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

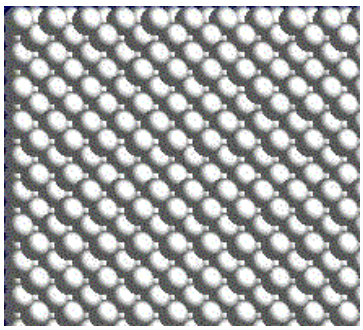
The U.S. Environmental Protection Agency (U.S. EPA) codes are K115 for nickel and P073 for nickel compounds. Shipping codes are UN1378 for nickel and UN2881 for nickel catalyst, dry.

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).

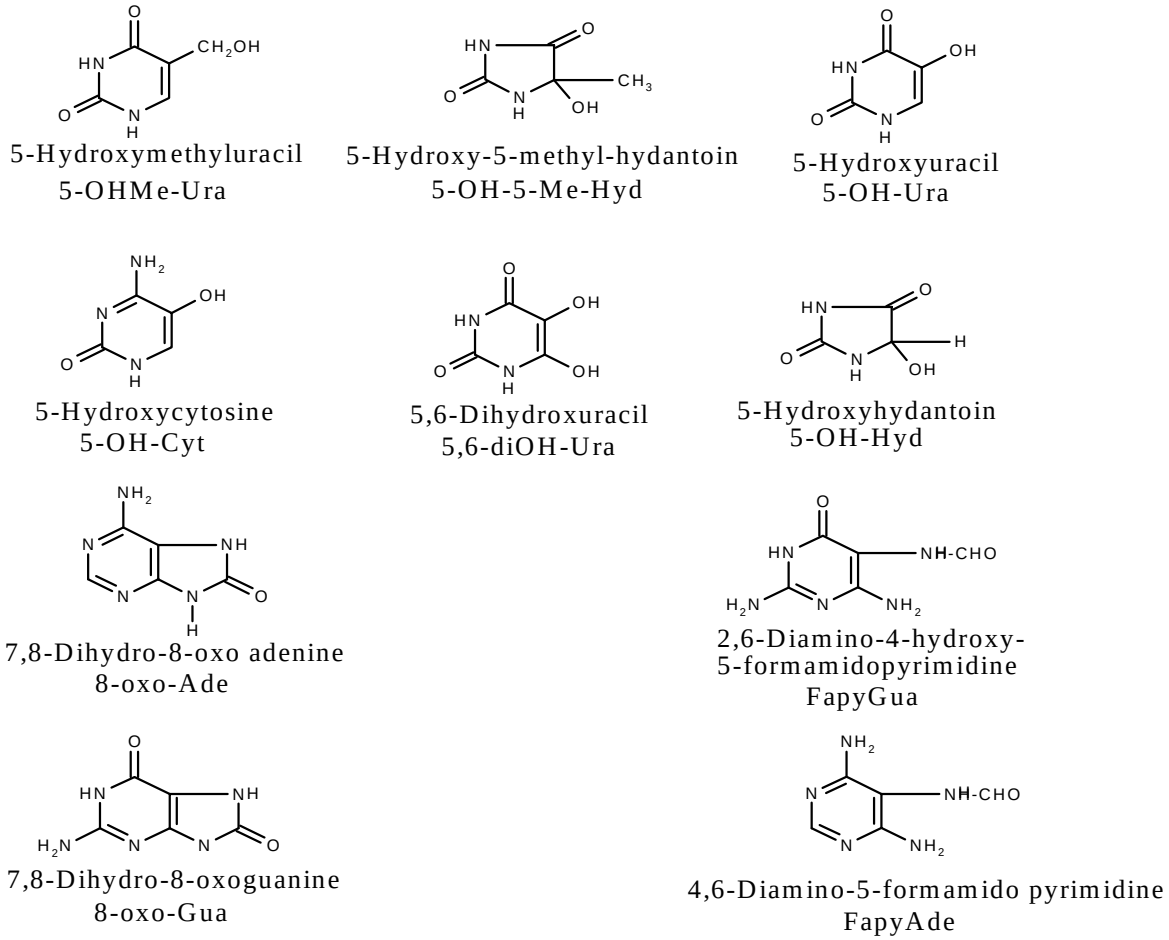
DNA base damage was significantly increased in the tissues of five-week-old male F344/NCr rats receiving a single i.p. injection of 90 µmol/kg of nickel(II)acetate. DNA damage was assayed via GC/mass spectroscopy with selected ion monitoring in renal and hepatic chromatin of the male rats, up to 14 days 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 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)

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.

NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups, in 1972, 1975, 1979, 1982 and 1987 (IARC, 1973, 1976, 1979, 1982, 1987). Since that time, new data have become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

1. Chemical and Physical Data

The list of nickel alloys and compounds given in Table 1 is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially and those that have been tested in biological systems. A number of intermediary compounds occur in refineries which cannot be characterized and are not listed.

1.1 Synonyms, trade names and molecular formulae of nickel and selected nickel-containing compounds

Table 1. Synonyms (Chemical Abstracts Service names are given in bold), trade names and atomic or molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Metallic nickel and nickel alloys				
Nickel	7440-02-0 (8049-31-8; 17375-04-1; 39303-46-3; 53527-81-4; 112084-17-0)	C.I. 77775; N1; Ni 233; Ni 270; Nickel 270; Nickel element; NP 2	Ni	0

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Ferronickel	11133-76-9 (11148-37-1; 12604-55-6)	**Iron alloy (base), Fe, Ni**; nickel alloy (non-base) Fe, Ni	Fe, Ni	0
Nickel aluminium alloys	61431-86-5 37187-84-1	**Raney nickel**; Raney alloy	NiAl	0
Nickel-containing steels[c]	12681-83-3	**Iron alloy (base)**; 21-6-9; 21-6-9 alloy; Alloy 21-6-9; AMS 5656C; Armco 21-6-9; ASTM XM10; 21-6-9 austenitic steel; Nitronic 40; Nitronic 40 stainless steel; Pyromet 538; 21-6-9 Stainless steel; Stainless steel 21-6-9; 21-6-9 steel; Steel 21-6-9	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	0
High nickel alloys[c]	12605-70-8	**ASTM B344-60Ni, 16 Cr**; Chromel C; 06Kh15N60; Kh15N60N; 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	0
	11121-96-3	AFNOR ZFeNC45-36; AISI 332; Alloy 800; **ASTM B163-800**; DIN 1.4876; IN 800; Incoloy alloy 800; JIS NCF 800; 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	0
	12675-92-2	**Haynes alloy No. 188**	Ni(Co)	0
	11105-19-4	Alloy 400; ASTM B127; **ASTM B164-A**; 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	0
Nickel oxides and hydroxides				
Nickel hydroxide (amorphous	12054-48-7 11113-74-9)	Nickel dihydroxide; nickel (II) hydroxide; nickel (2+) hydroxide; **nickel hydroxide ($Ni(OH)_2$)**; nickelous hydroxide	$Ni(OH)_2$	+2
Nickel monoxide	1313-99-1 11099-02-8	Black nickel oxide[d]; green nickel oxide; mononickel oxide; nickel monooxide; nickelous oxide; **nickel oxide (NiO)**; nickel (II) oxide; nickel (2+) oxide	NiO	+2
	34492-97-2	**Bunsenite (NiO)**		
Nickel trioxide	1314-06-3 (34875-54-2)	Black nickel oxide[d]; dinickel trioxide; nickelic oxide; nickel oxide; nickel (III) oxide; **nickel oxide (Ni_2O_3)**; nickel peroxide; nickel sesquioxide	Ni_2O_3	+3
Nickel sulfides				
Nickel disulfide	12035-51-7	**Nickel sulfide (NiS_2)**	NiS_2	+4
	12035-50-6	**Vaesite (NiS_2)**	NiS_2	+4

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Nickel sulfide (amorphous	16812-54-7 (1344-49-6) 11113-75-0)	Mononickel monosulfide; nickel monosulfide; nickel monosulfide (NiS); nickelous sulfide; nickel (II) sulfide; nickel (2+) sulfide; **nickel sulfide (NiS)**	NiS	+2
	1314-04-1 (61026-96-8)	**Millerite (NiS)**	NiS	+2
Nickel subsulfide	12035-72-2	Nickel sesquisulfide; nickel subsulfide (Ni_3S_2); **nickel sulfide (Ni_3S_2)**; trinickel disulfide	Ni_3S_2	NS
	12035-71-1	**Heazlewoodite (Ni_3S_2)**; Khizlevudite		
Pentlandite	53809-86-2	Pentlandite ($Fe_9Ni_9S_{16}$)	$Fe_9Ni_9S_{16}$	NS
	12174-14-0	Pentlandite	$(Fe_{0.4\text{-}0.6}Ni_{0.4\text{-}0.6})_9S_8$	NS
Nickel salts				
Nickel carbonate	3333-67-3	**Carbonic acid, nickel (2+) salt (1:1)**; nickel carbonate (1:1); nickel (II) carbonate; nickel (2+) carbonate; nickel carbonate ($NiCO_3$); nickel (2+) carbonate ($NiCO_3$); nickel monocarbonate; nickelous carbonate	$NiCO_3$	+2
Basic nickel carbonates	12607-70-4 (63091-15-6)	Carbonic acid, nickel salt, basic; nickel carbonate hydroxide ($Ni_3(CO_3)(OH)_4$); **nickel, (carbonato(2-)) tetrahydroxytri-**	$NiCO_3.2Ni(OH)_2$	+2
	12122-15-5	**Nickel bis(carbonato(2-))hexahydroxypenta-**; nickel hydroxycarbonate	$2NiCO_3.3Ni(OH)_2$	+2
Nickel acetate	373-02-4 (17593-69-0)	**Acetic acid, nickel (2+) salt**; nickel (II) acetate; nickel (2+) acetate; nickel diacetate; nickelous acetate	$Ni(OCOCH_3)_2$	+2
Nickel acetate tetrahydrate	6018-89-9	**Acetic acid, nickel (+2) salt, tetrahydrate**	$Ni(OCOCH_3)_2.4H_2O$	+2
Nickel ammonium sulfates	15699-18-0	Ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$); **sulfuric acid, ammonium nickel (2+) salt (2:2:1)**	$Ni(NH_4)_2(SO_4)_2$	+2
Nickel ammonium sulfate hexahydrate	25749-08-0	Ammonium nickel sulfate ($(NH_4)_2Ni_2(SO_4)_3$); **sulfuric acid, ammonium nickel (2+) salt (3:2:2)**	$Ni_2(NH_4)_2(SO_4)_3$	+2

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
	7785-20-8 (51287-85-5, 55526-16-4)	Ammonium nickel (2+) sulfate hexahydrate; ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); diammonium nickel disulfate hexahydrate; diammonium nickel (2+) disulfate hexahydrate; nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$) hexahydrate; nickel diammonium disulfate hexahydrate; **sulfuric acid, ammonium nickel (2+) salt (2:2:1), hexahydrate**	$Ni(NH_4)_2(SO4)_2.6H_2O$	+2
Nickel chromate	14721-18-7	**Chromium nickel oxide ($NiCrO_4$)**; nickel chromate ($NiCrO_4$); nickel chromium oxide ($NiCrO_4$)	$NiCrO_4$	+2
Nickel chloride	7718-54-9 (37211-05-5)	Nickel (II) chloride; nickel (2+) chloride; **nickel chloride ($NiCl_2$)**; nickel dichloride; nickel dichloride ($NiCl_2$); nickelous chloride	$NiCl_2$	+2
Nickel chloride hexahydrate	7791-20-0	**Nickel chloride ($NiCl_2$) hexahydrate**	$NiCl_2.6H_2O$	+2
Nickel nitrate hexahydrate	13478-00-7	Nickel (2+) bis(nitrate)hexahydrate; nickel dinitrate hexahydrate; nickel (II) nitrate hexahydrate; nickel nitrate ($Ni(NO_3)_2$) hexahydrate; nickelous nitrate hexahydrate; **nitric acid, nickel (2+) salt, hexahydrate**	$Ni(NO_3)_2.6H_2O$	+2
Nickel sulfate	7786-81-4	Nickel monosulfate; nickelous sulfate; nickel sulfate (1:1); nickel (II) sulfate; nickel (2+) sulfate; nickel (2+) sulfate (1:1); nickel sulfate ($NiSO_4$); **sulfuric acid, nickel (2+) salt (1:1)**	$NiSO_4$	+2
Nickel sulfate hexahydrate	10101-97-0	**Sulfuric acid, nickel (2+) salt (1:1), hexahydrate**	$NiSO_4.6H_2O$	+2
Nickel sulfate heptahydrate	10101-98-1	**Sulfuric acid, nickel (2+) salt (1:1), heptahydrate**	$NiSO_4.7H_20$	+2
Other nickel compounds				
Nickel carbonyl	13463-39-3 (13005-31-7, 14875-95-7, 36252-60-5, 42126-46-5, 71327-12-3)	**Nickel carbonyl ($Ni(CO)_4$), (T-4)-**; nickel tetracarbonyl; tetracarbonylnickel; tetracarbonylnickel (0)	$Ni(CO)_4$	0

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Nickel antimonide	12035-52-8 (73482-18-5)	**Antimony compound with nickel (1:1);** nickel antimonide (NiSb); nickel compound with antimony (1:1); nickel monoantimonide	NiSb	NS
	12125-61-0	**Breithauptite (SbNi)**	NiSb	NS
Nickel arsenides	27016-75-7 (12068-59-6, 24440-79-7)	**Nickel arsenide (NiAs)**	NiAs	NS
	1303-13-5 (23292-74-2)	Nickeline; **nickeline (NiAs)**; niccolite	NiAs	NS
	12256-33-6	**Nickel arsenide ($Ni_{11}As_8$)**; nickel arsenide tetragonal	$Ni_{11}As_8$	NS
	12044-65-4	**Maucherite ($Ni_{11}As_8$)**; Placodine; Temiskamite	Ni_5As_2	NS
	12255-80-0	**Nickel arsenide (Ni_5As_2)**; nickel arsenide hexagonal	Ni_5As_2	NS
Nickel selenide	1314-05-2	Nickel monoselenide; **nickel selenide (NiSe)**	NiSe	NS
	12201-85-3	Maekinenite; **Makinenite (NiSe)**	NiSe	NS
Nickel subselenide	12137-13-2	**Nickel selenide (Ni_3Se_2)**	Ni_3Se_2	NS
Nickel sulfarsenide	12255-10-6	**Nickel arsenide sulfide (NiAsS)**	NiAsS	NS
	12255-11-7	**Gersdorffite (NiAsS)**	NiAsS	NS
Nickel telluride	12142-88-0	Nickel monotelluride; **nickel telluride (NiTe)**	NiTe	NS
	24270-51-7	**Imgreite (NiTe)**	NiTe	NS
Nickel titanite	12035-39-1	Nickel titanate(IV); nickel titanate ($NiTiO_3$); **nickel titanium oxide ($NiTiO_3$)**; nickel titanium trioxide	$NiTiO_3$	+2
Chrome iron nickel black spinel	71631-15-7	CI 77504; **CI Pigment Black 30;** DCMA-13-50-9; nickel iron chromite black spinel	$(Ni,Fe)(CrFe)_2O_4$	NS

Table 1 (Contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Nickel ferrite brown spinel	68187-10-0	**CI Pigment Brown 34**; DCMA-13-35-7	$NiFe_2O_4$	NS
Nickelocene	1271-28-9 (51269-44-4)	Bis(η5-2,4-cyclopentadien-1-yl)nickel; di-π-cyclopentadienylnickel; dicyclopentadienylnickel; nickel, bis(η5-2,4-cyclopentadien-1-yl)-; nickel, di-π-cyclopentadienyl-	π-$(C_5H_5)_2Ni$	+2

[a]Replaced CAS Registry numbers are given in parentheses.

[b]NS, not specified; mixed formal oxidation states of nickel and/or complex coordination in the solid form

[c]Chemical Abstracts Service Registry lists hundreds of these compounds; some typical examples are given.

[d]In commercial usage, 'black nickel oxide' usually refers to the low-temperature crystalline form of nickel monoxide, but nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide'.

1.2 Chemical and physical properties of the pure substance

Known physical properties of some of the nickel compounds considered in this monograph are given in Table 2. Data on solubility refer to saturated solutions of the compound in water or other specified solvents. Nickel compounds are sometimes classed as soluble or insoluble in water; such a classification can be useful in technical applications of the various compounds but may not be relevant to determining their biological activity. Water-soluble nickel compounds include nickel chloride (642 g/L at 20°C) and nickel sulfate (293 g/L at 20°C), while nickel monosulfide (3.6 mg/L at 18°C) and nickel carbonate (93 mg/L at 25°C) are classed as insoluble (Weast, 1986). Compounds with solubilities towards the middle of this range are not easily classified in this way. Different forms of nominally the same nickel compound can have very different solubilities in a given solvent, and particle size, hydration and crystallinity can markedly affect the rate of dissolution. For example, anhydrous nickel sulfate and the hexahydrate are similarly soluble in unbuffered water (Grandjean, 1986), but the hexahydrate dissolves several orders of magnitude faster than the anhydrate.

Table 2. Physical properties of nickel and nickel compounds[a]

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Metallic nickel and nickel alloys					
Nickel	58.69	1455	2730	Lustrous white, hard ferromagnetic metal[b] or grey powder	Soluble in dilute nitric acid; slightly soluble in hydrochloric and sulfuric acids; insoluble in cold or hot water
Ferronickel alloy	–	–	–	Grey solid[c]	Combined properties of metallic iron and nickel, ammonia and alkali hydroxides
Nickel oxides and hydroxides					
Nickel hydroxide	92.70	230	–	Green crystals or amorphous solid	Nearly insoluble (0.13 g/l)[d] in cold water; soluble in acid, ammonium hydroxide
Nickel monoxide	74.69	1984	–	Grey, black or green[c] powder	Insoluble in water (0.0011 g/l at 20°C); soluble in acid, ammonium hydroxide[d]
Nickel sulfides					
Nickel disulfide	122.81	Decomposes at 400[d]	–	Black crystals[c] or powder	Insoluble in water[d]
Nickel sulfide					
Amorphous	90.75	797	–	Black crystals or powder	Nearly insoluble (0.0036 g/l, β-form)[d] in water at 18°C; soluble in aqua regia, nitric acid, potassium hydrosulfide; slightly soluble in acids
α-form	90.75	–	–	–	
β-form	90.75	–	–	Dark-green crystals[c]	
Nickel subsulfide (α-form)	240.19	790	–	Lustrous pale-yellowish or bronze metallic crystals	Insoluble in cold water; soluble in nitric acid

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Nickel salts					
Nickel acetate	176.78	Decom-poses	16.6	Dull-green crystals	Soluble in water (166 g/l at 20°C)[d]; in-soluble in ethanol
Nickel acetate tetra-hydrate	248.84	Decom-poses	16	Dull-green crystals	Soluble in water (160 g/l at 20°C)[d]; solu-ble in dilute ethanol
Nickel ammonium sulfates					
Hexahydrate	394.94	-	-	-	Soluble in water (104 g/l at 20°C)[d]
Anhydrous	286.88	Decom-poses[e]	-	Green crystals[e]	Soluble in water (300 g/l at 20°C)[d]; less soluble in ammonium sulfate solution; insoluble in ethanol[e]
Nickel carbonate	118.70	Decom-poses	-	Light-green crystals	Nearly insoluble (0.093 g/l) in water at 25°C; insoluble in hot water, soluble in acids
Nickel hydroxycarbonate	587.67	Decom-poses	-	Light-green crystals or brown powder[e] or wet green paste	Insoluble in cold water; decomposes in hot water; soluble in acids
Nickel chlorides					
Anhydrous	129.60	1001	Sublimes at 973	Yellow deliquescent scales	Soluble in water at 20°C (642 g/l) and at 100°C (876 g/l); soluble in ethanol, am-monium hydroxide; insoluble in nitric acid
Hexahydrate	237.70	-	-	Green deliquescent crys-tals	Soluble in water (2540 g/l at 20°C)[d]; very soluble in ethanol
Nickel chromate	174.71	-	-	Black crystals	Insoluble in water

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Nickel nitrate hexahydrate	290.79	56.7	Decomposes at 136.7	Green deliquescent crystals	Soluble in water (2385 g/l at 0°C), ammonium hydroxide and ethanol
Nickel sulfates					
Anhydrous	154.75	Decomposes at 848	-	Pale-green to yellow crystals	Soluble in water (293 g/l at 20°C); insoluble in ethanol and diethyl ether[d,e]
Hexahydrate	262.84	53.3	-	Blue or emerald-green crystals[e]	Soluble in water (625 g/l at 0°C); soluble in ethanol[d]
Heptahydrate	280.85	99	-	Green crystals	Soluble in water (756 g/l at 20°C); soluble in ethanol[d]
Other nickel compounds					
Nickel antimonide	180.44	1158	Decomposes at 1400	Light-copper to mauve crystals[c]	Insoluble in water[d]
Nickel arsenides NiAs	133.61	968	-	Grey crystals[c]	Insoluble in hot or cold water, soluble in aqua regia
$Ni_{11}As_8$	1244.96	1000	-	Platinum-grey crystals	Insoluble in water[d]
Ni_5As_2	443.39	993	-	Grey crystals[c]	Insoluble in water[d]
Nickel carbonyl	170.73	-25	43	Colourless to yellow liquid	Nearly insoluble (0.18 g/l) in water at 9.8°C; soluble in aqua regia, ethanol, diethyl ether, benzene, nitric acid; insoluble in dilute acids or dilute alkali

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Nickelocene	188.88	171–173[e]	–	Dark-green crystals[e]	Soluble in most organic solvents; insoluble in water; decomposes in acetone, ethanol, diethyl ether
Nickel selenide (NiSe)	137.65	Red heat	–	White or grey crystals	Insoluble in water and hydrochloric acid; soluble in aqua regia, nitric acid
Nickel subselenide (Ni_3Se_2)	333.99	–	–	Green crystals[c]	Insoluble in water[d]
Nickel telluride	186.29	Decomposes at 600–900[d]	–	Grey crystals[c]	Insoluble in water; soluble in nitric acid, aqua regia, bromine water[d]
Nickel titanate	154.57	Decomposes at 1000	–	Yellow crystals[c]	Insoluble in water[d]

[a]From Weast (1986), unless otherwise specified; –, depending on composition

[b]From Windholz (1983)

[c]From Sunderman (1984)

[d]From Grandjean (1986)

[e]From Sax & Lewis (1987)

1.3 Technical products and impurities

This section does not include nickel-containing intermediates and by-products specific to nickel production and use, which are considered in section 2.

