several epidemiological studies demonstrated excess incidences of cancers of the nasal cavity, lung, and possibly the larynx in workers exposed to nickel or nickel compounds. The cancer hazards seemed to be associated with the early stage of nickel refining, and with exposure primarily to nickel subsulfide and nickel oxide (IARC V.2, 1973; IARC V.11, 1976; IARC S.4, 1982; IARC S.7, 1987).

PROPERTIES

Nickel occurs as silver metallic cubic crystals. It is soluble in dilute nitric acid, slightly soluble in hydrochloric acid and sulfuric acid, insoluble in cold and hot water and ammonia. It is available with a 99.9% purity and in grades which include electrolytic, ingot, pellets, shot, sponge, powder, high-purity strip, and single crystals. Nickel reacts violently with fluorine (F_2), ammonium nitrate, hydrazine, ammonia, a mixture of hydrogen (H_2) and dioxane, performic acid, phosphorus, selenium, sulfur, or a mixture of titanium and potassium chlorate. Nickel acetate occurs as a green powder that effloresces somewhat in air. It is soluble in acetic acid and water and insoluble in alcohol. It is available in a grade with purity > 99.0%. When heated to decomposition, nickel acetate emits irritating fumes. Nickel carbonate occurs as light green rhombic crystals or as a brown powder. It is soluble in dilute acids and ammonia and insoluble in hot water. Nickel carbonate is available with a 99.5% purity and occurs naturally as the mineral zaratite. Nickel carbonate can react violently with iodine (I_2), hydrogen sulfide, or a mixture of barium oxide and air. Nickel carbonyl occurs as a colorless, volatile, inflammable liquid that has a musty odor. It is soluble in aqua regia, alcohol, ethanol, benzene, and nitric acid, slightly soluble in water, and insoluble in dilute acids and dilute alkalies. It is available in a technical grade. Nickel carbonyl explodes when exposed to heat or flame, and it can react violently with air, oxygen, bromine (Br_2), or a mixture of n-butane and oxygen. When heated or on contact with acid or acid fumes, nickel carbonyl emits toxic carbon monoxide fumes. Nickel hydroxide occurs as either green crystals or as an amorphous black powder. It is soluble in acid and ammonium hydroxide, but is practically insoluble in water. Nickel hydroxide is available in a grade containing about 60% nickel. Nickelocene occurs as dark green crystals. It is soluble in common organic solvents and insoluble in water. Nickelocene is a highly reactive compound which decomposes in air, acetone, alcohol, and ether. It is available as a grade containing 8 to 10% nickelocene in toluene. Nickel oxide is a green-black powder that becomes yellow when heated. It is soluble in acids and ammonium oxide and insoluble in both cold and hot water. It is available in a grade with 99% purity. Nickel subsulfide is a pale yellowish-bronze, metallic, lustrous solid. It is soluble in nitric acid and insoluble in cold and hot water. When heated to decomposition, nickel subsulfide emits toxic fumes of sulfur oxides (SO_x).

USE

In 1987, approximately 39% of the primary nickel consumed went into stainless and alloy steel production, 28% into nonferrous alloys, and 22% into electroplating. Ultimate end uses for nickel were: transportation, 24%; chemical industry, 15%; electrical equipment, 9%; construction, 9%; fabricated metal products, 8%; petroleum, 8%; household appliances, 7%; machinery, 7%; and other, 13% (USDOI, 1988). The many uses of nickel include use in alloys (e.g., low-alloy steels, stainless steel, dental fillings, copper and brass, permanent magnets, and electrical resistance alloys), electroplated protective coatings, electroformed coatings, alkaline storage batteries, fuel cell electrodes, and as a catalyst in the methanation of fuel gases and hydrogenation of vegetable oils. Nickel acetate is used as a catalyst and in the textiles industry as a mordant. Nickel carbonate is used in electroplating and in the preparation of nickel

catalysts, ceramic colors, and glazes. Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and continuous nickel coatings on steel and other metals. It also has many small-scale applications, e.g., vapor seating of nickel and depositing of nickel in semiconductor manufacturing. Nickel hydroxide finds use in the manufacture of nickel salts. Nickelocene is used as a catalyst and complexing agent. Nickel oxide is used in nickel salts, porcelain painting, fuel cell electrodes, and the manufacture of stainless and alloy steel. There is no reported use for nickel subsulfide (Sax, 1987; IARC V.2, 1978; IARC V.11, 1976).

PRODUCTION

The United States produced an estimated 8 million lb of nickel from domestic ore in 1990 (USDOI, 1991). Ferronickel was produced by a smelter near Riddle, OR. Byproduct crude nickel sulfate was produced by four copper refineries, two firms that treated secondary copper, and scrap, nickel-base alloy scrap, and copper scrap. One firm converted particulate wastes from stainless steel plants and spent catalysts into nickel-bearing pigs for making stainless steel. Another company processed nickel hydroxide waste from several hundred metal finishers, and its product was shipped to a smelter for nickel recovery. The U.S. imported 320 million lb and exported 48 million lb (6 million lb; 42 million lb secondary nickel) in 1990 (USDOI, 1991). In 1989 the U.S. produced 764 thousand lb of nickel from domestic ore, and imported more than 278 million lb. Nickel exports exceeded 48 million lb (4.6 million lb primary nickel. 42.7 million lb secondary nickel) in 1989. More than 308 million lb of nickel were imported into the U.S. in 1988, and almost 42 million lb (5.4 million lb primary, nickel; 36.5 million lb secondary nickel) exported. In 1987, there was no domestic mine production of nickel. Generally, nickel is produced either as a by-product from copper refining or recycled or reclaimed from secondary sources. The 110 million lb of nickel produced in 1987 were from secondary sources. Imports of nickel were 302 million lb and exports were 2 million lb in 1987. In 1986, the production of nickel was by the following methods: > 2.3 million lb from mine production, 2.3 million lb from plant production of domestic ore, and 87.5 million lb from secondary sources. Imports of nickel in 1986 were 258 million lb and exports were 5.6 million lb. In 1985, mine production of nickel was 12.3 million lb, plant production from domestic ore was 10.5 million lb, plant production from foreign matte was 62.5 million lb, and secondary production was 107 million lb. Imports of nickel in 1985 were 315 million lb and exports were 45.5 million lb (USDOI, 1988). In 1985, 25.0 million lb of nickel powders were imported (USDOI Imports, 1986). In 1984, 29.1 million lb of nickel were produced by mine production, 19.2 million lb were produced by plant production from domestic ore, 70.7 million lb were produced by plant production from foreign matte, and 110 million lb were produced from secondary sources. In 1984, imports of nickel were 353 million lb and nickel powders were 30.1 million lb, and exports of nickel were 63.3 million lb (USDOI, 1988; USDOC Imports, 1985). In 1983, 66.8 million lb of nickel were produced by plant production from foreign matte and 100 million lb were produced from secondary sources. About 304.7 million lb of nickel were imported and 46.7 million lb were exported in 1983. Mine production of nickel was 6.4 million lb, plant production from domestic ore was 6.9 million lb, plant production from foreign matte was 83 million lb, and secondary production was 86 million lb in 1982. Also in 1982, 259.6 million lb of nickel were imported and 74.7 million lb were exported. In 1981, mine production of nickel was 24.2 million lb, plant production from domestic ore was 20.6 million lb, plant production from foreign matte was 77 million lb, and secondary source production was 104 million lb. In 1981, 418 million lb and 39.2 million lb of nickel were imported and exported, respectively. In 1980, 29.3 million lb of nickel were produced by mine production, 22.5 million lb by plant production from domestic ore, 66 million lb by plant production from foreign matte, and 98.6 million lb from secondary sources. In 1980, 378.3 million lb of nickel were imported and 38.9 million lb were exported (USDOI, 1988; USDOI, 1985). The 1979 TSCA Inventory reported that in 1977, there were 21

companies producing 106.8 million lb of nickel and 30 companies importing 390.6 million lb (TSCA, 1979). In 1973, 36.6 million lb of nickel were produced from mine production (IARC V.11, 1976).

In 1985, 10.2 million lb of nickel compounds and 4.3 million lb of unspecified nickel compounds were imported, and 709,719 lb of unspecified nickel compounds were exported (USDOC Imports, 1986; USDOC Exports, 1986). Imports of nickel oxide in 1984 were 11.1 million lb and imports of unspecified nickel compounds were 195,840 lb (USDOC Imports, 1985). Also during 1984, exports of unspecified nickel compounds were 409,339 lb (USDOC Exports, 1985). The 1979 TSCA Inventory reported that in 1977, 15 companies produced 12.7 million lb and 2 companies imported 500 lb of nickel carbonate, with some site limitations; 13 manufacturers produced 781,000 lb of nickel hydroxide, with some site limitations; 27 companies produced 5.3 million lb and 12 companies imported 30.1 million lb of nickel oxide, with some site limitations; and 4 companies produced 121,200 lb of nickel subsulfide. The CBI Aggregate was less than 1 million lb for nickel carbonate and between 1 million and 100 million lb for nickel carbonyl and nickel subsulfide. Nickel acetate and nickelocene did not appear on the TSCA Inventory (TSCA, 1979).

EXPOSURE

The primary routes of potential human exposure to nickel and nickel compounds are ingestion, inhalation, and dermal contact. Possible exposures can occur because nickel is present in air, water, soil, food, and consumer products. NIOSH estimated that 250,000 workers in the United States were potentially exposed to nickel (including elemental nickel and inorganic nickel compounds) (NIOSHb, 1977a). OSHA estimated that 709,000 workers were possibly exposed to nickel and its compounds. Significant occupational exposure to nickel, through inhalation, at or near permissible levels may occur in a wide variety of occupations including battery makers, ceramic makers, electroplaters, enamelers, glass workers, jewelers, metal workers, nickel mine workers, refiners and smelters, paint-related workers, and welders. Inorganic nickel concentrations in workroom atmospheres usually range between 0.1 and 1 mg/m^3. In addition, exposure may occur to the workforce from dermal contact with cutting oils contaminated with nickel and nickel-containing or nickel-plated tools (ATSDR, 1995g). The ACGIH has established threshold limit values (TLVs) as 8-hr time-weighted averages (TWAs) of 1 mg/m^3 for nickel metal, 0.1 mg/m^3 for soluble nickel compounds, as nickel, and 0.05 ppm and 0.35 mg/m^3 for nickel carbonyl, as nickel (ACGIH, 1986).