(*a*) *Metallic nickel and nickel alloys*

Ferronickel contains 20-50% nickel (Sibley, 1985). Other components include carbon (1.5-1.8%), sulfur (<0.3%), cobalt (<2%), silicon (1.8-4%), chromium (1.2-1.8%) and iron (balance of alloy). It is delivered as ingots or granules (ERAMET-SLN, 1986).

Pure unwrought *nickel* is available commercially in the form of cathodes, powder, briquets, pellets, rondelles, ingots and shot. Its chemical composition is > 99% nickel, with carbon, copper, iron, sulfur and oxygen as impurities (Sibley, 1985). Metallic nickel undergoes surface oxidation in air; oxidation of finely divided nickel powder can result in the conversion of a large fraction of the metal to oxide upon prolonged storage (Cotton & Wilkinson, 1988).

Nickel-aluminium alloy (for the production of Raney nickel) is available as European Pharmacopoeia grade with the following typical analysis: nickel, 48-52%; aluminium, 48-52%; and chloride, 0.001% (Riedel-de Haën, 1986).

Nickel alloys can be categorized as nickel-chromium, nickel-chromium-cobalt, iron-nickel-chromium and copper-nickel alloys. Typical analyses are given in Table 3. Austenitic steels are the major group of nickel-containing steels. Typical compositions are given in Table 4.

(*b*) *Nickel oxides and hydroxides*

The temperature of formation of *nickel oxide* (up to 1045°C) determines the colour of the crystal (jet-black to apple green), the crystalline surface area and the nickel [III] content (<0.03-0.81% by weight). The temperature of formation may also affect the crystalline structure and the incidence of defects within it (Sunderman *et al.*, 1987; Benson *et al.*, 1988a).

Nickel monoxides are available commercially in different forms as laboratory reagents and as industrial products. Laboratory reagents are either green powder (Aldrich Chemical Co., Inc., 1988) or black powders; industrial products are either black powders, coarse particles (Sinter 75) or grey sintered rondelles (INCO, 1988; Queensland Nickel Sales Pty Ltd, 1989). Sinter 75 (76% Ni) contains about 22% oxygen and small amounts of copper (0.75%), iron (0.3%), sulfur (0.006%) and cobalt (1.0%) (Sibley, 1985). Sintered rondels (≥85% Ni) are formed by partially reducing a cylindrical pressing of granular nickel oxide to nickel metal. The degree of reduction achieved determines the nickel content of the finished rondel (Queensland Nickel Sales Pty Ltd, 1989).

Table 3. Elemental analyses of representative nickel alloys (weight %)[a]

Alloy	Ni	Cu	Cr	Co	Fe	Mo	W	Ta	Nb	Al	Ti	Mn	Si	C	Zr
Nickel–chromium															
Cast alloy 625	63.0	–	21.6	–	2.0	8.7	–	–	3.9	0.2	0.2	0.06	0.20	0.20	–
Hastelloy alloy X	47.0	–	22.0	1.5	18.5	9.0	0.6	–	–	–	–	0.50	0.50	0.10	–
Inconel alloy 617	54.0	–	22.0	12.5	–	9.0	–	–	–	1.0	–	–	–	0.07	–
Nickel–chromium–cobalt															
Haynes Alloy 1002	16.0	–	22.0	Bal	1.5	–	7.0	3.8	–	0.3	0.2	0.70	0.40	0.60	0.30
Haynes Alloy No. 188	22.0	–	22.0	39.0	3.0 max	–	14.0	–	–	–	–	1.25 max	0.40	0.10	–
Nickel–iron–chromium															
Haynes Alloy 556	20.0	–	22.0	20.0	29.0	3.0	2.5	0.9	0.1	0.3	–	1.50	0.40	0.10	–
Incoloy Alloy 800[b]	32.5	–	21.0	–	46.0	–	–	–	–	0.4	0.4	0.80	0.50	0.05	–
Nickel–copper															
Monel alloy 400[b]	66.5	31.5	–	–	1.3	–	–	–	–	–	–	1.0	0.25	0.15	–
Monel alloy K-500[b]	65.0	29.5	–	–	1.0	–	–	–	–	2.8	0.5	0.6	0.15	0.15	–

[a]From Nickel Development Institute (1987a); Bal, balance
[b]From Tien & Howson (1981)

Table 4. Typical composition of nickel-containing steels (weight %)[a]

Grade	Cr	Ni	Mn	Mo	C	Si	S	P	Fe
AISI-201	16-18	3.5-3.5	5.5-7.5	-	0.15	1.0	0.03	0.06	Balance
AISI-302	17-19	8.0-10.0	2.0	-	0.15	1.0	0.03	0.045	Balance
AISI-304	18-20	8.0-10.5	2.0	-	0.08	1.0	0.03	0.045	Balance
AISI-316	16-18	10-14	2.0	2-3	0.08	1.0	0.03	0.045	Balance

[a]From Nickel Development Institute (1987b); AISI, American Iron and Steel Institute

Nickel hydroxide is commercially available at 97% purity (Aldrich Chemical Co., Inc., 1988).

(*c*) *Nickel sulfides*

Nickel sulfide exists in three forms: the high-temperature, hexagonal crystal form, in which each nickel atom is octahedrally coordinated to six sulfur atoms; the low-temperature, rhombohedral form (which occurs naturally as millerite), in which each nickel atom is coordinated to two other nickel atoms and five sulfur atoms (Grice & Ferguson, 1974); and amorphous nickel sulfide. Amorphous nickel sulfide is gradually converted to nickel hydroxy sulfide on contact with air (Cotton & Wilkinson, 1988). Grice and Ferguson (1974) referred to the rhombohedral (millerite) form as β-nickel sulfide and the high-temperature hexagonal form as α-nickel sulfide. Different nomenclatures have been used by other authors (Abbracchio *et al.*, 1981; Grandjean, 1986). The term β-nickel sulfide is used to denote the rhombohedral millerite form throughout this monograph.

Nickel subsulfide exists in two forms: α-nickel subsulfide, the low-temperature, rhombohedral form (heazlewoodite), in which nickel atoms exist in distorted tetrahedral coordination and the sulfur atoms form an almost cubic body-centred sublattice, with six equidistant nickel neighbours; and β-nickel subsulfide, the high-temperature form (Sunderman & Maenza, 1976).

An examination of the surface of crystalline and amorphous nickel sulfide particles revealed that crystalline particles have a net negative surface charge, while the surface charge of amorphous nickel sulfide appears to be positive. X-Ray photoelectron spectroscopy analysis of amorphous and crystalline nickel sulfide showed that the outermost surface of the two compounds differed with respect to the Ni/S ratio and the sulfur oxidation state (Abbracchio *et al.*, 1981).

Nickel sulfides are intermediates in nickel smelting and refining which can be isolated as crude mattes for further processing but are not significant materials of commerce. Most nickel subsulfide is produced as an intermediate in many nickel refining processes (Boldt & Queneau, 1967).

(*d*) *Nickel salts*

Nickel acetate is available as the tetrahydrate at a purity of > 97% (Mallinckrodt, Inc., 1987).

Nickel ammonium sulfate hexahydrate is available as analytical reagent-grade crystals at a purity of 99.0% min or at a grade for nickel plating (purity, 99-100%; Riedel-de-Haën, 1986).

Nickel carbonate is available mainly as hydroxycarbonates, such as basic nickel carbonate. Laboratory reagent grades may contain 47.5% or 45% nickel; industrial grades, as green powders or wet pastes, contain approximately 45% nickel (INCO, 1981-82; Pharmacie Centrale, 1988).

Nickel chloride is available as the hexahydrate as a laboratory reagent of > 99% purity and as industrial products with about 24.7% nickel. It is also available in industrial quantities as an aqueous solution (ERAMET-SLN, 1985).

Nickel nitrate is available as the hexahydrate at > 99% purity and as crystals and flakes (J.T. Baker, 1988).

Nickel sulfate is available as the heptahydrate at > 99% purity and as the hexahydrate at 99% purity (Aldrich Chemical Co., Inc., 1988).

(*e*) *Other nickel compounds*

Nickelocene is available in solid form at > 90% purity or as an 8-10% solution in toluene (American Tokyo Kasei, 1988).

2. Production, Use, Occurrence and Analysis

2.1 Production

Nickel was first isolated in 1751 by a Swedish chemist, Cronstedt, from an arsenosulfide ore (Considine, 1974).

(*a*) *Metallic nickel and nickel alloys*

Table 5 gives world mine production of nickel by region. Table 6 shows world nickel plant production, including refined nickel, ferronickel and nickel recycled from scrap (Chamberlain, 1988).

Various combinations of pyrometallurgical, hydrometallurgical and vapometallurgical operations are used in the nickel producing industry (Boldt & Queneau, 1967; Evans *et al.*, 1979; Tien & Howsen, 1981; Tyroler & Landolt, 1988). The description that follows is a generalized discussion of some of the more common smelting and refining processes.

Table 5. World mine production of nickel, by region (thousand tonnes)[a]

Region	1982	1983	1984	1985	1986
Albania	6.0	7.2	9.2	9.6	9.7
Australia	87.7	76.6	77.1	85.8	69.9
Botswana	17.8	18.2	18.6	19.6	20.0
Brazil	14.5	15.6	23.6	20.3	23.1
Burma	0.02	0.02	0.02	0.02	0.02
Canada	88.7	128.1	174.2	170.0	181.0
China	12.0	13.0	14.0	25.1	25.5
Colombia	1.8	17.5	21.9	15.5	22.1
Cuba	36.2	37.7	31.8	32.4	32.7
Dominican Republic	5.4	19.6	24.0	25.4	22.1
Finland	6.3	5.3	6.9	7.9	6.5
France (New Caledonia)	60.2	46.2	58.3	73.0	65.1
German Democratic Republic	2.5	2.2	2.0	1.6	1.5
Greece	5.0	16.8	16.7	18.7	17.5
Indonesia	46.0	49.4	47.6	40.6	43.9
Morocco	0.13	--	--	--	--
Norway	0.39	0.36	0.33	0.44	0.40
Philippines	19.7	13.9	13.6	28.2	13.6
Poland	2.1	2.1	2.1	2.0	2.0
South Africa	22.0	20.5	25.1	25.1	25.1
USA	2.9	--	13.2	5.6	1.1
USSR	165.1	170.0	174.2	180.0	186.0
Yugoslavia	4.0	3.0	4.0	5.0	5.0
Zimbabwe	15.8	12.0	12.2	11.1	11.0
Total	622.24	675.28	770.65	802.96	784.82

[a]From Chamberlain (1988)

Table 6. World production of processed nickel by region (thousands of tonnes)[a]

Region	1982	1983	1984	1985	1986
Albania	45.9	41.8	38.7	40.9	41.9
Brazil	3.5	8.3	9.2	13.3	13.5
Canada	58.6	87.2	104.0	100.0	115.0
China	12.0	13.0	14.0	22.5	22.5
Colombia	1.3	13.1	17.1	11.8	18.6
Cuba	9.0	9.3	8.5	8.5	7.7
Czechoslovakia	1.5	3.0	4.5	4.5	4.5
Dominican Republic	5.3	21.2	24.2	25.8	22.0

Table 6. (contd)

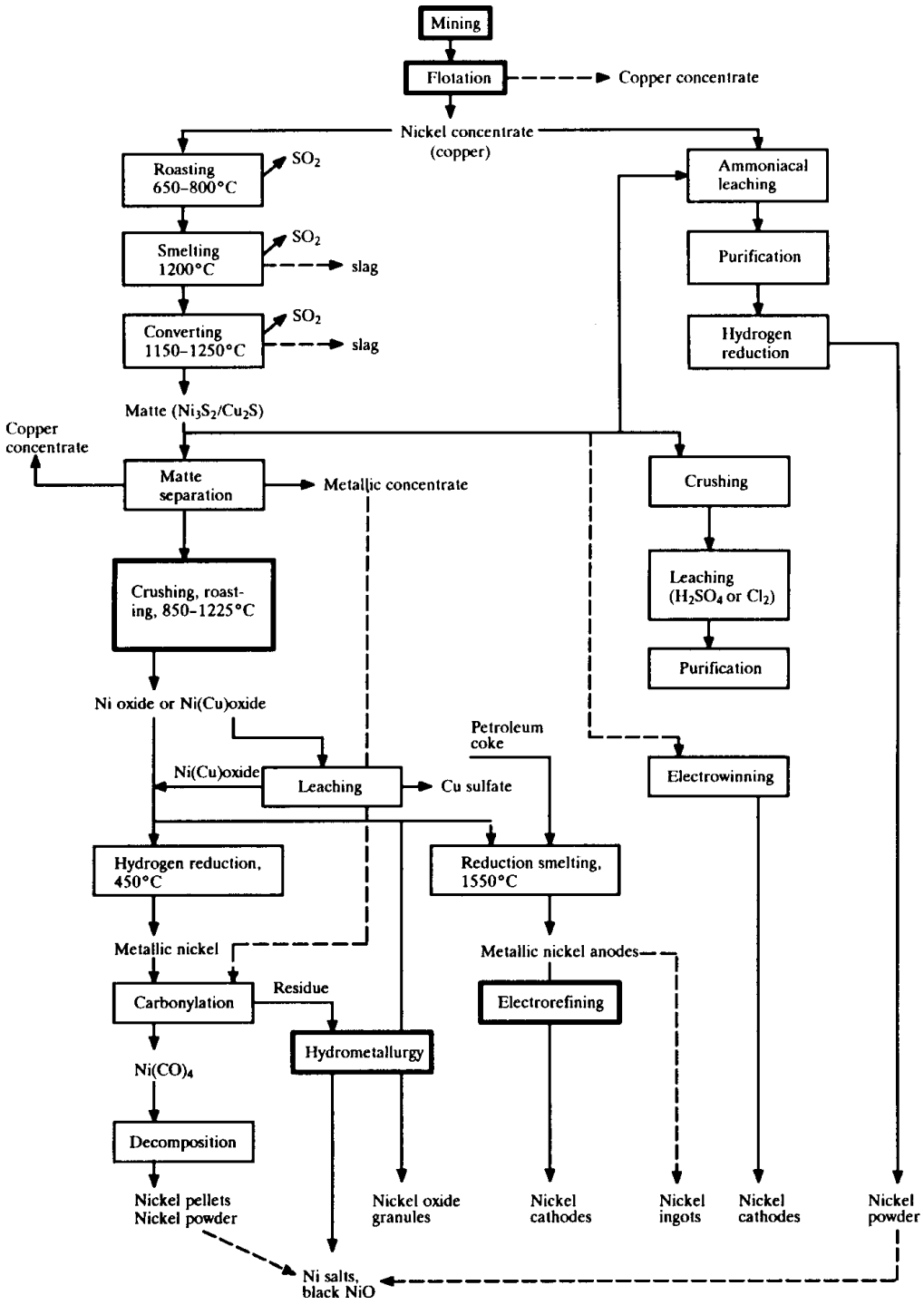
Region	1982	1983	1984	1985	1986
Finland	12.6	14.8	15.3	15.7	16.0
France	76.4	4.9	5.2	7.1	10.0
France (New Caledonia)	28.0	21.7	29.2	36.1	33.0
German Democratic Republic	3.0	3.0	3.0	3.0	3.0
Germany, Federal Republic of	1.2	1.2	1.0	0.7	-
Greece	4.5	12.9	15.8	16.0	12.0
Indonesia	5.0	4.9	4.8	4.8	5.0
Japan	90.6	82.2	89.3	92.7	88.8
Norway	25.8	28.6	35.6	37.5	38.2
Philippines	11.2	6.1	3.5	17.0	2.1
Poland	2.1	2.1	2.1	2.1	2.1
South Africa	14.4	17.0	20.5	20.5	20.0
UK	7.4	23.2	23.3	17.8	31.0
USA	40.8	30.3	40.8	33.0	1.5
USSR	180.0	185.1	191.4	198.0	215.0
Yugoslavia	1.5	1.5	2.0	3.0	3.0
Zimbabwe	13.3	10.2	10.3	9.4	9.8
Total	585.9	646.6	713.3	741.2	736.2

[a]From Chamberlain (1988)

Nickel is produced from two kinds of ore: sulfide and silicate-oxide. The latter occurs in tropical regions, such as New Caledonia, and in regions that used to be tropical, such as Oregon (USA). Both types of ore generally contain no more than % nickel (Warner, 1984). Mining is practised by open pit and underground methods for sulfide ores and by open pit for silicate-oxide ores. Sulfide ores are extracted by flotation and magnetic separation into concentrates containing nickel and various amounts of copper and other metals, such as cobalt, precious metals and iron. Silicate-oxide ores are extracted by chemical means.

The extractive metallurgy of sulfide nickel ores (see Fig. 1) is practised in a large variety of processes. Most of these processes begin with oxidation of iron and sulfur at high temperatures in multiple hearth roasters or in fluid bed roasters, or, in the early days, in linear calciners or on travelling grate sinter machines (‘sintering’). The roaster calcine is smelted in reverberatory or electric furnaces to remove rock and oxidized iron as a slag, leaving a ferrous nickel (copper) matte. In modern processes, both operations—roasting and smelting—are combined in a single operation called ‘flash smelting’. The furnace matte is upgraded by oxidizing and slagging most of the remaining iron in converters. If the converter matte or ‘Bessemer matte’ contains copper, the matte can be separated into nickel

Fig. 1. Extraction and refining of nickel and its compounds from sulfides ores[a]



[a]Modified from Mastromatteo (1986)

subsulfide, copper sulfide and metallic concentrates by a slow cooling process followed by magnetic concentration and froth flotation.

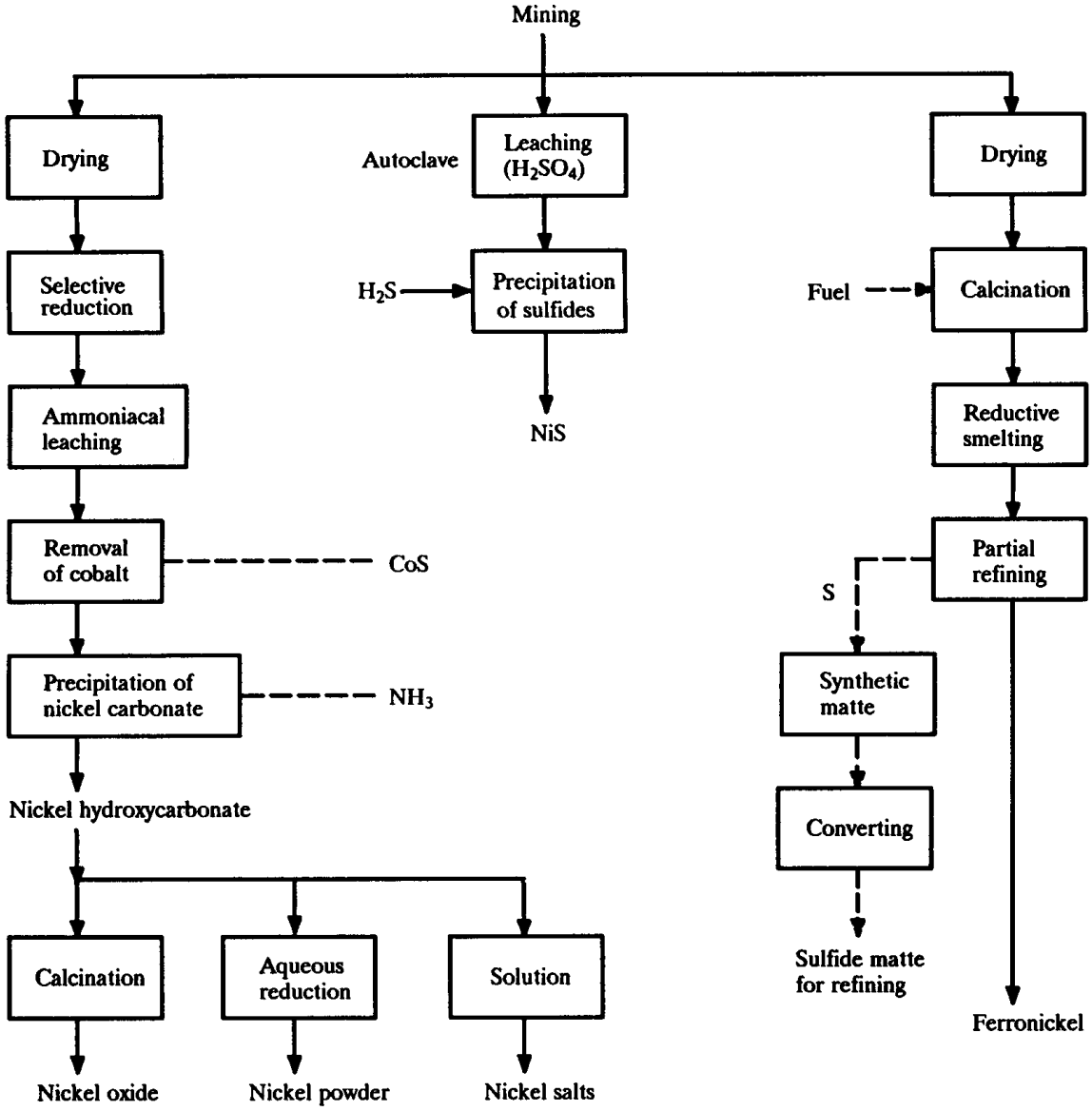
The high-grade nickel subsulfide concentrate is then refined by various processes. Most of them begin with roasting of the concentrate to a crude nickel oxide. When the copper content is low, this crude oxide is directly saleable ('Sinter 75'). In older processes, copper was leached directly from the crude oxide with sulfuric acid (as in Clydach, Wales) or by an acidic anolyte from copper electrowinning (as in Kristiansand, Norway). Refining can be pursued after reducing the crude nickel oxide to metal either in a rotary kiln or in an electric furnace with addition of a carbonaceous reductant. In the first case, the crude particulate metallic nickel is refined by the atmospheric pressure nickel-carbonyl process (Mond carbonyl process) which allows a clear-cut separation of nickel from other metals. Nickel is then produced either as nickel powder or as nickel pellets. The carbonylation residue is further processed to recover precious metals and some nickel and cobalt salts. In the second case, the molten crude nickel is cast into anodes which are 'electrorefined'. The anolyte is purified outside the electrolytic cell by removal of the main impurities, which are iron, arsenic, copper and cobalt. These impurities are generally extracted as filter cakes containing significant amounts of nickel, warranting recycling upstream in the process. Nickel is then produced in the form of electrolytic cathodes or small 'rounds'. This electrorefining process, which was used in Kristiansand, Norway, and Port Colborne, Ontario, is no longer practised there.

The Bessemer nickel (copper) matte can also be refined without roasting, either by a combination of hydrometallurgy and electrolysis ('electrowinning') or by hydrometallurgy alone. There are three types of nickel 'electrowinning' processes: (i) directly from matte cast into (soluble) anodes; (ii) from nickel sulfate solutions obtained by leaching matte with a very low sulfur content; and (iii) from nickel chloride solutions obtained by leaching matte with chloride solution in the presence of chlorine gas. In the three cases, the solutions obtained by dissolving the matte must be purified before plating pure nickel, as for the electrorefining process. In the chloride-electrowinning process, purification is accomplished through solvent extraction methods using tributylphosphate and aliphatic amines diluted in petroleum extracts.

Complete hydrometallurgy can be practised directly on sulfide concentrates or on Bessemer matte by ammonia leaching in sulfate medium in autoclaves. The solution is purified by precipitation of sulfides, and nickel is recovered as metal powder by hydrogen precipitation in autoclaves. The nickel powder can be further sintered into briquettes.

Silicate-oxide ores ('garnierites'/'laterites') are processed either by pyrometallurgy or by hydrometallurgy (Fig. 2). Pyrometallurgy consists of drying, calcining in rotary kilns, then reduction/smelting in electric furnaces. The crude ferronickel obtained (containing 20-40%

Fig. 2. Extraction and refining of nickel and its compounds from silicate-oxide (laterite) ores[a]



[f]Modified from Mastromatteo (1986)

Ni) is partially refined by thermic processes (in ladles) before being cast into ingots or granulated in water. With pyrometallurgy, nickel matte can be produced from silicate-oxide ore either by smelting the ore in the presence of calcium sulfate in a blast furnace (old process) or in an electric furnace, or by direct injection of molten sulfur into molten ferronickel.

Hydrometallurgy of silicate-oxide ores, preferentially poor in silica and magnesia, is practised by ammoniacal leaching or by sulfuric acid leaching. Ammoniacal leaching is used for ore that is selectively reduced in rotary kilns by a mixture of hydrogen and carbon monoxide. Cobalt, the main dissolved impurity, is removed from solution by precipitation as cobalt monosulfide (containing nickel monosulfide). This by-product is further refined to separate and refine nickel and cobalt. The purified nickel stream is then transformed into the hydroxycarbonate by ammonia distillation. The hydroxycarbonate is then dried, calcined and partially reduced to a saleable nickel oxide sinter. Sulfuric acid leaching is conducted under pressure in autoclaves. Nickel and cobalt are extracted from the process liquor by precipitation with hydrogen sulfide, and the mixed nickel-cobalt (10:1) sulfide is further refined in one of the processes described above.

Nickel is obtained not only by recovery from nickel ores but also by recycling process or consumer scrap. Nickel scrap is generated in forming and shaping operations in fabricating plants where nickel-containing materials are used and is also recovered from obsolete consumer goods containing nickel. Small amounts of nickel are also produced as a coproduct of copper and platinum metal refining (Sibley, 1985).

Nickel-containing steels (stainless steels and others) are produced by melting cast iron and adding ferronickel and/or pure nickel or steel scraps in large electric furnaces. The melt is transferred to a refining vessel to adjust the carbon content and impurity levels and is then cast into ingots or continuously into casting shapes. Defects in cast steel are repaired by cutting or scarfing or by chipping or grinding. The desired shapes are produced by a variety of operations, including grinding, polishing and pickling (Warner, 1984). Production volumes of stainless-steel are given in Table 7.

The technology for the production of nickel alloys is very similar to that used for steel production, except that melting and decarburizing units are generally smaller, and greater use is made of vacuum melting and remelting (Warner, 1984). In western Europe, it was estimated that 15% of nickel consumption was in nonferrous nickel alloys (Eurometaux, 1986).

Table 7. Stainless-steel[a] production (in thousands of tonnes) in selected regions[b]

Region	1987	1988
Austria	54	67
Belgium	182	254
Finland	189	206
France	720	784
Germany, Federal Republic of	957	1186
Italy	550	623
Spain	327	426
Sweden	457	482
United Kingdom	393	427
Yugoslavia	30	30
Total Europe	3859	4485
USA	1840	1995
Japan	2722	3161
Other countries	787	798
Total	9208	10 439

[a]Stainless steels with and without nickel
[b]ERAMET-SLN (1989a)

(*b*) *Nickel oxides and hydroxides*

Nickel oxide sinter (a coarse, somewhat impure form of nickel monoxide) is manufactured by roasting a semipure nickel subsulfide at or above 1000°C or by decomposing nickel hydroxycarbonate. The sinters produced commercially contain either 76% nickel or, in partially reduced form, 90% nickel. Nickel oxide sinter is produced in Australia, Canada and Cuba (Sibley, 1985).

Green nickel oxide, a finely divided, relatively pure form of nickel monoxide, is produced by firing a mixture of nickel powder and water in air at 1000°C (Antonsen, 1981). Nickel monoxide is currently produced by two companies in the USA, six in Japan, two in the UK and one in the Federal Republic of Germany (Chemical Information Services Ltd, 1988).

Black nickel oxide, a finely divided, pure nickel monoxide, is produced by calcination of nickel hydroxycarbonate or nickel nitrate at 600°C (Antonsen, 1981). It is produced by one company each in Argentina, Brazil, Canada, Japan, Mexico, the UK and the USA (Chemical Information Services Ltd, 1988).

Nickel hydroxide is prepared by (1) treating a nickel sulfate solution with sodium hydroxide to yield a gelatinous nickel hydroxide which forms a fine precipitate when neutralized, (2) electrodeposition at an inert cathode using metallic nickel as the anode and nickel nitrate as the electrolyte, or (3) extraction with hot alcohol of the gelatinous precipitate formed by nickel nitrate solution and potassium hydroxide (Antonsen, 1981). Nickel hydroxide is currently produced by four companies in Japan, three in the USA and one each in the Federal Republic of Germany and the UK (Chemical Information Services Ltd, 1988).

(*c*) *Nickel sulfides*

Purified nickel sulfide can be prepared by (i) fusion of nickel powder with molten sulfur or (ii) precipitation using hydrogen sulfide treatment of a buffered solution of a nickel[II] salt (Antonsen, 1981).

Nickel subsulfide can be made by the direct fusion of nickel with sulfur. Impure nickel subsulfide is produced during the processing of furnace matte.

Nickel sulfide and nickel subsulfide are formed in large quantities as intermediates in the processing of sulfidic and silicate-oxide ores and are traded and transported in bulk quantities for further processing. No data on production volumes are available for any of the nickel sulfides.

(*d*) *Nickel salts*

Nickel acetate is produced by heating nickel hydroxide with acetic acid in the presence of metallic nickel (Sax & Lewis, 1987). This salt is currently produced by six companies in the USA, three each in Argentina, Brazil, Italy, Japan and the UK, two each in the Federal Republic of Germany and Mexico, and one each in Australia and Spain (Chemical Information Services Ltd, 1988).

An impure basic *nickel carbonate* (roughly $2NiCO_3.3Ni(OH)_2.4H_2O$) is obtained as a precipitate when sodium carbonate is added to a solution of a nickel salt. A pure nickel carbonate is prepared by oxidation of nickel powder in ammonia and carbon dioxide (Antonsen, 1981). Nickel carbonate is currently produced by six companies each in the USA and Japan, three each in India and the Federal Republic of Germany, two each in Argentina, France, Italy, Mexico and the UK, and one each in Belgium, Brazil, Canada, Spain and Switzerland (Chemical Information Services Ltd, 1988). Finland and Japan produce the largest volumes of nickel carbonate (ERAMET-SLN, 1989b).

Nickel ammonium sulfate is prepared by reacting nickel sulfate with ammonium sulfate and crystallizing the salt from a water solution (Antonsen, 1981; Sax & Lewis, 1987). Nickel ammonium sulfate (particular form unknown) is currently produced by three companies in the UK, two in the USA and one in Japan (Chemical Information Services, Ltd, 1988).

Nickel chloride (hexahydrate) is prepared by the reaction of nickel powder or nickel oxide with hot aqueous hydrochloric acid (Antonsen, 1981). It is currently produced by eight companies in the USA, six in India, four each in the Federal Republic of Germany, Japan and the UK, three in Mexico, two each in Brazil, France and Italy and one each in Spain, Switzerland and Taiwan (Chemical Information Services Ltd, 1988). The countries or regions that produce the largest volumes are: Czechoslovakia, Federal Republic of Germany, France, Japan, Taiwan, UK, USA and USSR (ERAMET-SLN, 1989b).

Nickel nitrate (anhydrous) can be prepared by the reaction of fuming nitric acid and nickel nitrate hexahydrate. The hexahydrate is prepared by reaction of dilute nitric acid and nickel carbonate (Antonsen, 1981). Nickel nitrate hexahydrate is manufactured on a commercial basis by three methods: (1) slowly adding nickel powder to a stirred mixture of nitric acid and water; (2) a two-tank reactor system, one with solid nickel and one with nitric acid and water; and (3) adding nitric acid to a mixture of black nickel oxide powder and hot water (Antonsen, 1981). Nickel nitrate is currently produced by six companies in the USA, four each in Brazil, Japan and the UK, two each in the Federal Republic of Germany, France, India, Italy and Spain and one each in Argentina, Australia, Belgium, Mexico and Switzerland (Chemical Information Services Ltd, 1988).

Nickel sulfate hexahydrate is made by adding nickel powder or black nickel oxide to hot dilute sulfuric acid or by the reaction of nickel carbonate and dilute sulfuric acid. Large-scale manufacture of the anhydrous form may be achieved by gas-phase reaction of nickel carbonyl with sulfur dioxide and oxygen at 100°C or in a closed-loop reactor that recovers the solid product in sulfuric acid (Antonsen, 1981).

Nickel sulfate hexa- and heptahydrates are currently produced by nine companies each in Japan and the USA, six in India, four each in Argentina, the Federal Republic of Germany, Mexico and the UK, three in Canada, two each in Austria, Belgium, Brazil and Italy, and one each in Australia, Czechoslovakia, Finland, the German Democratic Republic, Spain, Sweden, Switzerland, Taiwan and the USSR (Chemical Information Services Ltd, 1988). The countries or regions that produce nickel sulfate in the largest volumes are: Belgium, Czechoslovakia, the Federal Republic of Germany, Finland, Japan, Taiwan, the UK, the USA and the USSR (ERAMET-SLN, 1989b).

(*e*) *Other nickel compounds*

Nickel carbonyl can be prepared by the Mond carbonyl process, described above for nickel. Two commercial processes are used to manufacture nickel carbonyl. In the UK, the pure compound is produced by an atmospheric method in which carbon monoxide is passed over freshly reduced nickel. In Canada, high-pressure carbon monoxide is used in the

formation of iron and nickel carbonyl, which are separated by distillation. In the USA, nickel carbonyl was prepared commercially by the reaction of carbon monoxide with nickel sulfate solution (Antonsen, 1981). Nickel carbonyl is currently produced by two companies each in the Federal Republic of Germany and the USA and by one in Japan (Chemical Information Services, Ltd., 1988).

Nickelocene is formed by the reaction of nickel halides with sodium cyclopentadienide (Antonsen, 1981). It is currently produced by two companies in the USA (Chemical Information Services Ltd, 1988).

Nickel selenide (particular form unknown) is produced by one company each in Japan and the USA, *nickel titanate* by one company each in the UK and the USA and *potassium nickelocyanate* by one company each in India and the USA (Chemical Information Services Ltd, 1988).

2.2 Use

Uncharacterized alloys of nickel have been used in tools and weapons since 1200 AD or earlier (Considine, 1974; Tien & Howsen, 1981). In fact, the principal use of nickel has always been in its metallic form combined with other metals and nonmetals as alloys. Nickel alloys are typically characterized by their strength, hardness and resistance to corrosion (Tien & Howsen, 1981). The principal current uses of nickel are in the production of stainless and heat-resistant steels, nonferrous alloys and superalloys. Other major uses of nickel and nickel salts are in electroplating, in catalysts, in the manufacture of alkaline (nickel-cadmium) batteries, in coins, in welding products (coated electrodes, filter wire) and in certain pigments and electronic products (Antonsen, 1981; Tien & Howsen, 1981; Mastromatteo, 1986). Nickel imparts strength and corrosion resistance over a wide range of temperatures and pressures (Sibley, 1985; Chamberlain, 1988).

Worldwide demand for nickel in 1983 was 685 000 tonnes (Sibley, 1985). US consumption of nickel ranged from approximately 93 000 to 122 000 tonnes over the period 1982-86 (Chamberlain, 1988). Table 8 shows the US consumption pattern by end-use for 1983. In 1978, 44% was used in stainless steels and alloy steels, 33% in nonferrous and high-temperature alloys, 17% in electroplating and the remaining 6% primarily as catalysts, in ceramics, in magnets and as salts (Tien & Howson, 1981). In western Europe, it was estimated that, in 1982, 50% of the nickel was used in stainless steels, 10% in alloy steel, 15% in nonferrous alloys, 10% in foundry alloys, 10% in plating and 5% in other applications, such as catalysts and batteries (Eurométaux, 1986).

Table 8. US consumption pattern of nickel in l983 (%)[a]

Use	Consumption (%)
Transportation	
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

[a]From Sibley (1985)

(*a*) *Metallic nickel and nickel alloys*

Pure nickel metal is used to prepare nickel alloys (including steels). It is used as such for plating, electroforming, coinage, electrical components, tanks, catalysts, battery plates, sintered components, magnets and welding rods (Eurométaux, 1986).

Ferronickel is used to prepare steels. Stainless and heat-resistant steels accounted for 93% of its end use in 1986 (Chamberlain, 1988).

Nickel-containing steels with low nickel content (< 5% Ni) are used for construction and tool fabrication. Stainless steels are used for general engineering equipment, chemical equipment, domestic applications, hospital equipment, food processing, architectural panels and fasteners, pollution control equipment, cryogenic uses, automotive parts and engine components.

Nickel-copper *alloys* are used for coinage, in industrial piping and valves, marine components, condenser tubes, heat exchangers, architectural trim, thermocouples, desalination plants, ship propellers, etc. Nickel-chromium alloys are used in many high-temperature applications, such as furnaces, jet engine parts and reaction vessels. Molybdenum-containing nickel alloys are notable for their corrosion resistance and thermal stability, as are the nickel-iron-chromium alloys, and are used in nuclear and fossil-fuel steam generators, food-processing equipment and chemical-processing and heat-treating equipment. The majority of permanent magnets are made from nickel-cast iron alloys (Mastromatteo, 1986). The other groups of nickel alloys are used according to their specific properties for acid-resistant equipment, heating elements for furnaces, low-expansion alloys,

cryogenic uses, storage of liquefied gases, high magnetic-permeability alloys and surgical implant prostheses.

(*b*) *Nickel oxides and hydroxides*

The *nickel oxide sinters* are used in the manufacture of alloys, steels and stainless steels (Antonsen, 1981).

Green nickel oxide is used to make nickel catalysts and in the ceramics industry. In specialty ceramics, it is added to frit compositions used for porcelain enamelling of steel; in the manufacture of magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes; and as a colourant in glass and ceramic stains used in ceramic tiles, dishes, pottery and sanitary ware (Antonsen, 1981).

Black nickel oxide is used in the manufacture of nickel salts and specialty ceramics. It is also used to enhance the activity of three-way catalysts containing rhodium, platinum and palladium used in automobile exhaust control. Like green nickel oxide, black nickel oxide is also used for nickel catalyst manufacture and in the ceramic industry (Antonsen, 1981).

The major use of *nickel hydroxide* is in the manufacture of nickel-cadmium batteries. It is also used as a catalyst intermediate (Antonsen, 1981).

(*c*) *Nickel sulfides*

Nickel sulfide is used as a catalyst in petrochemical hydrogenation when high concentrations of sulfur are present in the distillates. The major use of nickel monosulfide is as an intermediate in the hydrometallurgical processing of silicate-oxide nickel ores.

(*d*) *Nickel salts*

Nickel acetate is used as a catalyst intermediate, as an intermediate in the formation of other nickel compounds, as a dye mordant, as a sealer for anodized aluminium and in nickel electroplating (Antonsen, 1981).

Nickel carbonate is used in the manufacture of nickel catalysts, in the preparation of coloured glass, in the manufacture of nickel pigments, in the production of nickel oxide and nickel powder, as a neutralizing compound in nickel electroplating solutions, and in the preparation of specialty nickel compounds (Antonsen, 1981).

Nickel ammonium sulfate has limited use as a dye mordant and is used in metal-finishing compositions and as an electrolyte for electroplating (Sax & Lewis, 1987).

Nickel chloride is used as an intermediate in the manufacture of nickel catalysts and to absorb ammonia in industrial gas masks. The hexahydrate is used in nickel electroplating (Antonsen, 1981) and hydrometallurgy (Warner, 1984).

Nickel nitrate hexahydrate is used as an intermediate in the manufacture of nickel catalysts, especially sulfur-sensitive catalysts, and as an intermediate in loading active mass

in nickel-cadmium batteries of the sintered-plate type (Antonsen, 1981).

Nickel sulfate hexahydrate is used as an electrolyte primarily for nickel electroplating and also for nickel electrorefining. It is also used in 'electro-less nickel plating, as a nickel strike solution for replacement coatings or for nickel flashing on steel that is to be porcelain-enamelled, as an intermediate in the manufacture of other nickel chemicals, such as nickel ammonium sulfate, and as a catalyst intermediate (Antonsen, 1981).

(*e*) *Other nickel compounds*

The primary use for *nickel carbonyl* is as an intermediate in the Mond carbonyl-refining process to produce highly pure nickel. Other uses of nickel carbonyl are in chemical synthesis as a catalyst, as a reactant in carbonylation reactions such as the synthesis of acrylic and methacrylic esters from acetylene and alcohols, in the vapour plating of nickel, and in the fabrication of nickel and nickel alloy components and shapes (Antonsen, 1981; Sax & Lewis, 1987).

Nickelocene is used as a catalyst and complexing agent and *nickel titanate* as a pigment (Sax & Lewis, 1987).

No information was available on the use of *nickel selenides* or *potassium nickelocyanate.*

2.3 Occurrence

(*a*) *Natural occurrence*

Nickel is widely distributed in nature, forming about 0.008% of the earth's crust (0.01% in igneous rocks). It ranks twenty-fourth among the elements in order of abundance (Grandjean, 1984), just above copper, lead and zinc (Mastromatteo, 1986). The core of the earth contains about 8.5% nickel; meteorites have been found to contain 5-50% (National Research Council, 1975). Nickel is also an important constituent of deep-sea nodules, typically comprising about 1.5% (Mastromatteo, 1986). Nickel-containing ores are listed in Table 9.

Laterites are formed by the long-term weathering of igneous rocks which are rich in magnesia and iron and contain about 0.25% nickel. Leaching by acidified groundwater over a long period removes the iron and magnesia, leaving a nickel-enriched residue with nickel contents up to 2.5%. Nickel is found as mixed nickel/iron oxide and as nickel magnesium silicate (garnierite) (Grandjean, 1986; Mastromatteo, 1986). Laterite deposits have been mined in many regions of the world, including New Caledonia, Cuba, the Dominican Republic, Indonesia, the USSR, Greece, Colombia, the Philippines, Guatemala and the USA (Mastromatteo, 1986).