The Toxic Chemical Release Inventory (EPA) listed 912 industrial facilities that produced, processed, or otherwise used nickel in 1988 (TRI, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of nickel to the environment which were estimated to total 1.5 million lb. EPA estimated that nearly 720,000 people living within 12.5 miles of primary sources may possibly be exposed to nickel at concentrations up to 15.8 $\mu g/m^3$ (median 0.2 $\mu g/m^3$). As many as 160 million people live within 12.5 miles of all sources of nickel and nickel compounds, and they may possibly be exposed to median concentrations of 0.05 $\mu g/m^3$. Ambient air concentrations of nickel in the United States are 6 ng/m^3 in nonurban areas, and about 20 ng/m^3 in urban areas, with higher values of up to 150 ng/m^3 in large cities (New York City) and industrial areas (Merian, 1984). Also, the entire U.S. population may possibly be exposed to low levels of nickel (300-600 µg/day) in food and water. The following are typical concentrations of nickel found in various food categories: grains, vegetables, and fruits, 0.02-2.7 µg/g; meats, 0.06-0.4 µg/g; and seafoods, 0.02-20 µg/g. Cow's milk has been found to contain nickel concentrations of < 100 µg/L, and the typical concentration of nickel in mother's milk ranges between 20 and 500 µg. Dietary nickel levels

can increase because of food processing methods that leach nickel from nickel-containing alloys. Dietary intake of nickel has been estimated to range from 100 to 300 µg/day (ATSDR, 1995g). Nickel also is an essential micronutrient for plants; thus, eating plant material may be another potential source of exposure. There is a significant vector of exposure to the general population such as users of nickel-containing kitchen utensils and tableware (Sax, 1981). In the United States, nickel levels in drinking water are estimated to be less than 10 µg/L. Cigarette smoke is reported to contain up to 3 µg nickel/cigarette (OSH, 1982).

Environmental sources of nickel include emissions from coal- and oil-fired boilers, coke ovens, diesel-fuel burning, and gray-iron foundries. Total annual emissions from these types of sources was estimated to be 22.4 million lb. Crude oil contains on the average about 5 ppm nickel. In the United States, it was calculated that 60% of the atmospheric nickel emissions originate from oil-fired vessels. Soils normally contain 5-500 ppm nickel; soils from serpentine rock may contain as much as 5,000 ppm. The earth's crust and soils contain about 50 ppm of nickel, mostly in igneous rocks. Fresh and sea waters contain about 0.3 µg/L of nickel, ground water almost none. Urban effluents may contain 60 µg/L of nickel, of which 40% accumulate in sewage sludge. It has been determined that sewage sludges contain 20-1,000 ppm nickel with an average of 150 ppm. U.S. river basins contain 3-17 µg/L of nickel (Merian, 1984).

REGULATIONS

In 1980 CPSC preliminarily determined that nickel carbonyl was not present in consumer products under its jurisdiction. Subsequently, public comment was solicited to verify the accuracy of this information; no comments were received. Pending receipt of new information, CPSC plans no action on this chemical. EPA regulates nickel and nickel compounds under the Clean Water Act (CWA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), and Superfund Amendments and Reauthorization Act (SARA). Effluent guidelines have been established for nickel and nickel compounds under CWA. Reportable quantities (RQs) have been established for nickel, nickel carbonyl, and nickel hydroxide under CERCLA. RCRA regulates nickel and nickel compounds as hazardous wastes. RCRA and SARA subject nickel and nickel compounds to report/recordkeeping requirements. SARA also establishes threshold planning quantities. FDA has taken no action on nickel as a carcinogen because the data available are not adequate to assess its carcinogenicity through dietary exposure. Nickel is a compound generally recognized as safe (GRAS) when used as a direct human food ingredient. OSHA adopted permissible exposure limits (PELs) of 0.007 mg/m^3 as an 8-hour TWA for nickel carbonyl and 1 mg/m^3 as an 8-hour TWA for nickel metal and soluble nickel compounds; OSHA adopted these standards for toxic effects other than cancer. NIOSH recommended to OSHA that exposure to nickel be limited to 15 $\mu g/m^3$ (10-hour TWA) because of observed carcinogenicity of nickel metal and all inorganic nickel compounds. OSHA regulates nickel and certain nickel compounds under the Hazard Communication Standard and as chemical hazards in laboratories. Regulations are summarized in Volume II, Table B-75.