Table 9. Nickel-containing minerals[a]

Name	Chemical composition[a]
Breithauptite	NiSb
Niccolite	NiAs
Zaratite	$NiCO_3 2Ni(OH)_2.4H_20$
Bunsenite	NiO
Morenosite	$NiSO_4.7H_20$
Millerite	NiS
Vaesite	NiS_2
Polydomite	Ni_3S_4
Heazlewoodite	Ni_3S_2
Pentlandite	$(Ni,Fe)_9S_8$
Pyrrhotite, nickeliferous	$(Fe,Ni)_{1-x}S$[b]
Garnierite	$(Ni,Mg)Si0_3.nH_2O$

[a]From Grandjean (1986)
[b]From Warner (1984); Grandjean (1986)

Nickel and sulfur combine in a wide range of stoichiometric ratios. Nickel monosulfide (millerite), nickel subsulfide (heazlewoodite), nickel disulfide (vaesite) and Ni_3S_4 (polydymite) are found in mineral form in nature (Considine, 1974). Sulfide nickel ores contain a mixture of metal sulfides, principally pentlandite, chalcopyrite ($CuFeS_2$) and nickeliferous pyrrhotite in varying proportions. The major nickel mineral is pentlandite. While pentlandite may contain about 35% of nickel by weight, the nickel content of pyrrhotite is usually 1% or less, and the sulfide ore available for nickel production generally contains only 1-2% nickel (Grandjean, 1986). A large deposit of pentlandite is located in Sudbury, Ontario, Canada.

Other nickel ores include the nickel-arsenicals and the nickel-antimonials, but these are of much less commercial importance (Mastromatteo, 1986).

(*b*) *Occupational exposures*

Occupational exposure to nickel may occur by skin contact or by inhalation of dusts, fumes or mists containing nickel or by inhalation of gaseous nickel carbonyl. Nickel-containing dusts may also be ingested by nickel workers (Grandjean, 1984). The National Institute for Occupational Safety and Health (1977a) published a list of occupations with potential exposure to nickel (Table 10); it has estimated that about 1.5 million workers in the USA are exposed to nickel and nickel compounds (National Institute for Occupational Safety and Health, 1977b).

Table 10. Occupations with potential exposure to nickel[a]

Battery makers, storage	Mould makers
Catalyst workers	Nickel miners
Cemented carbide makers	Nickel refiners
Ceramic makers	Nickel smelters
Chemists	Nickel workers
Disinfectant makers	Oil hydrogenators
Dyers	Organic chemical synthesizers
Electroplaters	Paint makers
Enamellers	Penpoint makers
Gas-mask makers	Petroleum refinery workers
Ink makers	Spark-plug makers
Jewellers	Stainless-steel makers
Magnet makers	Textile dyers
Metallizers	Vacuum tube makers
Mond process workers	Varnish makers
Nickel-alloy makers	Welders

[a]Adapted from National Institute for Occupational Safety and Health (1977b)

Occupational exposure to nickel is evaluated by monitoring air and blood serum, plasma or urine. (For recent reviews on this subject, see Rigaut, 1983; Grandjean, 1984; Nieboer *et al.*, 1984a; Warner, 1984; Grandjean, 1986; Sunderman *et al.*, 1986a). Tables 11-13 summarize exposure to nickel as measured by air and biological monitoring in various industries and occupations. The biological indicator levels are influenced by the chemical and physical properties of the nickel compound studied and by the time of sampling. It should be noted that the nickel compounds, the timing of collection of biological samples (normally at the end of a shift) and the analytical methods used differ from study to study, and elevated levels of nickel in biological fluids and tissue samples (Table 11) are mentioned only as indications of uptake of nickel, and may not correlate directly to exposure levels (Angerer *et al.*, 1989). (See also section 3.3(b) and the monographs on chromium and chromium compounds, and on welding.)

Table 11. Occupational exposure to nickel in the nickel producing industry

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Mines, Ontario (Canada) [1976]		20	6–40				Rigaut (1983)
Mines, Oregon (USA) [1981]		30					Rigaut (1983)
Mines, New Caledonia [1982]		20	6–40				Rigaut (1983)
Smelter, producing ferronickel and matte, New Caledonia		5–76[a]	2–274[b]	< 10 (86% of samples) < 20 (98% of samples)			Warner (1984)
Laterite mining and smelting, Oregon (USA)[b]							Warner (1984)
Ore handling	3	52	5–145				
Drying	4	17	9–21				
Calcining	4	90	37–146				
Skull drilling	8	16	4–43				
Ferrosilicon manufacturing	15	32	4–214				
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				
Refinery, Clydach (Wales, UK)							Morgan & Rouge (1984)
Kiln							
Before shut-down[c]		310 (26 samples)	10–5000	24±24 (67 samples)		8.9±5.9 (37 samples)	
On return to work[c]				14±7 (20 samples)		3.0±2.0 (20 samples)	

Table 11 (contd)

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Refinery, Clydach (Wales, UK)							
Kiln (contd)							
One month later		190 (30 samples)	10–2890	22±10 (14 samples)		5.5±2.0 (16 samples)	
New powder plant		310 (20 samples)	90–1530				
Before shut-down[c]				37±30 (48 samples)		7.2±4.8 (25 samples)	
On return to work[c]				13±12 (17 samples)		4.0±2.3 (17 samples)	
One month later		500 (22 samples)	50–1810	31±13 (16 samples)		7.6±3.5 (15 samples)	
Old powder plant		1460 (5 samples)	80–5000	33±13 (12 samples)		9.0±3.7 (6 samples)	
Wet-treatment (A)[d]		1540 (8 samples)	220–4180	39±28 (15 samples)		7.4±5.1 (7 samples)	
Wet-treatment (B)[e]		90 (17 samples)	30–150	34±24 (36 samples)		3.4±1.9 (13 samples)	
Refinery, Kristiansand (Norway)[b]							Høgetveit *et al.* (1978)
Roasting-smelting	24	860±1200		65±58		7.2±2.8	
Electrolytic department	90	230±420		129±106		11.9±8.0	
Other processes	13	420±490		45±27		6.4±1.9	

Table 11 (contd)

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Refinery, Kristiansand (Norway)							Torjussen &
Roasting-smelting	97			34±35		5.2±2.7	Andersen (1979)
Electrolysis	144			73±85		8.1±6.0	
Other processes	77			22±18		4.3±2.2	
Electrolytic refinery (USA)	15	489	20–2200	222 124 (μg/g creatinine)	8.6–813 6.1–287		Bernacki *et al.* (1978a)
Electrolytic refinery (FRG)		50		14.8 (μg/g creatinine)	2.5–63		Raithel (1987)
Electrolytic refinery (Czechoslovakia)		600	86–1265	264	125–450		Rigaut (1983)
Hydrometallurgical refinery (Canada)							Warner (1984)
Acid leaching of matte		99	5–1630				
Purification of nickel electrolyte:							
Tube filterman	12	144	13–316				
	12[f]	129	11–316				
Filter pressman	16	209	61–535				
	16[f]	152	31–246				
Filter-press area	11	242	64–508				
	11[f]	221	52–466				

Table 11 (contd)

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Hydrometallurgical refinery (Canada) (contd)							
Purification of nickel electrolyte[a]:							
Cementation of copper on nickel in Pachuca tanks	39	168	48–644				
	39[f]	38	1–133				
Removal of iron slimes with a tube filter	56	200	27–653				
	56[f]	85	3–433				
Oxidizing cobalt with chlorine	47	183	30–672				
	47[f]	66	1–267				
General operations in a tank house using insoluble anodes	96[a]	336	40–1100				
	45[b]	185	80–400				
Tankhouse using nickel matte anodes:							
General area	11[a]	48	14–223				
	11[a,f]	29	5–210				
Tankman	15[b]	48	18–88				
	15[b,f]	30	12–71				
Anode scrapman	11[b]	179	43–422				
	11[b,f]	52	1–236				

[a]Area air sampling

[b]Personal air sampling

[c]Specimens obtained before and after six months' closure of refinery operations

[d]Short exposures to high levels of insoluble nickel compounds

[e]Chronic exposures to soluble nickel sulfate

[f]Soluble nickel

Table 12. Occupational exposure in industries using primary nickel products

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Reference
		Mean	Range	Mean	Range	
Stainless-steel production						Warner (1984)
Electric furnace shop	8[a]	36	9–65			
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[b]	5	111[c]	13–188[c]			
Heat treating	1	54[d]	< 1–104[d]			
Rolling and forging	6	49	< 11–72			
Other operations (maintenance, pickling)	5	58	10–107			
High nickel alloy production (FRG) (a few persons exposed to nickel powder)	59	300[e]		2.6	0.5–52	Raithel (1987)
High nickel alloy production[f]						Warner (1984)
Weighing and melting	369	83[f]	1–4400			
Hot working	153	111	1–4200			
Cold working	504	64	1–2300			
Grinding	96	298	1–2300			
Pickling and cleaning	18	8	1–15			
Maintenance	392	58	1–73			
Production of wrought nickel and alloys *via* metal powder foundries	226	1500[f]	1–60000			Warner (1984)

Table 12 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Reference
		Mean	Range	Mean	Range	
Six jobbing foundries processing alloys containing 0–60% nickel, averaging 10–15% nickel:						Scholz & Holcomb (1980)
Melting	15	21	< 5–62			
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:						Warner (1984)
Melting and casting	16	13	ND[g]–70			
Cleaning room:						
Air arc gouging	7	310	40–710			
Welding	34	67	10–170			
Three low alloy (0–2% nickel) iron and steel foundries						Warner (1984)
Melting and casting	16	13	4–32			
Cleaning room (grinding, air arc gouging, welding)	18	54	7–156			
Steel foundry (Finland) (steel cutters)	4	518	145–1100	39	18–77	Aitio *et al.* (1985)
Production of soluble nickel salts (Wales, UK)[f]	66	500	10–20 000	(68) 65[h]	10–200[h]	Morgan & Rouge (1979)
	60	450	< 10–12 070	(60) 49[h]	< 10–210[h]	

Table 12 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Reference
		Mean	Range	Mean	Range	
Production of nickel salts from nickel or nickel oxide:						Warner (1984)
Nickel sulfate	12	117[f]	9–590			
Nickel chloride	10	196[f,i]	20–485[i]			
Nickel acetate/nitrate	6	155[f]	38–525			

[a]Companies reporting exposures

[b]Samples taken outside protective hood

[c]Excludes one suspiciously high measurement (1460 μg Ni/m³)

[d]Excludes one suspiciously high measurement (500 μg Ni/m³)

[e]The median nickel concentration in workroom air was 300 μg/m³; values that exceeded 500 μg/m³ were found at 2 of 8 measuring stations

[f]Mainly from personal sampling

[g]Not detected

[h]Corrected to 1.6 g/l creatinine

[i]Excludes one suspiciously high value (2780 μg Ni/m³)

Table 13. Occupational exposure in industries using nickel in special applications

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Ni/Cd-battery production with nickel and nickel hydroxide; assembly and welding of plates	36	378[a,b]	20–1910[a,b]					Warner (1984)
Ni/Cd-battery production (FRG)	51			4.0[c]	1.9–10.9			Raithel (1987)
Ni/Cd or Ni/Zn-battery production (USA)	6			11.7±7.5 10.2	3.4–25 7.2–23 (μg/g creatinine)			Bernacki *et al.* (1978a)
Ni/H_2-battery production	7			32.2±40.4	2.8–103			
Ni/Cd-battery production			12–33		24–27 (μg/g creatinine)			Adamsson *et al.* (1980)
Ni-catalyst production (Netherlands)	73		< 200–5870	64 (μg/g creatinine)	9–300	8	2–41	Zwennis & Franssen (1983)
Ni-catalyst production from nickel sulfate (USA)	7 5	150[a] 370[d]	10–600[a] 190–530[d]					Warner (1984)
Ni-catalyst use; coal gasification workers (USA)	9			4.2 3.2	0.4–7.9 0.1–5.8 (μg/g creatinine)			Bernacki *et al.* (1978a)
Electroplating								Warner (1984)
Sulfate bath, 45°C								
Area 1 sample	16	< 6	< 5–< 8					
Area 2 samples	3	< 4	< 2–< 7					
Personal samples	6	< 11	< 7–< 16					

Table 13 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Electroplating (contd)								
Sulfate bath, 70°C								
Area samples	6	< 3	< 2–< 3					
Sulfamate bath, 45–55°C								
Area 1 sample	9	< 4	< 4					
Area 2 samples	6	< 4	< 4					
Electroplating (Finland)		90	20–170	53.5	12–109	6.1	1.2–14.1	Tossavainen *et al.* (1980)
Electroplating (Finland)		-	30–160	-	25–120	-	3–14	Tola *et al.* (1979)
Electroplating (USA)		9.3[a]	0.5–21.2	48	5–262			Bernacki *et al.* (1980)
Electroplating (USA)	21			30.4 (21.0	3.6–85 2.4–62 μg/g creatinine)			Bernacki *et al.* (1978a)
Electroplating (India)	12			12.2	11–26			Tandon *et al.* (1977)
Electroplating (FRG)		10 (soluble anode)						Gross (1987)
		110 (insoluble anode)						
		7 (insoluble anode and wetting agent)			1.7–3.6			
Exposed persons in the hollow glass industry (FRG)	9		3–3800	11.9 (946 samples)	3.6–42.1[e]	1.6	0.75–3.25[e] (288 samples)	Raithel (1987)
Flame sprayer			3–600	25.3 (114 samples)	8.5–81.5	1.95	0.75–3.25 (40 samples)	

Table 13 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Grinder, polisher			18–3800	7.4 (406 samples)	2.9–24.3	0.9	0.75–2.05 (140 samples)	
Mixed mechanical work and flame spraying			300–410	17.5 (394 samples)	4.9–53.9	1.65	0.75–4.10 (108 samples)	
Plasma spraying (FRG)	6	200			3.4–12.5			Gross (1987)
Spark eroding (FRG)	6	< 10			0.7–2.1			Gross (1987)
Flame spraying (USA)	5	2.4	< 1–6.5	17.2 (16.0	1.4–26 1.4–54 μg/g creatinine)			Bernacki *et al.* (1978a)
Plasma cutting (FRG)	17		< 100		1.1–6.5			Gross (1987)
Painting								
Spray painting in a construction shipyard (USA)	13			3.2	< 0.5–9.2	4.4	< 0.5–17.2	Grandjean *et al.* (1980)
Painting in repair shipyard (USA)	18					5.9	< 0.5–13	Grandjean *et al.* (1980)
Manufacturing paints (USA)	10			15.3±11.1	6–39			Tandon *et al.* (1977)
Buffing, polishing, grinding								
Buffers and polishers (aircraft engine factory) (USA)	7	26	< 1–129	4.1 (2.4	0.5–9.5 0.5–4.7 μg/g creatinine)			Bernacki *et al.* (1978a)
Grinders (abrasive wheel grinding of aircraft parts) (USA)	9	1.6	< 1–9.5	5.4 (3.5	2.1–8.8 1.7–6.1 μg/g creatinine)			Bernacki *et al.* (1978a)

Table 13 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Polisher, grinder (FRG)	15	140			0.7–9.9			Gross (1987)
Polisher, grinder (stainless steel) (FRG)	46	350[c]	10–10 000[f]	28	(12) 3–7[l]			Heidermanns *et al.* (1983)
Miscellaneous exposure								
Bench mechanics (assembling, fittings and finishing aircraft parts made of Ni-alloys) (USA)	8	52	< 1–252	12.2 (7.2	1.4–41 0.7–20 μg/g creatinine)			Bernacki *et al.* (1978a)
Riggers/carpenters (construction shipyard) (USA)	16			3.7	1.1–13.5	3.3	1.1–13.5	Grandjean *et al.* (1980)
Riggers/carpenters (repair shipyard) (USA)	11					3.6	< 0.5–7.4	Grandjean *et al.* (1980)
Shipfitters/pipefitters (construction shipyard (USA)	6			4.9	3.7–7.1	4.1	1.5–6.8	Grandjean *et al.* (1980)
Shipfitters/pipefitters (repair shipyard) (USA)	15					9.1	0.5–3.8	Grandjean *et al.* (1980)

[a]Personal air sampling

[b]Excludes three suspiciously high values (5320; 18 300; 53 300 μg/m³)

[c]Median

[d]Area air monitoring

[e]68th percentile range

[f]90th percentile range

(i) *Nickel mining and ore comminution*

On the basis of personal gravimetric sampling among Canadian underground miners of nickel, the time-weighted average concentration of total airborne nickel was about 25 $\mu g/m^3$ and that of respirable nickel, < 5 $\mu g/m^3$ (see Table 11; Warner, 1984). Ore miners may also be exposed to radon, oil mist, diesel exhausts and asbestos (see IARC, 1977, 1988a, 1989).

(ii) *Nickel roasting, calcining, smelting and refining*

The nickel content of air samples from a Sudbury (Canada) smelter seldom exceeded 0.5 mg/m^3 but could be as high as 1 mg/m^3. The average concentrations of airborne nickel were higher in the roaster areas (0.048 mg/m^3) than in the converter areas (0.033 mg/m^3), because the handling of fine solids is a greater source of dust than the handling of molten phases. Thus, work-place air may contain roaster feed and product, which include various nickel-containing minerals and solid solutions of nickel in iron oxides. Nickel-bearing dusts from converters contain mainly nickel subsulfide (Warner, 1984). Arsenic, silica, copper, cobalt and other metal compounds may also occur in work-place air.

Emissions from the high-temperature ore calcining and smelting furnaces used to produce ferronickel from lateritic ores would contain nickel predominantly in the form of silicate oxides and iron-nickel mixed/complex oxides of the ferrite or spinel type. The nickel content of these dusts can range from 1 to 10% (International Committee on Nickel Carcinogenesis in Man, 1990).

Average concentrations of airborne nickel in refining operations can be considerably higher than those encountered in mining and smelting because of the higher nickel content of the materials being handled in the refining process (Table 11). The nickel species that may be present in various refining operations include nickel subsulfide, nickel monoxide, nickel-copper oxides, nickel-iron oxides, metallic nickel, pure and alloyed, nickel sulfate, nickel chloride and nickel carbonate. Other possible exposures would be to hydrogen sulfide, ammonia, chlorine, sulfur dioxide, arsenic and polycyclic aromatic hydrocarbons (Warner, 1984; International Committee on Nickel Carcinogenesis in Man. 1990).

A recent attempt has been made, in conjunction with a large epidemiological study (International Committee on Nickel Carcinogenesis in Man, 1990), to estimate past exposures in various nickel refineries using different processes. Exposure estimates were made first for total airborne nickel, based either on historical measurements (after 1950) or on extrapolation of recent measurements. In all cases, further estimates were made of nickel species (metallic, oxidic, sulfidic and soluble), as defined in the report, on the basis of knowledge of the processes and rough estimates of the ratio of the various species generated in each process.

Prior to the widespread use of personal samplers, high-volume samplers were used to take area samples; however, in many instances, neither personal gravimetric nor high-volume samples were available, and konimeter readings were the only available means of assessing the level of airborne dust. No measurement of the actual concentration of nickel, and especially nickel species, in work places exists for any refining operation prior to 1950. More recently, measurements have been made of total dust and, in some cases, total nickel content of dust or mist in refinery work-place air. Conversion of high-volume sampler and konimeter measurements to concentrations comparable to personal gravimetric sampler measurements introduces another uncertainty in the environmental estimates. The main reason for this uncertainty is that it is impossible to derive unique conversion factors to interrelate measurements from the three devices; different particle size distributions give rise to different conversion factors. Information concerning particle size in airborne dusts was seldom available in the work places under study (International Committee on Nickel Carcinogenesis in Man, 1990).

Estimates of nickel exposure were further divided into four categories representing different nickel species: (i) metallic nickel, (ii) oxidic nickel [undefined, but generally understood to include nickel oxide combined with various other metal oxides, such as iron, cobalt and copper oxides], (iii) sulfidic nickel (including nickel subsulfide) and (iv) soluble nickel, defined as consisting 'primarily of nickel sulfate and nickel chloride but may in some estimates include the less soluble nickel carbonate and nickel hydroxide'. No actual measurement of specific nickel species in work-place air was available upon which to base exposure estimates. As a result, the estimates are necessarily very approximate. This is clear, for example, from the estimates for linear calciners at the Clydach refinery (Wales, UK), which gave total nickel concentrations of 10-100 mg/m^3, with 0-5% soluble nickel. Because of the inherent error in the processes of measurement and speciation and the uncertainty associated with extrapolating estimates from recent periods to earlier periods, the estimated concentrations of nickel species in work places in this study (International Committee on Nickel Carcinogenesis in Man, 1990) must be interpreted as broad ranges indicating only estimates of the order of magnitude of the actual exposures.

(iii) *Production of stainless steel and nickel alloys*

While some stainless steels contain up to 25-30% nickel, nearly half of that produced contains only 8-10% nickel. Nickel oxide sinter is used as raw material for stainless and alloy steelmaking in some plants, and oxidized nickel may be found in the fumes from many melting/casting and arc/torch operations in the melting trades. The nickel concentrations in air in the stainless and alloy producing industries were given in Table 12. Occupational exposure in alloy steel making should generally be lower than those observed for

comparable operations with stainless steel. The normal range of nickel in alloy steels is 0.3-5% but the nickel content can be as high as 18% for certain high-strength steels. The production of 'high nickel' alloys consumes about 80% of the nickel used for nonferrous applications. The technology is very similar to that used for stainless steel production except that melting and decarburizing units are generally smaller and greater use is made of vacuum melting and remelting. Since these alloys contain more nickel than stainless and alloy steels, the concentrations of nickel in workroom air are generally higher than for comparable operations with stainless and alloy steels (Warner, 1984).

(iv) *Steel foundries*

In foundries, shapes are cast from a wide variety of nickel-containing materials. Melts ranging in size from 0.5 to 45 tonnes are prepared in electric arc or induction furnaces and cast into moulds made of sand, metal or ceramic. The castings are further processed by chipping and grinding and may be repaired by air arc gouging and welding. Foundry operations can thus be divided roughly into melting/casting and cleaning room operations. Typical levels of airborne nickel in steel foundries were presented in Table 12 (Warner, 1984). Health hazards in foundry operations include exposure to silica and metal fumes and to degradation products from moulds and cores, such as carbon monoxide, formaldehyde and polycyclic aromatic hydrocarbons (see IARC, 1984).

(v) *Production of nickel-containing batteries*

The principal commercial product in nickel-containing batteries is the electrochemical couple nickel/cadmium. Other couples that have been used include nickel/iron, nickel/hydrogen and nickel/zinc. In nickel-cadmium batteries, the positive electrode is primarily nickel hydroxide, contained in porous plates. The positive material is made from a slurry of nickel hydroxide, cobalt sulfate and sodium hydroxide, dried and ground with graphite flake. Sintered nickel plates impregnated with the slurry may also be used. The nickel/hydrogen system requires a noble metal catalyst and operates at high pressures, requiring a steel pressure vessel. Nickel/iron batteries can be produced using nickel foil (Malcolm, 1983).

The concentrations of nickel in air and in biological samples from workers in the nickel-cadmium battery industry were summarized in Table 13. Workers in such plants are also exposed to cadmium.

(vi) *Production and use of nickel catalysts*

Metallic nickel is used as a catalyst, often alloyed with copper, cobalt or iron, for hydrogenation and reforming processes and for the methane conversion and Fischer-Tropsch reactions. Mixed, nickel-containing oxides are used as partial oxidation catalysts and as hydrodesulfuration catalysts (cobalt nickel molybdate) (Gentry *et al.*, 1983). Occupational exposure occurs typically in the production of catalysts from metallic nickel

powder and nickel salts such as nickel sulfate (Warner, 1984), but coal gasification process workers who use Raney nickel as a hydrogenation catalyst have also been reported to be exposed to nickel (Bernacki *et al.*, 1978a). Exposure levels are generally higher in catalyst production than during the use of catalysts (see Table 13).

(vii) *Nickel plating*

Metal plating is an operation whereby a metal, commonly nickel, is deposited on a substrate for protection or decoration purposes. Nickel plating can be performed by electrolytic processes (electroplating) or 'electroless' processes (chemical plating), with aqueous solutions (the 'baths'). During electroplating, nickel is taken out of the solution and deposited on the substrate, which acts as the cathode. Either soluble anodes, made from metallic nickel feed, or insoluble anodes, in which the nickel is introduced as the hydroxycarbonate, are used. The baths contain a mixture of nickel sulfate and/or chloride or, less often, sulfamate. In electroless processes, a hypophosphite medium is used, the nickel feed being nickel sulfate.

The electrolyte contains soluble nickel salts, such as nickel fluoborate, nickel sulfate and nickel sulfamate (Warner, 1984). Nickel plating can be performed with a soluble (metallic nickel) or insoluble anode. The principal source of air contamination in electroplating operations is release of the bath electrolyte into the air. Electroplaters are exposed to readily absorbed soluble nickel salts by inhalation, which subsequently causes high levels in urine (Tola *et al.*, 1979; see Table 13).

(viii) *Welding*

Welding produces particulate fumes that have a chemical composition reflecting the elemental content of the consumable used. For each couple of process/material of application, there is a wide range of concentrations of elements present in the fume. Nickel and chromium are found in significant concentrations in fumes from welding by manual metal arc, metal inert gas and tungsten inert gas processes on stainless and alloy steels. Typical ranges of total fume and nickel, as found in the breathing zone of welders, are presented in Table 14. Certain special process applications not listed can also produce high nickel and chromium concentrations, and manual metal arc and metal inert gas welding of nickel in confined spaces produce significantly higher concentrations of total fume and elemental constituents. Exposure to welding fumes that contain nickel and chromium can lead to elevated levels of these elements in tissues, blood and urine (see monograph on welding for details).

(ix) *Thermal spraying of nickel*

Thermal spraying of nickel is usually performed by flame spraying or plasma spraying (Gross, 1987). For flame spraying, nickel in wire form is fed to a gun

Table 14. Total fume and nickel concentrations found in the breathing zone of welders[a]

Process[b]	Total fume[c] (mg/m^3)	Ni (μg/m^3)
MMA/SS	4-10	10-1000
MIG/SS	2-5	30-500
TIG/SS	2-6	10-40

[a]Compiled from Table 4 of monograph on welding

[b]MMA, manual metal arc; SS, stainless steel; MIG, metal inert gas; TIG, tungsten inert gas

[c]50-90% range

fuelled by a combustible gas such as acetylene, propane or natural gas. The wire is melted in the oxygen-fuel flame, atomized with compressed air, and propelled from the torch at velocities up to 120 m/s. The material bonds to the workpiece by a combination of mechanical interlocking of the molten particles and a cementation of partially oxidized material.

The material can also be sprayed in powder form, the fuel gases being either acetylene or hydrogen and oxygen. The powder is aspirated by an air stream, and the molten particles are deposited on the workpiece with high efficiency. For plasma spraying, an electric arc is established in the controlled atmosphere of a special nozzle. Argon is passed through the arc, where it ionizes to form a plasma that continues through the nozzle and recombines to create temperatures as high as 16 700°C. Powder is melted in the stream and released from the gun at a velocity of approximately 10 m/s (Burgess, 1981; Pfeiffer & Willert, 1986).

Workers who construct or repair nickel-armoured moulds in hollow-glass and ceramics factories use flame spraying with metallic powder (70-98% Ni) and are exposed to nickel dusts (as metallic and oxidic nickel) and fumes. After the moulds have been polished with grinding discs, abrasives and emery paper, they are installed in glass-making machines. Exposure levels in various types of thermal spraying, cutting and eroding were shown in Table 13.

(x) *Production and use of paints*

Some pigments for paints (e.g., nickel flake) and colours for enamels (e.g., nickel oxide) contain nickel. Exposure to nickel can occur when spraying techniques are used and when the paints are manufactured (Tandon *et al.*, 1977; Mathur & Tandon, 1981). Paint and pigment workers have slightly higher concentrations of nickel in plasma and urine than controls (see Table 13). Sandblasters may be exposed to dusts from old paints containing

nickel and, additionally, to nickel-containing abrasive materials (Stettler *et al.*, 1982).

(xi) *Grinding & polishing and buffing of nickel-containing metals*

Grinding, polishing and buffing involve controlled use of bonded abrasives for metal finishing operations; in many cases the three operations are conducted in sequence (for review, see Burgess, 1981). Grinding includes cutting operations in foundries for removal of gates, sprues and risers, rough grinding of forgings and castings, facing off of welded assemblies and grinding out major surface imperfections. Grinding is done with wheels made of selected abrasives in bonding structural matrices. The commonly used abrasives are aluminium oxide and silicon carbide. The wheel components normally make up only a small fraction of the total airborne particulates released during grinding, and the bulk of the particles arise from the workpiece. Polishing techniques are used to remove workpiece surface imperfections such as tool marks, and this may remove as much as 0.1 mm of stock from a workpiece. In buffing, little metal is removed from the workpiece, and the process merely provides a high lustre surface by smearing any surface roughness with a high weight abrasive; e.g., ferric oxide and chromium oxide are used for soft metals, aluminium oxide for harder metals. Sources of airborne contaminants from grinding, polishing and buffing have been identified (Burgess, 1981; König *et al.*, 1985). Grinding, polishing and buffing cause exposures to metallic nickel and to nickel-containing alloys and steels (see Table 13).

(xii) *Miscellaneous exposure to nickel*

A group of employees exposed to metallic nickel dust was identified among employees of the Oak Ridge Gaseous Diffusion Plant in the USA. In one department, finely-divided, highly pure, nickel powder was used to manufacture ‘barrier’, a special porous medium employed in the isotope enrichment of uranium by gaseous diffusion. The metallic powder was not oxidized during processing. Routine air sampling was performed at the plant from 1948 to 1963, during which time 3044 air samples were collected in seven areas of the barrier plant and analysed for nickel content. The median nickel concentration was 0.13 mg/m^3 (range, <0.1-566 mg/m^3), but the authors acknowledged that the median exposures were probably underestimated (Godbold & Tompkins, 1979). Other determinations of nickel in miscellaneous industries and activities were presented in Table 13.

(*c*) *Air*

Nickel enters the atmosphere from natural sources (e.g., volcanic emissions and windblown dusts produced by weathering of rocks and soils), from combustion of fossil fuels in stationary and mobile power sources, from emissions from nickel mining and refining operations, from the use of metals in industrial processes and from incineration of

wastes (Sunderman, 1986a; US Environmental Protection Agency, 1986). The estimated global emission rates are given in Table 15. The predominant forms of nickel in the ambient air appear to be nickel sulfate and complex oxides of nickel with other metals (US Environmental Protection Agency, 1986).

Table 15. Emission of nickel into the global atmosphere[a]

Source	Emission rate (10^6 kg/year)
Natural	
Wind-blown dusts	4.8
Volcanoes	2.5
Vegetation	0.8
Forest fires	0.2
Meteoric dusts	0.2
Sea spray	0.009
Total	8.5
Anthropogenic[b]	
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

[a]From Bennett (1984)

[b]Emissions during the mid-1970s

Nickel concentrations in the atmosphere at remote locations were about 1 ng/m^3 (Grandjean, 1984). Ambient levels of nickel in air ranged from 5 to 35 ng/m^3 at rural and urban sites (Bennett, 1984). Surveys have indicated wide variations but no overall trend. In the USA, atmospheric nickel concentrations averaged 6 ng/m^3 in nonurban areas and 17 ng/m^3 (in summer) and 25 ng/m^3 (in winter) in urban areas (National Research Council, 1975). Salmon *et al.* (1978) reported nickel concentrations in 1957-74 at a semirural site in England to range from 10 to 50 ng/m^3 (mean, 19 ng/m^3). Nickel concentrations at seven sites in the UK ranged, with one exception, from < 2 to 4.8 ng/kg [< 2.5 to 5.9 ng/m^3] (Cawse, 1978). Annual averages in four Belgian cities were 9-60 ng/m^3 during 1972-77 (Kretzschmar *et al.*, 1980). Diffuse sources (traffic, home heating, distant sources) generally predominated.

High levels of nickel in air (110-180 ng/m^3) were recorded in heavily industrialized areas and larger cities (Bennett, 1984).

Local airborne concentrations of nickel are high around locations where nickel is mined (e.g., 580 ng/m^3 in Ontario, Canada) (McNeely *et al.*, 1972). The average atmospheric nickel concentration near a nickel refinery in West Virginia (USA) was 1200 ng/m^3, compared to 40 ng/m^3 at six sampling stations not contiguous to the nickel plant. The highest concentration on a single day was about 2000 ng/m^3 near a large nickel production facility (Grandjean, 1984).

Average exposure to nickel by inhalation has been estimated to be 0.4 μg/day (range, 0.2-1.0 μg/day) for urban dwellers and 0.2 μg/day (range, 0.1-0.4 μg/day) for rural dwellers (Bennett, 1984).

(*d*) *Tobacco smoke*

Cigarette smoking can cause a daily absorption of nickel of 1 μg/pack due to the nickel content of tobacco (Grandjean, 1984). Sunderman and Sunderman (1961) and Szadkowski *et al*. (1969) found average nickel contents of 2.2 and 2.3 μg/cigarette, respectively, with a range of 1.1-3.1. The latter authors also showed that 10-20% of the nickel in cigarettes is released in mainstream smoke; most of the nickel was in the gaseous phase. The nickel content of mainstream smoke ranges from 0.005 to 0.08 μg/cigarette (Klus & Kuhn, 1982). It is not yet known in what form nickel occurs in mainstream smoke (US Environmental Protection Agency, 1986); it has been speculated that it may be present as nickel carbonyl (Grandjean, 1984), but, if so, it must occur at concentrations of < 0.1 ppm (Alexander *et al.*, 1983). Pipe tobacco, cigars and snuff have been reported to contain nickel at levels of the same magnitude (2-3 μg/g tobacco) (National Research Council, 1975).

(*e*) *Water and beverages*

Nickel enters groundwater and surface water by dissolution of rocks and soils, from biological cycles, from atmospheric fallout, and especially from industrial processes and waste disposal, and occurs usually as nickel ion in the aquatic environment. Most nickel compounds are relatively soluble in water at pH values less than 6.5, whereas nickel exists predominantly as nickel hydroxides at pH values exceeding 6.7. Therefore, acid rain has a pronounced tendency to mobilize nickel from soil and to increase nickel concentrations in groundwater.

The nickel content of groundwater is normally below 20 μg/L (US Environmental Protection Agency, 1986), and the levels appear to be similar in raw, treated and distributed municipal water. In US drinking-water, 97% of all samples (n = 2503) contained ≤20 μg/L, while about 90% had ≤10 μg/L (National Research Council, 1975). Unusually high levels were found in groundwater polluted with soluble nickel compounds from a nickel-plating facility (up to 2500 μg/L) and in water from 12 wells (median, 180 μg/L) (Grandjean, 1984).

The median level in Canadian groundwater was < 2 μg/L, but high levels were reported in Ontario (Méranger *et al.*, 1981). In municipal tap-water near large open-pit nickel mines, the average nickel concentration was about 200 μg/L, while that in a control area had an average level of about 1 μg/L (McNeely *et al.*, 1972).

Nickel concentrations in drinking-water in European countries were reported to range in general from 2-13 μg/L (mean, 6 μg/L) (Amavis *et al*., 1976). Other studies have suggested low background levels in drinking-water, e.g., in Finland an average of about 1 μg/L (Punsar *et al.*, 1975) and in Italy mostly below 10 μg/L. In the German Democratic Republic, drinking-water from groundwater showed an average level of 10 μg/L nickel, slightly below the amount present in surface water (Grandjean, 1984). In the Federal Republic of Germany, the mean concentration of nickel in drinking-water was 9 μg/L, with a maximal value of 34 μg/L (Scheller *et al.*, 1988).

The nickel concentration in seawater ranges from 0.1 to 0.5 μg/L, whereas the average level in surface waters is 15-20 μg/L. Freshly fallen arctic snow was reported to contain 0.02 μg/kg, a level that represents 5-10% of those in annual condensed layers (Mart, 1983).

Nickel concentrations of 100 μg/L have been found in wine; average levels of about 30 μg/L were measured in beer and levels of a few micrograms per litre in mineral water (Grandjean, 1984). In the Federal Republic of Germany, however, the mean concentration of nickel in mineral waters was 10 μg/L, with a maximal value of 31 μg/L (Scheller *et al.*, 1988).

(*f*) *Soil*

The nickel content of soil may vary widely, depending on mineral composition: a normal range of nickel in cultivated soils is 5-500 μg/g, with a typical level of 50 μg/g (National Research Council, 1975). In an extensive survey of soils in England and Wales, nickel concentrations were generally 4-80 μg/g (median, 26 μg/g; maximum, 228 μg/g) (Archer, 1980). Farm soils from different parts of the world contained 3-1000 μg/g. Nickel may be added to agricultural soils by application of sewage sludge (National Research Council, 1975).

The nickel content of coal was 4-24 μg/g, whereas crude oils (especially those from Angola, Colombia and California) contained up to 100 μg/g (Tissot & Weltle, 1984; World Health Organization, 1990).

(*g*) *Food*

Nickel levels in various foods have been summarized recently (Grandjean, 1984; Smart & Sherlock, 1987; Scheller *et al.*, 1988; Grandjean *et al.*, 1989). Table 16 gives the results of analyses for nickel in various foodstuffs in Denmark; the mean level of nickel in meat, fruit and vegetables was ≤0.2 mg/kg fresh weight. This result was confirmed by analysis of hundreds of food samples from Denmark, the Federal Republic of Germany and the UK (Nielsen & Flyvholm, 1984; Veien & Andersen, 1986; Smart & Sherlock, 1987; Scheller *et al*., 1988): the nickel content of most samples was < 0.5 mg/kg. The nickel concentration in nuts was up to 3 mg/kg (Veien & Andersen, 1986) and that in cocoa up to 10 mg/kg (Nielsen & Flyvholm, 1984). The nickel content of wholemeal flour and bread was significantly higher than that of more refined products due to the high nickel content of wheat germ (Smart & Sherlock, 1981). High nickel levels in flour may also originate from contamination during milling. In addition, fats can contain nickel, probably owing to the use of nickel catalysts in commercial hydrogenation. Margarine normally contains less than 0.2 mg/kg, but levels up to 6 mg/kg have been found (Grandjean, 1984).

Table 16. Nickel content (mg/kg) in foods in the average Danish diet[a]

Food	No. of samples	Range	Mean
Milk products			
Full milk	63	BDL[b]-0.13	0.02
Yogurt	3	0.004-0.03	0.01
Cream	3	0.01-0.04	0.03
Cheese	25	0.02-0.34	0.10
Meat, fish, eggs			
Beef	32	0.01-0.03	0.02
Pork	20	<0.02-0.02	0.02
Chicken	9	0.02-0.24	0.11
Lamb	12	<0.02-0.02	0.02
Liver, kidney	108	0-0.94	0.11
Fish	658	0.005-0.303	0.04
Egg	30	0.01-0.35	0.05
Roots and vegetables			
Potatoes	45	BDL-0.44	0.14
Carrots	17	<0.01-0.16	0.04
Celery root	8	0.04-0.1	0.06
Beetroot	7	0.01-0.3	0.12
Cabbage	31	0.01-0.63	0.17
Cauliflower	5	0.03-1.0	0.3

Table 16. (contd)

Food	No. of samples	Range	Mean
Roots and vegetables (contd)			
Kale	2	0.15-0.24	0.20
Lettuce	21	BDL-1.4	0.36
Spinach	15	0.02-2.99	0.52
Asparagus	1	-	0.42
Cucumber	8	0.01-0.11	0.04
Tomatoes	21	0.01-0.25	0.07
Peas	24	0.13-0.8	0.42
Fruits			
Apples	11	BDL-0.03	0.01
Pears	10	0.07-0.42	0.14
Plums	10	0.03-0.20	0.12
Currants	13	0.01-0.2	0.06
Strawberries	9	0.03-0.08	0.05
Rhubarb	10	0.01-0.22	0.13
Grapes	4	0.01-0.04	0.02
Raisins	3	0.02-0.04	0.03
Citrus fruits	3	0.01-0.04	0.03
Bananas	4	0.01-0.03	0.02
Canned fruits	65	0.02-1.36	0.31
Juice	11	0.01-0.17	0.04
Meal, grain and bread			
Wheat flour	32	0.03-0.3	0.13
Rye flour	15	0.03-0.3	0.1
Oatmeal	18	0.80-4.7	1.76
Rice	16	0.08-0.45	0.21
Other			
Butter	4	0.03-0.2	0.1
Margarine	13	0.2-2.5	0.34
Sugar	22	0.01-0.09	0.05

[a]From Grandjean *et al.* (1989)
[b]BDL below detection limit [not specified]

Stainless-steel kitchen utensils have been shown to release nickel into acid solutions, especially during boiling (Christensen & Moller, 1978). The amount of nickel liberated depends on the composition of the utensil, the pH of the food and the length of contact. The average contribution of kitchen utensils to the oral intake of nickel is unknown, but they could augment alimentary exposure by as much as 1 mg/day (Grandjean *et al.*, 1989).

A study of hospital diets in the USA showed that the general diet contained 160 μg/day, and special diets varied by less than 40% from this level (Myron *et al.*, 1978). A recent study (Nielsen & Flyvholm, 1984) suggested a daily intake of 150 μg in the average Danish diet. Knutti and Zimmerli (1985) found dietary intakes in Switzerland of 73 ± 9 μg in a restaurant, 83 ± 9 μg in a hospital, 141 ± 33 μg in a vegetarian restaurant and 142 ± 20 μg in a military canteen. The mean nickel intake in the UK in 1981-84 was 140-150 μg/day (Smart & Sherlock, 1987).

(*h*) *Humans tissues and secretions*

The estimated average body burden of nickel in adults is 0.5 mg/70 kg (7.4 μg/kg bw). In post-mortem tissue samples from adults with no occupational or iatrogenic exposure to nickel compounds, the highest nickel concentrations were found in lung, bone, thyroid and adrenals, followed by kidney, heart, liver, brain, spleen and pancreas in diminishing order (Seemann *et al.*, 1985; Sunderman, 1986b; Raithel, 1987; Raithel *et al.*, 1987; Rezuke *et al.*, 1987; Kollmeier *et al.*, 1988; Raithel *et al.*, 1988). Reference values for nickel concentrations in autopsy tissues from unexposed persons are listed in Table 17.

The mean nickel concentration in lung tissues from 39 nickel refinery workers autopsied during 1978-84 was 150 (1-1344) μg/g dry weight. Workers employed in the roasting and smelting department had an average nickel concentration of 333 (7-1344) μg/g, and those who had worked in the electrolysis department had an average nickel concentration of 34 (1-216) μg/g dry weight. Lung tissue from 16 persons who were connected with the refinery contained an average level of 0.76 (0.39-1.70) μg/g dry weight (Andersen & Svenes, 1989).

The concentrations of nickel in body fluids have diminished substantially over the past ten years as a consequence of improved analytical techniques, including better procedures to minimize nickel contamination during collection and assay. Concentrations of nickel in human body fluids and faeces are given in Table 18 (see also Sunderman, 1986b; Sunderman *et al.*, 1986a).

(*i*) *Iatrogenic exposures*

Potential iatrogenic sources of exposure to nickel are dialysis treatment, leaching of nickel from nickel-containing alloys used as prostheses and implants and contaminated intravenous medications (for review, see Grandjean, 1984; Sunderman *et al.*, 1986a).

Table 17. Concentrations of nickel in human autopsy tissues

Tissue	No. of subjects	Nickel concentration				Reference
		ng/g wet weight		ng/g dry weight		
		Mean ± SD	Range	Mean ± SD	Range	
Lung	4	16 ± 8	8-24	86 ± 56	33-146	Rezuke *et al*. (1987)
	8	119 ± 50	48-221	-	-	
	9	-	-	132 ± 99	50-290	
	41	7 ± 10	<1-70	-	-	
	9	18 ± 12	7-46	173 ± 94	71-371	
	15	-	-	180 ± 105	43-361	Seemann *et al*. (1985)
	70	137 ± 187	-	754 ± 1010	-	Kollmeier *et al*. (1988)
	30	20-40[a]	8-120[a]	107-195[a]	42-600[a]	Raithel *et al*. (1988)
	16	-	-	760 ± 390	390-1700	Andersen & Svenes (1989)
Kidney	8	11 ± 4	7-15	-	-	Rezuke *et al*. (1987)
	6	-	-	125 ± 54	50-120	
	36	14 ± 27	<1-165	-	-	
	10	9 ± 6	3-25	62 ± 43	19-171	
	18	-	-	34 ± 22	<5-84	Seemann *et al*. (1985)
Liver	4	9 ± 3	5-13	32 ± 12	21-48	Rezuke *et al*. (1987)
	8	8 ± 2	6-11	-	-	
	10	10 ± 7	8-21	50 ± 31	11-102	
	23	-	-	18 ± 21	<5-86	Seemann *et al*. (1985)
Heart	4	6 ± 2	4-8	23 ± 6	16-30	Rezuke *et al*. (1987)
	8	7 ± 2	4-9	-	-	
	9	8 ± 5	1-14	54 ± 40	10-110	
Spleen	22	-	-	23 ± 20	<5-85	Seemann *et al*. (1985)
	10	7 ± 5	1-15	37 ± 31	9-95	Rezuke *et al*. (1987)

[a]Range of median values and 68th percentile of range on the basis of 600 lung specimens from 30 autopsies

Table 18. Nickel concentrations in specimens from healthy, unexposed adults[a]

Specimen	Mean ± SD	Range	Units
Whole blood	0.34 ± 0.28	<0.05-1.05	µg/L
Serum	0.28 ± 0.24	<0.05-1.08	µg/L
Urine (spot collection)	2.0 ± 1.5	0.5-6.1	µg/L
	2.0 ± 1.5	0.4-6.0	µg/g creatinine
	2.8 ± 1.9	0.5-8.8	µg/L[b]
Urine (24-h collection)	2.2 ± 1.2	0.7-5.2	µg/L
	2.6 ± 1.4	0.5-6.4	µg/day
Faeces (3-day collection)	14.2 ± 2.7	10.8-18.7	µg/g (dry weight)
	258 ± 126	80-540	µg/day

[a]From Sunderman *et al.* (1986a)
[b]Factored to specific gravity = 1.024

Hypernickelaemia has been observed in patients with chronic renal disease who are maintained by extracorporeal haemodialysis or peritoneal dialysis (Table 19; Linden *et al.*, 1984; Drazniowsky *et al.*, 1985; Hopfer *et al.*, 1985; Savory *et al.*, 1985; Wills *et al.*, 1985). In one severe incident, water from a nickel-plated stainless-steel water-heater contaminated the dialysate to approximately 250 µg/L, resulting in plasma nickel levels of 3000 µg/L and acute nickel toxicity (Webster *et al.*, 1980). Even during normal operation, the average intravenous uptake of nickel may be 100 µg per dialysis (Sunderman, 1983a).

Nickel-containing alloys may be implanted in patients as joint prostheses, plates and screws for fractured bones, surgical clips and steel sutures (Grandjean, 1984). Corrosion of these prostheses and implants can result in accumulation of alloy-specific metals in the surrounding soft tissues and in release of nickel to the extracellular fluid (Sunderman *et al.*, 1986a, 1989a).

High concentrations of nickel have been reported in human albumin solutions prepared by six manufacturers for intravenous infusion. In three lots that contained 50 g/L albumin, the average nickel concentration was 33 µg/L (range, 11-17 µg/L); in nine lots that contained 250 g/L albumin, the average nickel concentration was 83 µg/L (range, 26-222 µg/L) (Leach & Sunderman, 1985). Meglumine diatrizoate ('Renografin-76'), an X-ray contrast medium, tends to be contaminated with nickel. Seven lots of this preparation (containing 760 g/L diatrizoate) contained nickel at 144 ± 44 µg/L. Serum nickel

Table 19. Nickel concentrations in dialysis fluids and in serum specimens from patients with chronic renal disease (CRD)[a]

Region and patients	No. of subjects	Ni conc. in dialysis fluid	Serum Ni concentration (μg/L)	
		(μg/L)	Pre-dialysis	Post-dialysis
USA				
Healthy controls	30		0.3 ± 0.2	
Non-dialysed CRD patients	7		0.6 ± 0.3	
CRD patients on haemodialysis				
Hospital A	40	0.82	6.2 ± 1.8	7.2 ± 2.2
Hospital B	9	0.40-0.42	3.9 ± 2.0	5.2 ± 2.5
Hospital C	10	0.68	3.0 ± 1.3	3.7 ± 1.3
USA				
Healthy controls	50		0.4 ± 0.2	
CRD patients on haemodialysis	28		3.7 ± 1.5	
UK and Hong Kong				
Healthy controls	71		1.0 (<0.6-3.0)	
Non-dialysed CRD patients	31		1.6 (<0.6-3.6)	
CRD patients on haemodialysis				
Hospital A	25	2-3	8.6 (0.6-16.6)	8.8 (3.8-21.4)
Hospital B	16		2.9 (1.8-4.0)	3.4 (2.2-5.4)
CRD patients on peritoneal dialysis	13	2-3	8.6 (5.4-11.4)	

[a]From Sunderman *et al.* (1986a)

concentrations in 11 patients who received intra-arterial injections of 'Renografin-76' (164 ± 10 mL per patient [giving 19.1 ± 4.0 μg Ni per patient]) for coronary arteriography increased from a pre-injection level of 1.33 μg/L (range, 0.11-5.53 μg/L) to 2.95 μg/L (range, 1.5-7.19 μg/L) 15 min post-injection. Serum levels remained significantly elevated for 4 h and returned to baseline levels only 24 h post-injection (Leach & Sunderman, 1987).

(*j*) *Regulatory status and guidelines*

Occupational exposure limits for nickel in various forms are given in Table 20.

Table 20. Occupational exposure limits for airborne nickel in various forms[a]

Country or region	Year	Nickel species	Concentration (mg/m^3)	Interpretation[b]
Belgium	1987	Nickel metal and insoluble nickel compounds (as Ni)	0.1	TWA
		Nickel carbonyl (as Ni)	0.35	TWA
Brazil	1987	Nickel carbonyl (as Ni)	0.28	TWA
Chile	1987	Soluble nickel compounds (as Ni)	0.08	TWA
China	1987	Nickel carbonyl (as Ni)	0.001	TWA
Denmark	1988	Nickel metal	0.5	TWA
		Nickel carbonyl	0.007	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Insoluble nickel compounds (as Ni)	1	TWA
Finland	1987	Nickel metal	1	TWA
		Nickel carbonyl	0.007	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
France	1986	Nickel sulfide (as Ni)	1	TWA
German Democratic Republic	1987	Nickel compounds (as Ni)	0.25	TWA
		Nickel carbonyl (as Ni)	0.01	TWA
		Nickel compounds (as Ni)	0.5	STEL
		Nickel carbonyl (as Ni)	0.03	STEL
Hungary	1987	Nickel compounds (as Ni)	0.005	TWA/STEL
		Nickel carbonyl (as Ni)	0.007	TWA/STEL
India	1987	Nickel carbonyl (as Ni)	0.35	TWA
Indonesia	1987	Nickel metal and insoluble nickel compounds (as Ni)	1	TWA
		Nickel carbonyl (as Ni)	0.007	TWA
Italy	1987	Nickel carbonyl (as Ni)	0.007	TWA
Japan	1987	Nickel	1	TWA
		Nickel carbonyl (as Ni)	0.007	TWA
Mexico	1987	Nickel metal and insoluble nickel compounds (as Ni)	1	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Nickel carbonyl (as Ni)	0.35	TWA

Table 20. (contd)

Country or region	Year	Nickel species	Concentration (mg/m^3)	Interpretation[b]
Netherlands	1986	Nickel	1	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Nickel carbonyl (as Ni)	0.35	TWA
Poland	1987	Nickel carbonyl (as Ni)	0.007	TWA
Romania	1987	Nickel carbonyl (as Ni)	0.002	TWA
		Nickel carbonyl (as Ni)	0.005	Ceiling
Sweden	1987	Nickel metal	0.5	TWA
		Nickel carbonyl	0.007	TWA
		Nickel subsulfide	0.01	TWA
		Other nickel compounds (as Ni)	0.1	TWA
Switzerland	1987	Nickel metal and insoluble nickel compounds (as Ni)	0.5	TWA
		Soluble nickel compounds (as Ni)	0.05	TWA
Taiwan	1987	Nickel carbonyl (as Ni)	0.35	TWA
UK	1987	Nickel and insoluble nickel compounds (as Ni)	1	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Soluble nickel compounds (as Ni)	0.3	STEL (10 min)
		Insoluble nickel compounds (as Ni)	3	STEL (10 min)
		Nickel carbonyl (as Ni)	0.35	TWA
USA				
ACGIH	1988	Nickel metal; nickel sulfide roasting, fume and dust (as Ni)	1	TWA
		Soluble compounds (as Ni)	0.1	TWA
		Nickel carbonyl	0.35	TWA
NIOSH	1988	Nickel, inorganic compounds (as Ni)	0.015	TWA
		Nickel carbonyl	0.007	TWA
OSHA	1987	Metallic nickel	1	TWA
		Nickel carbonyl	0.007	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA

Table 20. (contd)

Country or region	Year	Nickel species	Concentration (mg/m^3)	Interpretation[b]
USSR	1987	Nickel metal and insoluble nickel compounds (as Ni)	0.5	MAC
		Nickel carbonyl (as Ni)	0.0005	MAC
		Nickel monoxide, oxide, sulfide	0.5	MAC

[a]From Arbeidsinspectie, 1986; Institut National de Recherche et de Sécurité, 1986; National Institute for Occupational Safety and Health (NIOSH), 1988; Arbetarskyddsstyrelsens, 1987; Cook, 1987; Health and Safety Executive, 1987; Työsuojeluhallitus, 1987; US Occupational Safety and Health Administration (OSHA), 1987; American Conference of Governmental Industrial Hygienists (ACGIH), 1988; Arbejdstilsynet, 1988

[b]TWA, time-weighted average; STEL short-term exposure limit; MAC, maximum allowable concentration

2.4 Analysis

Typical methods for the analysis of nickel in air, water, food and biological materials are summarized in Table 21. A method has been developed for classifying nickel in airborne dust samples into four species—'water-soluble', 'sulfidic', 'metallic' and 'oxidic'—on the basis of a sequential leaching procedure (Blakeley & Zatka, 1985; Zatka, 1987, 1988; Zatka *et al.*, undated).

Atomic absorption spectrometry and differential pulse anodic stripping voltammetry (DPASV) are the most common methods for analysis of nickel in environmental and biological media. Air samples are collected on cellulose ester membrane filters, wet digested with nitric acid — perchloric acid and analysed by electrothermal atomic absorption spectrometry (EAAS) or inductively coupled argon plasma emission spectrometry (ICP) (National Institute for Occupational Safety and Health, 1984; Kettrup *et al.*, 1985). The National Institute for Occupational Safety and Health (1977b, 1981) has recommended standard procedures for personal air sampling and analysis of nickel. The routine procedure does not permit identification of individual nickel compounds.

Assessment of individual nickel compounds, especially as components of complex mixtures, necessitates procedures such as X-ray diffraction and would not be feasible for routine monitoring. Sampling and analytical methods used to monitor air, water and soil have been summarized (US Environmental Protection Agency, 1986).

Nickel concentrations in blood, serum or urine are used as biological indicators of exposure to or body burden of nickel. Biological monitoring as a part of biomedical surveillance has been evaluated in several reviews (Aitio, 1984; Norseth, 1984; Sunderman *et al.*, 1986a).

Table 21. Methods for the analysis of nickel

Sample matrix	Sample preparation	Assay procedure[a]	Sensitivity/detection limit	Reference
Air	Collect on cellulose ester membrane filter; digest with nitric acid and perchloric acid	AAS	–	National Institute for Occupational Safety and Health (1981)
	Collect on cellulose acetate membrane filter; digest with nitric acid and hydrochloric acid	AAS	1 μg absolute; 10 μg/m³ (sample volume, 0.1 m³)	Hauptverband der gewerblichen Berufsgenossenschaften (1981)
	Collect on cellulose ester membrane filter; digest with nitric acid and perchloric acid	ICP	1.5 μg/sample	National Institute for Occupational Safety and Health (1984)
	Collect on cellulose ester membrane filter; digest with nitric acid	AAS	20 ng/m³ (sample volume, 1.5 m³)	Kettrup *et al.* (1985)
Water	Chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	AAS	0.04 μg/l	McNeely *et al.* (1972)
	Filter; irradiate with ultraviolet	DPASV (dimethylglyoxime-sensitized)	1 ng/l	Pihlar *et al.* (1981)
	Chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	0.2 μg/l	Sunderman (1986b)
Food	Digest with acid	AAS	–	Evans *et al.* (1978)
	Wet digest with nitric acid, hydrogen peroxide and sulfuric acid	DPASV (dimethylglyoxime-sensitized)	1 ng/l digestion solution	Pihlar *et al.* (1981)
	Dry ash	DPASV (dimethylglyoxime-sensitized)	5 ng/sample	Meyer & Neeb (1985)
	Dry ash, chelate with sodium(ditrifluorethyl)dithiocarbamate	Chelate–GC	100 ng/sample	Meyer & Neeb (1985)
Blood	Wet digest with nitric acid, hydrogen peroxide and sulfuric acid	DPASV (dimethylglyoxime-sensitized)	1 ng/l digestion solution	Pihlar *et al.* (1981)

Table 21 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Sensitivity/detection limit	Reference
Serum/whole blood	Digest with nitric acid; heat	EAAS (Zeeman)	0.05 µg/l serum 0.1 µg/l whole blood	Sunderman *et al.* (1984a)
Body fluids/ tissues	Digest with nitric acid, perchloric acid and sulfuric acid; chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	0.2 µg/l body fluids 0.4 µg/kg tissues	Sunderman (1986b)
Tissues	Homogenize; digest with nitric acid, perchloric acid and sulfuric acid	EAAS (Zeeman)	0.01 µg/g dry wt	Sunderman *et al.* (1985a)
	Digest with nitric acid and sulfuric acid	EAAS (Zeeman)	0.8 µg/g wet wt	Raithel *et al.* (1987)
Serum/urine	Digest with nitric acid, perchloric acid and sulfuric acid; chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	-	Brown *et al.* (1981)
Urine	Chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	0.5 µg/l	Schaller & Zober (1982)
	Digest with nitric acid, perchloric acid and sulfuric acid	DPASV	1 µg/l	Schramel *et al.* (1985)
	Chelate; extract with hexamethylene ammonium: hexamethylene dithiocarbamate: diisopropylketone	AAS	0.2 µg/l	Angerer & Schaller (1985)
	Dilute with nitric acid	EAAS (Zeeman)	0.5 µg/l	Sunderman *et al.* (1986b)
	Dilute directly with nitric acid	EAAS	1.2 µg/l	Kiilunen *et al.* (1987)

[a]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

Choice of specimen, sampling strategies, specimen collection, transport, storage and contamination control are of fundamental importance for an adequate monitoring programme (Sunderman *et al.*, 1986a). As discussed in recent reviews (Stoeppler, 1980; Schaller *et al.*, 1982; Stoeppler, 1984a,b; Sunderman *et al.*, 1986a, 1988a), EAAS and DPASV are practical, reliable techniques that furnish the requisite sensitivity for measurements of nickel concentrations in biological samples. The detection limits for determination of nickel by EAAS with Zeeman background correction are approximately 0.45 μg/L for urine, 0.1 μg/L for whole blood, 0.05 μg/L for serum or plasma, and 10 ng/g (dry wet) for tissues, foods and faeces (Andersen *et al.*, 1986; Sunderman *et al.*, 1986a,b; Kiilunen *et al.*, 1987; Angerer & Heinrich-Ramm, 1988). An EAAS procedure for the determination of nickel in serum and urine, which was developed on the basis of collaborative interlaboratory trials involving clinical biochemists in 13 countries, has been accepted as a reference method by the International Union of Pure and Applied Chemists (Brown *et al.*, 1981). This procedure, with additional applications for analysis of nickel in biological matrices, water and intravenous fluids, has also been accepted as a reference method by the IARC (Sunderman, 1986b). A new working method based on EAAS and Zeeman background correction for the analysis of nickel in serum, whole blood, tissues, urine and faeces has been recommended (Sunderman *et al.*, 1986a,b, 1988a). Sample preparation depends on the specimen and involves acid digestion for tissue and faeces protein precipitation with nitric acid and heat for serum and whole blood, and simple acidification for urine.

Greater sensitivity can be achieved with DPASV analysis using a dimethylglyoxime-sensitized mercury electrode; this method has been reported to have a detection limit of 1 ng/L for determination of nickel in biological media (Flora & Nieboer, 1980; Pihlar *et al.*, 1981; Ostapczuk *et al.*, 1983). However, DPASV techniques are generally more cumbersome and time consuming than EAAS procedures. Isotope dilution mass spectrometry provides the requisite sensitivity, specificity and precision for determination of nickel (Fassett *et al.*, 1985) but has not yet been used to analyse nickel in biological samples.

Nickel carbonyl has been measured in air and exhaled breath by gas chromatography and chemiluminescence (Sunderman *et al.*, 1968; Stedman *et al.*, 1979).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

Experimental studies on animals exposed to nickel and various nickel compounds were reviewed previously in the *IARC Monographs* (IARC, 1976, 1987). Recent reviews on the biological and carcinogenic properties of nickel have been compiled by Fairhurst and Illing (1987), Kasprzak (1987) and Sunderman (1989), among others. In addition, a detailed document on the health effects of nickel has been prepared for the Ontario (Canada) Ministry of Labour (Odense University, 1986). A comprehensive technical report on nickel, emphasizing mutagenicity and carcinogenicity, was published by the European Chemical Industry Ecology and Toxicology Centre (1989).

(*a*) *Metallic nickel and nickel alloys*

(i) *Inhalation*

Mouse: A group of 20 female C57Bl mice, two months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure; particle diameter, ≤4 μm) for 6 h per day on four or five days per week for 21 months. All mice had died by the end of the experiment. No lung tumour was observed. No control group was available (Hueper, 1958). [The Working Group noted the short duration of treatment.]

Rat: Groups of 50 male and 50 female Wistar rats and 60 female Bethesda black rats, two to three months of age, were exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel; particle diameter, ≤4 μm) for 6 h per day on four or five days per week for 21 months and observed up to 84 weeks. Histological examination of the lungs of 50 rats showed numerous multicentric, adenomatoid alveolar lesions and bronchial proliferations that were considered by the author as benign neoplasms. No specific control was included in the study (Hueper, 1958).

[1]The Working Group was aware of studies in progress of the carcinogenicity of nickel, nickel acetate tetrahydrate, nickel alloys, nickel-aluminium alloys, nickel chloride hexahydrate, nickel oxide, nickel sulfide and nickel sulfate hexa- and heptahydrate in experimental animals by intraperitoneal, subcutaneous, inhalation and intratracheal administration (IARC, 1988b).

In a further experiment with Bethesda black rats, exposure to metallic nickel powder (99.95% nickel; particle diameter, 1-3 μm) was combined with 20-35 ppm (50-90 mg/m^3) sulfur dioxide as a mucosal irritant; powdered chalk was added to prevent clumping. Exposure was for 5-6 h per day [nickel concentration unspecified]. Forty-six of 120 rats lived for longer than 18 months. No lung tumour was observed, but many rats developed squamous metaplasia and peribronchial adenomatoses (Hueper & Payne, 1962).

Guinea-pig A group of 32 male and 10 female strain 13 guinea-pigs, about three months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel) for 6 h per day on four or five days per week for 21 months. Mortality was high: only 23 animals survived to 12 months and all animals had died by 21 months. Almost all animals developed adenomatoid alveolar lesions and terminal bronchiolar proliferations. No such lesion was observed in nine controls. One treated guinea-pig had an anaplastic intra-alveolar carcinoma, and another had an apparent adenocarcinoma metastasis in an adrenal node, although the primary tumour was not identified (Hueper, 1958).

(ii) *Intratracheal instillation*

Rat: Two groups of female Wistar rats [number unspecified], 11 weeks of age, received either ten weekly intratracheal instillations of 0.9 mg metallic nickel powder [purity unspecified] or 20 weekly injections of 0.3 mg metallic nickel powder in 0.3 mL saline (total doses, 9 and 6 mg, respectively) and were observed for almost 2.5 years. Lung tumour incidence in the two groups was 8/32 (seven carcinomas, one mixed) and 10/39 (nine carcinomas, one adenoma), respectively; no lung tumour developed in 40 saline-treated controls maintained for up to 124 weeks. Pathological classification of the tumours in the two groups combined revealed one adenoma, four adenocarcinomas, 12 squamous-cell carcinomas and one mixed tumour. Average time to observation of the tumours was 120 weeks, the first tumour being observed after 98 weeks (Pott *et al.*, 1987).

Hamster: In a study reported in an abstract, groups of 100 Syrian golden hamsters received either a single intratracheal instillation of 10, 20 or 40 mg of metallic nickel powder (particle diameter, 3-8 μm) or of one of two nickel alloy powders (particle diameter, 0.5-2.5 μm; 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 intratracheal instillations of 20 mg of one of the substances every six months (total dose, 80 mg). In the groups receiving single instillations of alloy II, the incidence of malignant intrathoracic tumours was reported as 1, 8 and 12%, respectively, suggesting a dose-response relationship. In the group receiving multiple instillations of alloy II, 10% of the animals developed intrathoracic malignant neoplasms, diagnosed as fibrosarcomas, mesotheliomas and rhabdomyosarcomas.

Metallic nickel induced comparable numbers and types of intrathoracic neoplasms, but no tumour was observed in animals treated with alloy I or in control animals (Ivankovic *et al.*, 1987).

A group of approximately 60 male and female Syrian golden hamsters (strain Cpb-ShGa 51), ten to 12 weeks of age, received 12 intratracheal instillations of 0.8 mg metallic nickel powder (99.9% nickel; mass median diameter, 3.1 μm) in 0.15 mL saline at two-week intervals (total dose, 9.6 mg). Additional groups were treated similarly with 12 intratracheal instillations of 3 mg pentlandite (containing 34.35% nickel; total dose, 36 mg), 3 or 9 mg chromium/nickel stainless-steel dust (containing 6.79% nickel; total doses, 36 and 108 mg) or 9 mg chromium stainless-steel dust (containing 0.5% nickel; total dose, 108 mg). The median lifespan was 90-130 weeks in the different groups. Two lung tumours were observed: an adenocarcinoma in the group that received nickel powder and an adenoma in the pentlandite-treated group. No lung tumour was observed in vehicle-treated controls or in the groups treated with stainless-steels (Muhle *et al*., 1992). [The Working Group noted that no lung tumour was observed in the positive control group.]

(iii) *Intrapleural administration*

Rat: A group of 25 female Osborne-Mendel rats, six months of age, received injections of a 12.5% suspension of metallic nickel powder in 0.05 mL lanolin into the right pleural cavity [6.25 mg nickel powder] once a month for five months. A group of 70 rats received injections of lanolin only. The experiment was terminated after 16 months. Four of the 12 treated rats that were examined had developed round-cell and spindle-cell sarcomas at the site of injection; no control animal developed a local tumour [$p < 0.01$] (Hueper, 1952).

A group of five male and five female Fischer 344 rats, 14 weeks of age, received injections of 5 mg metallic nickel powder suspended in 0.2 mL saline into the pleura (total dose, 25 mg) once a month for five months. Two rats developed mesotheliomas within slightly over 100 days; no tumour occurred in 20 controls (Furst *et al.*, 1973). [The Working Group noted the limited reporting of the experiment.]

(iv) *Subcutaneous administration*

Rat: Groups of five male and five female Wistar rats, four to six weeks of age, received four subcutaneous implants of pellets (approximately 2×2 mm) of metallic nickel or nickel-gallium alloy (60% nickel) used for dental prostheses and were observed for 27 months. Local sarcomas were noted in 5/10 rats that received the metallic nickel and in 9/10 rats that received the nickel-gallium alloy. No local tumour occurred in ten groups of rats that received similar implants of other dental materials (Mitchell *et al.*, 1960).

(v) *Intramuscular administration*

Rat: A group of ten female hooded rats, two to three months of age, received a single intramuscular injection of 28.3 mg pure metallic nickel powder in 0.4 mL fowl serum into the right thigh. All animals developed rhabdomyosarcomas at the injection site within 41 weeks. Historical controls injected with fowl serum alone did not develop local tumours (Heath & Daniel, 1964).

Groups of 25 male and 25 female Fischer 344 rats [age unspecified] received five monthly intramuscular injections of 5 mg metallic nickel powder in 0.2 mL trioctanoin. Fibrosarcomas occurred in 38 treated animals but in none of a group of 25 male and 25 female controls given trioctanoin alone (Furst & Schlauder, 1971).

Two groups of ten male Fischer 344 rats, three months of age, received a single intramuscular injection of metallic nickel powder (3.6 or 14.4 mg/rat) in 0.5 mL penicillin G procaine. Surviving rats were killed 24 months after the injection. Sarcomas at the injection site were found in 0/10 and 2/9 treated rats, respectively, as compared with 0/20 vehicle controls (Sunderman & Maenza, 1976). [The Working Group noted the small number of animals used.]

Groups of 20 WAG rats [sex and age unspecified] received a single intramuscular injection of 20 mg metallic nickel powder in an oil vehicle [type unspecified]. A group of 56 control rats received 0.3 mL of the vehicle alone. Local sarcomas developed in 17/20 treated and 0/56 control rats (Berry *et al.*, 1984). [The Working Group noted the inadequate reporting of tumour induction.]

Groups of 20 or 16 male Fischer 344 rats, two to three months of age, received a single intramuscular injection of 14 mg metallic nickel powder (99.5% pure) or 14 mg (as nickel) of a ferronickel alloy ($NiFe_{1.6}$) in 0.3-0.5 mL penicillin G vehicle into the right thigh. Of the 20 rats receiving nickel powder, 13 developed tumours at the site of injection (mainly rhabdomyosarcomas), with an average latency of 34 weeks. No local tumour developed in the 16 rats given the ferronickel alloy, in 44 controls given penicillin G or in 40 controls given glycerol (Sunderman, 1984).

Groups of 40 male inbred WAG rats, 10-15 weeks of age, received a single intramuscular injection of 20 mg metallic nickel in paraffin oil. One group also received intramuscular injections of interferon at 5×10^4 U/rat twice a week beginning in the tenth week after nickel treatment. Rhabdomyosarcomas occurred in 14/30 and 5/10 rats in the two groups, respectively. Metallic nickel depressed natural killer cell activity. Prospective analysis of individual natural killer cell responses indicated that a persistent depression was restricted to rats that subsequently developed a tumour (Judde *et al.*, 1987).

Hamster: Furst and Schlauder (1971) compared the tumour response in Syrian hamsters with that of Fischer 344 rats (see above) to metallic nickel powder. Groups of 25 male and 25 female hamsters, three to four weeks old, received five monthly intramuscular injections

of 5 mg nickel powder in 0.2 mL trioctanoin. Two fibrosarcomas occurred in males. No local tumour occurred in 25 male and 25 female controls injected with trioctanoin alone.

(vi) *Intraperitoneal administration*

Rat: As reported in an abstract, a group of male and female Fischer rats [numbers unspecified], weighing 80-100 g, received intraperitoneal injections of 5 mg metallic nickel powder in 0.3 mL corn oil twice a month for eight months. A control group received injections of corn oil only. In the treated group, 30-50% of rats were reported to have developed intraperitoneal tumours (Furst & Cassetta, 1973).

A group of 50 female Wistar rats, 12 weeks of age, received ten weekly intraperitoneal injections of 7.5 mg metallic nickel powder [purity unspecified] (total dose, 75 mg). Abdominal tumours (sarcomas, mesotheliomas or carcinomas) developed in 46/48 (95.8%) rats at an average tumour latency of approximately eight months. Concurrent controls were not reported, but, in non-concurrent groups of saline controls, abdominal tumours were found in 0-6% of animals (Pott *et al.*, 1987).

Groups of female Wistar rats, 18 weeks of age, received single or repeated intraperitoneal injections of metallic nickel powder (100% nickel) or of one of three nickel alloys in 1 mL saline once or twice a week. All animals were sacrificed 30 months after the first injection. The incidences of local sarcomas and mesotheliomas in the peritoneal cavity are shown in Table 22. A dose-response trend was apparent for metallic nickel, and the tumour responses to the nickel alloys increased with the proportion of nickel present and the dose (Pott *et al.*, 1989, 1992). [The Working Group noted that the results at 30 months were available as an extended abstract only.]

(vii) *Intravenous administration*

Mouse: A group of 25 male C57Bl mice, six weeks old, received two intravenous injections of 0.05 mL of a 0.005% suspension of matallic nickel powder in 2.5% gelatin into the tail vein. Nineteen animals survived more than 52 weeks, and six survived over 60 weeks. No tumour was observed. No control group was used (Hueper, 1955). [The Working Group noted the short period of observation.]

Rat: A group of 25 Wistar rats [sex unspecified], 24 weeks of age, received intravenous injections of 0.5 mL/kg bw metallic nickel powder as a 0.5% suspension in saline into the saphenous vein once a week for six weeks. Seven rats developed sarcomas in the groin region along the injection route [probably from seepage at the time of treatment]. No control group was used (Hueper, 1955).

Table 22. Tumour responses of rats to intraperitoneal injection of nickel and nickel alloys[a]

Compound	Total dose (mg, as Ni)	Schedule	Mesotheliomas at two years	Sarcomas at two years	Local tumours at 30 months[b]
Metallic nickel	6	Single injection	3	0	4/34
	12	2 × 6 mg	3	2	5/34
	25	25 × 1 mg	16	9	25/35
Alloy (50%) Ni)	50	Single injection	1	7	8/35
	150	3 × 50 mg	2	8	13/35
Alloy (29%) Ni)[c]	50	Single injection	0	0	2/33
	100	2 × 50 mg	0	1	1/36
Alloy (66% Ni)[d]	50	Single injection	0	11	12/35
	150	3 × 50 mg	4	20	22/33
Saline		3 × 1 mL	0	1	1/33
		50 × 1 mL	0	0	0/34

[a]From Pott *et al.* (1989, 1992)
[b]Results not given separately for mesotheliomas and sarcomas
[c]Before milling: 32% Ni, 21% Cr, 0.8% Mn, 55% Fe
[d]Before milling: 74% Ni, 16% Cr, 7% Fe

(viii) *Intrarenal administration*

Rat: A group of 20 female Sprague-Dawley rats, weighing 120-140 g, received an injection of 5 mg metallic nickel in 0.05 mL glycerine into each pole of the right kidney. No renal carcinoma or erythrogenic response developed within the 12-month period of observation (Jasmin & Riopelle, 1976).

Groups of male Fischer 344 rats, approximately two months of age, received an intrarenal injection of 7 mg metallic nickel powder or of a ferronickel alloy ($NiFe_{1·6}$; 7 mg Ni per rat) in 0.1 or 0.2 mL saline solution into each pole of the right kidney. The study was terminated after two years; the median survival time was 100 weeks in the two treated groups compared with 91 weeks in controls. Renal cancers occurred in 0/18 and 1/14 rats, respectively, compared with 0/46 saline-treated controls. The tumour was a nephroblastoma which was observed at 25 weeks (Sunderman *et al.* 1984b).

(ix*) Implantation of ear-tags*

Rat: In a study carried out to assess the carcinogenicity of cadmium chloride, 168 male Wistar rats, six weeks of age, received identification ear-tags fabricated of nickel copper alloy (65% Ni, 32% Cu, 1% Fe, 1% Mn). A total of 14 tumours, mostly osteosarcomas, developed within 104 weeks at the site of implantation. The authors implicated nickel in the

alloy as the probably causative agent and apparent local microbial infection as a contributory factor (Waalkes *et al.*, 1987).

(x) *Other routes of administration*

Rat: In groups of 20 WAG rats [sex and age unspecified] *subperiosteal injection* of 20 mg metallic nickel powder resulted in local tumours in 11/20 rats; *intramedullary injection* of 20 mg metallic nickel resulted in local tumours in 9/20 rats (Berry *et al.*, 1984). [The Working Group noted the absence of controls and the inadequate reporting of tumour induction.]

(xi) *Administration with known carcinogens*

Rat: Four groups of female Wistar rats [initial numbers unspecified], four to six weeks old, received intratracheal instillations of 1 or 5 mg 20-methylcholanthrene (MC) alone or with 10 mg metallic nickel powder (99.5% nickel). A fifth group received 10 mg metallic nickel powder only. At 12 weeks, squamous-cell carcinomas had developed as follows: 5 mg MC, 2/7; 5 mg MC plus Ni, 3/5; 1 mg MC, 0/8; 1 mg MC plus Ni, 0/7; metallic Ni alone, 0/7. Pretumorous lesions were more marked and the amount of epithelial metaplasia enhanced in groups receiving the combined treatment or MC only (Mukubo, 1978). [The Working Group noted the small number of animals used and the short duration of observation.]

(*b*) *Nickel oxides and hydroxides*

The compounds considered under this heading include a variety of substances of nominally similar composition, which, however, may vary considerably due to differences in production methods. These differences were not generally defined in the studies described below, beyond the relatively recent designation of green and black nickel oxide.

(i) *Inhalation*

Rat: Groups of six or eight male Wistar rats, two months of age, were exposed by inhalation to 0.6 or 8.0 mg/m^3 nickel monoxide (green) particles (median aerodynamic diameter, 1.2 μm) for 6 h per day on five days per week for one month, after which they were maintained with no further exposure for an additional 20 months. Histopathological examination revealed one adenocarcinoma and one adenomatous lesion of the lung in the low-exposure rats and one adenomatosis in the high-exposure group. Bronchial glandular hyperplasia was seen in five and six rats in the low- and high-dose groups, respectively; a malignant histiocytoma that emanated from the paranasal region was noted in the upper respiratory tract of one rat [group unspecified]. None of the five control rats developed these lesions, although both control and exposed animals exhibited some squamous metaplasia (Horie *et al.*, 1985). [The Working Group noted the small number of animals used and the short exposure period.]

Groups of 40 and 20 male Wistar rats, five weeks of age, were exposed by inhalation to 60 and 200 μg/m^3 nickel as nickel monoxide aerosol (particle size, < 0.3 μm) continuously for 18 months, followed by an observation period of one year under normal atmospheric conditions. At 24 months, 80% of animals in the treatment group had died, and at termination of the study (30 months) 62.5% of controls had died. No carcinogenic effect was observed (Glaser *et al.*, 1986). [The Working Group noted that the toxic effects, particularly alveolar proteinosis, were severe, that the survival of the animals was too short for carcinogenicity to be evaluated fully, and that nickel oxide aerosols were generated by atomization of aqueous nickel acetate solutions.]

Hamster: A group of 51 male Syrian golden hamsters, two months of age, was exposed by inhalation to a mean aerosol concentration of 53.2 mg/m^3 nickel monoxide (mean particle diameter, 0.3 μm) for 7 h per day on five days per week for life. Another group of 51 males was exposed to nickel monoxide plus cigarette smoke. Two control groups of 51 animals were exposed to smoke and sham dust or to sham smoke and sham dust. Massive pneumoconiosis with lung consolidation developed in the nickel monoxide-exposed animals but did not affect their lifespan. Mean lifespan was 19.6 ± 1.6 months for animals exposed to smoke and nickel monoxide, 16.1 ± 1.1 for sham-exposed nickel oxide-treated animals and 19.6 ± 1.4 and 15.3 ± 1.3 months for the respective controls. No significant increase in the incidence of respiratory tumours or any evidence of cocarcinogenic interaction with cigarette smoke was noted for nickel monoxide. One osteosarcoma occurred in the nickel monoxide-treated group and one osteosarcoma and one rhabdomyosarcoma in the muscle of the thorax were seen in the group given nickel monoxide plus cigarette smoke (Wehner *et al.*, 1975, 1979).

(ii) *Intratracheal instillation*

Rat: Groups of female Wistar rats [numbers unspecified], 11 weeks of age, received ten weekly intratracheal instillations of 5 or 15 mg nickel as nickel monoxide (99.99% pure) in 0.3 mL saline to give total doses of 50 and 150 mg nickel, respectively. A control group of 40 rats received injections of saline only and were observed for 124 weeks. Lung tumour incidence in the two treated groups was 10/37 (27%) and 12/38 (31.6%), respectively; the tumours in the two groups consisted of four adenocarcinomas, two mixed tumours and 16 squamous-cell carcinomas. No lung tumour occurred in controls (Pott *et al.*, 1987).

Hamster: In an experiment designed to study the effects of particulates on the carcinogenesis of *N*-nitrosodiethylamine, groups of 25 male and 25 female hamsters [strain unspecified], five weeks old, received intratracheal instillations of 0.2 mL of a suspension of 2 g nickel monoxide (particle size, 0.5-1.0 μm) in 100 mL 0.5% w/v gelatin/saline once a week for 30 weeks. A group of 50 controls received injections of carbon dust in the vehicle.

Only three hamsters in each group survived beyond 48 weeks. One respiratory tract tumour [unspecified] was found in the 47 nickel monoxide-treated animals that were necropsied and four in controls. A high incidence of respiratory-tract tumours was observed in animals treated with *N*-nitrosodiethylamine alone (Farrell & Davis, 1974). [The Working Group noted the poor survival of treated and control animals.]

(iii) *Intrapleural administration*

Rat: A group of 32 male Wistar rats, three months of age, received a single intrapleural injection of 10 mg nickel monoxide in 0.4 mL saline suspension. A positive control group of 32 rats received a 10 mg injection of crocidolite, and a negative control group of 32 rats received saline alone. After 30 months, 31/32 rats in the nickel monoxide-treated group had developed injection-site tumours (mostly rhabdomyosarcomas). Median survival time was 224 days. Nine of 32 rats in the crocidolite-treated group had local tumours, but none of the saline controls developed local sarcomas (Skaug *et al.*, 1985).

(iv) *Intramuscular administration*

Mouse: Two groups of 50 Swiss and 52 C3H mice, equally divided by sex, two to three months of age, received single intramuscular injections of 5 mg nickel monoxide in penicillin G procaine into each thigh muscle and were observed for up to 476 days. Local sarcomas (mainly fibrosarcomas) occurred in 33 Swiss and 23 C3H mice. No control was reported (Gilman, 1962).

Rat: A group of 32 Wistar rats [sex unspecified], two to three months of age, received single intramuscular injections of 20 mg nickel monoxide powder into each thigh muscle and were observed for up to 595 days. Twenty-one rats developed a total of 26 tumours at the site of injection; 80% of the tumours were rhabdomyosarcomas, and the average latent period was 302 days. No control was reported (Gilman, 1962).

Groups of 20 Fischer rats [sex and age unspecified] received single intramuscular injections at two sites of either nickel hydroxide or nickel monoxide [dose unspecified] in aqueous penicillin G procaine. Local sarcomas developed in 15/20 (19 tumours at 40 sites) and 2/20 rats, respectively. Concurrent vehicle controls were not used. Seventeen of 20 animals given nickel subsulfide [dose unspecified] as positive controls developed local sarcomas. No tumour developed at the injection sites in two other groups of rats in the same experimental series injected intramuscularly with either nickel sulfate or nickel sulfide [presumed to be amorphous] (Gilman, 1966).

Ten male and ten female Wistar rats, weighing 150-170 g, received an intramuscular injection of 3 mg nickel trioxide powder. No control group was reported. No neoplasm developed at the injection site (Sosiński, 1975).

A group of 15 male Fischer 344 rats, two months of age, received a single intramuscular injection of nickel at 14 mg/rat as nickel monoxide (bunsenite, green-grey (Sunderman, 1984); 99.9% pure; particle diameter, <2 μm) in 0.3 mL of a 1:1 v/v glycerol:water vehicle into the right thigh and were observed for 104 weeks. Fourteen animals developed local sarcomas (mostly rhabdomyosarcomas) with a median tumour latency of 49 weeks and a median survival time of 58 weeks; metastases occurred in 4/14 rats. None of 40 control rats injected with vehicle alone developed tumours at the site of injection; 25/40 control rats were still alive at termination of the experiment (Sunderman & McCully, 1983).

Groups of 20 male Wistar rats, weighing 200-220 g, received a single intramuscular injection of 120 μmol [7.1 mg] nickel as one of three nickel hydroxide preparations — an air-dried gel, crystalline industrial nickel hydroxide and a freshly prepared colloidal nickel hydroxide — in 0.1 mL distilled water. A positive control group was treated with 120 μmol [7.1 mg] nickel as nickel subsulfide (see also p. 337) and a negative control group was treated with sodium sulfate. Seven rats treated with the colloidal preparation and one treated with the gel died from haematuria one to two weeks after the treatment. Six ulcerating, tumour-like growths developed between five and six months after treatment in the crystalline-treated group, but these regressed and were not included in tabulations. Local tumours occurred in 5/19 rats (four rhabdomyosarcomas, one fibrosarcoma) given the dried gel, 3/20 (all rhabdomyosarcomas) given the crystalline compound, 0/13 given the colloidal preparation, 16/20 positive controls and 0/20 negative controls (Kasprzak *et al.*, 1983). [See also pp. 360-361.]

In the study by Berry *et al.* (1984) described on p. 321, no tumour was induced by 20 mg nickel monoxide by either the intramuscular or subperiosteal route in groups of 20 rats.

In the study by Judde *et al.* (1987) described on p. 321, no tumour was induced by 20 mg nickel trioxide in ten rats.

(v) *Intraperitoneal administration*

Rat: A group of 50 female Wistar rats, 12 weeks of age, received two intraperitoneal injections of 500 mg nickel as nickel monoxide (99.99% pure); 46/47 of the animals developed abdominal tumours (sarcomas, mesotheliomas or carcinomas) with an average tumour latency of 31 months. Concurrent controls were not reported but, in other groups of saline controls, the incidence of abdominal tumours ranged from 0 to 6% (Pott *et al.*, 1987).

In a study described earlier (p. 322), single injections of 25 and 100 mg nickel as nickel monoxide induced local sarcomas and mesotheliomas in the peritoneal cavity in 12/34 and 15/36 female Wistar rats, respectively, after 30 months (Pott *et al.*, 1989, 1992). [The

Working Group noted that the results at 30 months were available as an extended abstract only.]

(vi) *Intrarenal administration*

Rat: A group of 12 male Fischer 344 rats, two months of age, received an injection of nickel monoxide (green; 7 mg/rat nickel) in 0.1 or 0.2 mL saline into each pole of the right kidney and were observed for two years. No renal carcinoma was observed (Sunderman *et al.*, 1984b; see also p. 323).

(vii) *Intracerebral injection*

Rat: A group of ten male and ten female Wistar rats, weighing 150-170 g, received an intracerebral injection of 3 mg nickel trioxide powder into the cerebral cortex. No control group was reported. Cerebral sarcomas [gliomas] were observed in two rats that were killed at 14 and 21 months, respectively, and a meningioma was found in one rat that was killed at 21 months (Sosiński, 1975).

(*c*) *Nickel sulfides*

The experiments described below refer primarily to α-nickel subsulfide and to other crystalline forms of nickel sulfide, except where specifically stated that an amorphous form was tested.

(i) *Inhalation*

Rat: A group of 122 male and 104 female Fischer 344 rats [age unspecified] was exposed by inhalation to 0.97 mg/m^3 nickel subsulfide (particle diameter, < 1.5 μm) for 6 h per day on five days per week for 78 weeks. The remaining rats were observed for another 30 weeks, by which time survival was less than 5%. Survival of a group of 241 control rats exposed to filtered room air was 31% at 108 weeks. A significant increase in the incidence of benign and malignant lung tumours was observed compared to controls. Among treated rats, 14 malignant (ten adenocarcinomas, three squamous-cell carcinomas, one fibrosarcoma) and 15 benign lung tumour-bearing animals were identified; one adenocarcinoma and one adenoma developed among controls. The earliest tumour appeared at 76 weeks, and the average tumour latency was approximately two years. An elevated incidence of hyperplastic and metaplastic lung lesions was also noted among nickel subsulfide-treated rats (Ottolenghi *et al.*, 1974).

(ii) *Intratracheal instillation*

Mouse: Groups of 20 male B6C3F1 mice, eight weeks of age, received intratracheal instillations of 0.024, 0.056, 0.156, 0.412 or 1.1 mg/kg bw nickel subsulfide (particle size, <2 μm) in saline once a week for four weeks and were observed for up to 27 months, at

which time about 50% of the animals had died. Lung tumours occurred in all groups; no significant difference from controls and no dose-response relationship was observed. No damage to the respiratory tract that was attributable to treatment was seen (Fisher *et al.*, 1986). [The Working Group noted the low doses used.]

Rat: Groups of 47, 45 and 40 female Wistar rats, 11 weeks of age, received intratracheal instillations of 0.063, 0.125 or 0.25 mg/animal nickel subsulfide in 0.3 mL saline (total doses, 0.94, 1.88 and 3.75 mg/animal) once a week for 15 weeks. At 120 weeks, 50% of the animals were still alive; the experiment was terminated at 132 weeks. The incidences of malignant lung tumours were 7/47, 13/45 and 12/40 in the low-, medium- and high-dose groups; 12 adenocarcinomas, 15 squamous-cell carcinomas and five mixed tumours occurred in the lungs of treated animals. No lung tumour occurred in 40 controls given 20 intratracheal injections of 0.3 mL saline (Pott *et al.*, 1987).

Hamster: In the study reported on p. 320 (Muhle *et al.*, 1992), no lung tumour was seen in 62 animals given 12 doses of 0.1 mg α-nickel subsulfide by intratracheal instillation. [The Working Group noted the low total dose given.]

(iii) *Intrapleural administration*

Rat: A group of 32 male Wistar rats, three months of age, received a single intrapleural injection of 10 mg nickel subsulfide in 0.4 mL saline. Average survival was 177 days. Local malignant tumours (mainly rhabdomyosarcomas) developed in 28/32 animals but in none of 32 saline-injected controls (Skaug *et al.*, 1985)

(iv) *Topical administration*

Hamster: Groups of male golden Syrian hamsters of the LVG/LAK strain, two to three months of age, were painted on the mucosa of the buccal pouches with 1 or 2 mg α-nickel subsulfide in 0.1 mL glycerol three times a week for 18 weeks (six to seven animals; total doses, 54 and 108 mg nickel subsulfide) or with 5 or 10 mg three times a week for 36 weeks (13-15 animals; total doses, 540 and 1080 mg nickel subsulfide), and were observed for more than 19 months. Two control groups received applications of glycerol. No tumour developed in the buccal pouch, oral cavity or intestinal tract in the treated or control groups. Squamous-cell carcinomas of the buccal pouch developed in all four hamsters that received applications of 1 mg dimethylbenz[*a*]anthracene in glycerol three times a week for 18 weeks (Sunderman, 1983b).

(v) *Intramuscular administration*

Mouse: Groups of 45 Swiss and 18 C3H mice, approximately equally divided by sex, two to three months of age, received single intramuscular injections of 5 mg nickel subsulfide into both or only one thigh muscle. Local tumours (mainly sarcomas) developed

in 27 and nine mice, respectively. No control was reported (Gilman, 1962).

Three groups of ten female and one group of ten male NMRI mice, six weeks of age, received an injection of 10 mg labelled nickel subsulfide into the left thigh muscle, or of 5 mg into the interscapular subcutaneous tissue, in 0.1 mL olive oil:streptocillin (3:1). Two mice from each group were killed two months after injection for whole-body autoradiography; no tumour was seen at this stage. The remaining animals were autopsied at 14 months, when local sarcomas were seen in 7/8 and 4/8 females that received subcutaneous injections and in 4/8 males and 4/8 females that received intramuscular injections. Metastases to the lung, liver and regional lymph nodes occurred in approximately half of the 19 tumour-bearing mice. No control group was used (Oskarsson *et al.*, 1979).

Groups of four male and six female DBA/2 and five male and five female C57Bl6 mice, two to three months of age, received a single intramuscular injection of 2.5 mg α-nickel subsulfide in 0.1-0.5 mL penicillin G procaine solution into one thigh muscle. Local sarcomas developed in six DBA/2 ($p < 0.01$) and in five C57Bl6 ($p < 0.05$) mice, with median latent periods of 13 and 14 months, respectively. None of nine control mice of each strain injected with penicillin G alone developed a sarcoma (Sunderman, 1983b).

Rat: A group of 32 male and female Wistar rats, two to three months of age, received a single intramuscular injection of 20 mg nickel subsulfide into one or both thigh muscles. After an average of 21 weeks, 25/28 rats had developed 36 local tumours. Vehicle controls were not available, but two further groups of 30 rats each injected with ferrous sulfide did not develop tumours at the site of injection after 627 days (Gilman, 1962).

Groups of ten male and ten female Fischer rats, five months of age, were administered nickel subsulfide either by an intramuscular injection of 10 mg powder (particle size, 2-4 μm), by implantation of an intact 11-mm disc (500 mg), by implantation of 3-5-mm disc fragments or by implantation of 10 mg powder in a 0.42-μm porosity millipore diffusion chamber. Local tumours (mostly rhabdomysarcomas) developed in 71-95% of rats, which demonstrated diffusion of soluble nickel from the chambers. The mean tumour latency for the last group was 305 days, almost twice that for the other three groups. Among 19 controls given 38 implants of empty diffusion chambers, one tumour developed after 460 days. The authors considered that the experiment demonstrated that the induction of neoplasms by nickel subsulfide is a chemical rather than a physical (foreign-body) reaction and that phagocytosis is not essential for nickel tumorigenesis (Gilman & Herchen, 1963).

Groups of 15 Fischer rats received implants of nickel subsulfide discs (250 mg) or 8 × 1-mm discs of ferric oxide (control) in opposite sides of the gluteal musculature. The nickel

subsulfide discs were removed in a geometric sequence at two, four, eight... up to 256 days after implantation, and average tumour incidence after 256 days was 66%. The critical exposure (tissue contact) period necessary for nickel subsulfide to induce malignant transformation was 32-64 days (Herchen & Gilman, 1964).

Groups of 15 male and 15 female hooded and 15 male and 12 female NIH (Bethesda) black rats, two to three months of age, received injections of 10 mg nickel subsulfide in penicillin G procaine into each gastrocnemius muscle. NIH Black rats were less susceptible to local tumour induction (14/23 rats) than hooded rats (28/28). Massive phagocytic invasion of the nickel injection site occurred in the NIH black rats (Daniel, 1966).

Groups of 20 male and 20 female Fischer 344 rats, five weeks of age, received a single subcutaneous injection of 10 or 3.3 mg nickel subsulfide in 0.25 mL saline. Two further groups received single intramuscular injections of 10 or 3.3 mg nickel subsulfide. A group of 60 male and 60 female control rats received injections of 0.25 mL saline twice a week for 52 weeks, and a further control group received no treatment. At 18 months, the groups injected subcutaneously with nickel subsulfide had tumour incidences of 90 and 95%, and the groups injected intramuscularly had tumour incidences of 85% and 97%. Most tumours in both groups were rhabdomyosarcomas. No local tumour occurred in controls (Mason, 1972).

Groups of ten male Fischer 344 rats, three months of age, received intramuscular injections of amorphous nickel sulfide and α-nickel subsulfide in 0.5 mL penicillin G procaine suspension at two comparable dose levels (about 5 and 20 mg/rat), to provide 60 and 240 μg Ni per rat. A further group received injections of nickel ferrosulfide matte (85 and 340 μg atom of nickel per rat). Sarcomas at the injection site developed in 8/10 and 9/9 of the low- and high-dose nickel subsulfide-treated groups and in 1/10 and 8/10 of the low- and high-dose nickel ferrosulfide matte-treated groups, respectively. No local sarcoma developed in the groups given nickel sulfide, among control rats given penicillin G procaine suspension alone or in two control groups treated with metallic iron powder (Sunderman & Maenza, 1976).

Groups of 63 male and female inbred Fischer and 20 male and female hooded rats, ten to 14 weeks old, received an intramuscular injection of 10 mg nickel subsulfide in penicillin G procaine. Tumour-bearing rats were autopsied 30 days after detection of the tumour. Tumours occurred in 59/63 Fischer and 11/20 hooded rats; 81.9% of tumours in hooded rats metastasized, compared to 25.4% in Fischer rats. Metastatic lesions were observed in the heart, pleura, liver and adrenal glands, as well as in lungs and lymph nodes of nine hooded rats. Of the primary tumours, 67% were rhabdomyosarcomas (Yamashiro *et al.*, 1980).

Groups of 30 male Fischer 344 rats, approximately two months of age, received a single intramuscular injection of 0.6, 1.2, 2.5 or 5 mg nickel subsulfide. Local sarcomas were recorded in 7/30, 23/30, 28/30 and 29/30 of the animals, respectively [$p < 0.01$], indicating a dose-related increase in incidence. No such tumour developed in 60 untreated controls (Sunderman *et al.*, 1976). In an extension of this study, a total of 383 animals received injections of 0.63-20 mg α-nickel subsulfide. Sarcoma incidence at 62 weeks after treatment ranged from 24% at the lowest dose level to 100% at the highest dose level. Of the 336 sarcomas induced, 161 were rhabdomyosarcomas, 91 undifferentiated sarcomas, 72 fibrosarcomas, nine liposarcomas, two neurofibrosarcomas and one a haemangiosarcoma. Metastasis was seen in 137 of the 336 tumour-bearing animals (Sunderman, 1981).

In a study on the relationship between physical and chemical properties and carcinogenic activities of 18 nickel compounds at a standard 14-mg intramuscular dose of nickel under comparable experimental conditions in male Fischer 344 rats (see p. 321), five nickel sulfides were among the compounds tested. Three of these (α-nickel subsulfide, crystalline β-nickel sulfide and nickel ferrosulfide matte) induced local sarcomas in 100% of animals (9/9, 14/14 and 15/15). Metastases developed in 56, 71 and 67%, respectively, of the tumour-bearing rats. Nickel disulfide induced local tumours in 86% (12/14) animals and amorphous nickel sulfide in 12% (3/25). Median latent periods were 30 weeks for nickel subsulfide, 40 weeks for crystalline nickel sulfide, 36 weeks for nickel disulfide, 41 weeks for amorphous nickel sulfide, but only 16 weeks for nickel ferrosulfide. Median survival times were 39, 48, 47, 71 and 32 weeks, respectively (Sunderman, 1984).

In the study by Berry *et al.* (1984) described on p. 321, tumours developed in 10/20 rats given 5 mg nickel subsulfide intramuscularly, in 0/20 treated subperiosteally and in 10/20 given intrafemoral injections.

In the study by Judde *et al.* (1987) described on p. 321, a single intramuscular injection of 5 mg nickel subsulfide induced tumours in 2/100 rats.

[The Working Group was aware of several other studies in which nickel subsulfide was used as a positive control or as a model for the induction of rhabdomyosarcomas.]

Hamster: Groups of 15 or 17 male Syrian hamsters, two to three months of age, received a single intramuscular injection of 5 or 10 mg nickel subsulfide in 0.02-0.5 mL sterile saline. Of the 15 animals receiving the 5-mg dose, four developed local sarcomas, with a median latent period of ten months. At the 10-mg dose, 12/17 hamsters had local tumours, with a mean latency of 11 months [$p < 0.01$, trend test]. No tumour occurred among 14 controls injected with saline alone (Sunderman, 1983a).

Rabbit: Six-month-old white rabbits [sex and number unspecified] received intramuscular implants of agar-agar blocks containing approximately 80 mg nickel subsulfide powder. Sixteen rabbits with local tumours (rhabdomyosarcomas) were examined. Tumours were first observed about four to six months after implantation as small growths, which usually ceased active progression for up to 80 weeks then grew rapidly over the next four or five weeks (Hildebrand & Biserte, 1979a,b). [The Working Group noted the limited reporting of the study.]

Four male New Zealand albino rabbits, two months old, received bilateral intramuscular injections of 25 mg α-nickel subsulfide (50 mg/rabbit) in 0.1-0.5 mL penicillin G procaine suspension. All animals died between 16 and 72 months. No local tumour was found on autopsy (Sunderman, 1983a). [The Working Group noted the short observation period.]

(vi) *Intraperitoneal administration*

Rat: Of a group of 37 Fischer rats [sex and age unspecified] that received a single intraperitoneal injection of nickel subsulfide [dose unspecified], nine developed tumours, eight of which were rhabdomyosarcomas and one a mesothelioma (Gilman, 1966). [The Working Group noted the limited reporting of the study.]

A group of 50 female Wistar rats, 12 weeks of age, received a single intraperitoneal injection of 25 mg nickel subsulfide. Abdominal tumours (sarcomas, mesothliomas and carcinomas) occurred in 27/42 animals, with an average latent period of eight months (Pott *et al.*, 1987).

In a study described above (p. 322), three doses of nickel subsulfide were injected into the peritoneal cavities of groups of female Wistar rats. Local tumours were observed at 30 months in 20/36 animals that received 6 mg (as Ni) as a single injection, in 23/35 receiving 12 mg (as Ni) as two 6-mg injections and in 25/34 given 25 mg (as Ni) as 25 1-mg injections. The tumours were mesotheliomas or sarcomas of the abdominal cavity (Pott *et al.*, 1989, 1992). [The Working Group noted that the results at 30 months were available as an extended abstract only.]

(vii) *Intrarenal administration*

Rat: Groups of 16 and 24 female Sprague-Dawley rats, weighing 120-140 g, received a single injection of 5 mg nickel subsulfide in 0.05 mL glycerine or 0.5 mL saline into each pole of the right kidney. Renal-cell carcinomas occurred in 7/16 and 11/24 animals compared with 0/16 in animals given 0.5 mL glycerine (Jasmin & Riopelle, 1976).

In a second experiment (Jasmin & Riopelle, 1976), the activity of other nickel compounds and divalent metals was investigated under identical experimental conditions using glycerine as the vehicle; all rats were autopsied after 12 months' exposure. In one group of 18 rats, nickel sulfide [probably amorphous] exhibited no renal tumorigenic

activity. [The Working Group noted that it was not stated whether crystalline or amorphous nickel sulfide was used.]

Groups of male and female Wistar Lewis, NIH black, Fischer 344 and Long-Evans rats, eight weeks of age, received an intrarenal injection of 5 mg α-nickel subsulfide. The incidence of malignant renal tumours 100 weeks after exposure was 7/11 in Wistar Lewis, 6/12 in NIH black, 9/32 in Fischer and 0/12 in Long-Evans rats. Groups of 11-24 male Fischer rats were given an intrarenal injection of 0.6, 1.2, 2.5, 5 or 10 mg nickel subsulfide; no tumour was seen with 0.6, 1.2 or 2.5 mg, but responses of 5/18 and 18/24 were obtained with 5 mg and 10 mg, showing a dose-response effect. All tumours were malignant, but the authors could not establish whether the tumours were of epithelial or mesenchymal origin; 70% had distant metastases (Sunderman *et al.*, 1979a).

Groups of male Fischer 344 rats [initial number unspecified], approximately eight weeks old, received an intrarenal injection of 7 mg nickel as one of several sulfides in 0.1 or 0.2 mL saline or in glycerol:distilled water (1:1, v/v) in each pole of the right kidney and were observed for two years after treatment. The incidence of renal cancer was significantly elevated in treated groups: nickel disulfide, 2/10 (fibrosarcomas); crystalline, β-nickel sulfide, 8/14 (three fibrosarcomas, three other sarcomas, one renal-cell carcinoma, one carcinosarcoma); and α-nickel subsulfide, 4/15 (mesangial-cell sarcomas). Renal cancers occurred in 1/12 (sarcoma) rats treated with nickel ferrosulfide and in 0/15 rats treated with amorphous nickel sulfide. No local tumour developed in vehicle controls (Sunderman *et al.*, 1984b).

(viii) *Intratesticular administration*

Rat: A group of 19 male Fischer 344 rats, eight weeks of age, received an injection of 10 mg α-nickel subsulfide in 0.3 mL saline into the centre of the right testis and were observed for 20 months, at which time all the animals had died. A control group of 18 rats received an injection of 0.3 mL saline only, and a further two groups of four rats each received injections of either 10 mg metallic iron powder in saline or 2 mg zinc[III] as zinc chloride in distilled water. Of the nickel subsulfide-treated rats, 16/19 developed sarcomas in the treated testis, ten of which were fibrosarcomas, three malignant fibrous histiocytomas and three rhabdomyosarcomas. Four of the rats had distant metastases. No tumour occurred in the other groups (Damjanov *et al.*, 1978).

(ix) *Intraocular administration*

Rat: A group of 14 male and one female Fischer 344 rats, four weeks of age, received an injection of 0.5 mg α-nickel subsulfide in 20 μL saline into the vitreous cavity of the right eye under anaesthetic. Eleven male controls were similarly injected with saline alone. The experiment was terminated at 40-42 weeks after treatment, when 11 control and one

surviving treated rats were killed. Between 26 and 36 weeks after injection, 14/15 rats developed ocular tumours. Five of the tumorous eyes contained multiple neoplasms, and 22 distinct ocular tumours were identified as 11 melanomas, four retinoblastomas, three gliomas, one phakocarcinoma [lens capsular tumour] and three unclassified malignant tumours. No tumour developed in either the controls or in the uninjected, left eyes of treated rats. It was postulated that the very high incidence (93%) and short latent periods may have been due in part to the relative isolation of the vitreous bodies from the systemic circulation (blood-retina barrier), which would result in a high concentration of nickel[II]. The authors also pointed out that nickel particles within the vitreous body were relatively sequestered from phagocytosis. The visibility of developing tumours within the chamber permits their very early recognition (Albert *et al.*, 1980; Sunderman, 1983b).

Salamander A group of eight lentectomized Japanese common newts received a single injection of 40-100 μg nickel subsulfide into the vitreous chamber of the eye under anaesthetic. Seven newts developed ocular melanoma-like tumours within nine months, while no tumour occurred in six controls injected with 2-3 μL sterile 0.6% saline or eye-dropper oil after lens extirpation. The lens regenerated in each of the control eyes. The site of tumour origin could not be determined, although it was suggested to be the iris, which showed numerous aberrant proliferating cells at three months (Okamoto, 1987).

(x) *Transplacental administration*

Rat: A group of eight pregnant female Fischer 344 rats, 120-150 days of age, received an intramuscular injection of 20 mg α-nickel subsulfide in 0.2 mL procaine penicillin G suspension on day 6 of gestation, allowing for gradual dissolution of the nickel subsulfide throughout the remainder of the pregnancy. A group of controls received an injection of vehicle only. No difference in the incidence of benign or malignant tumours was seen between the 50 pups born to treated dams and 53 control pups observed for 26 months (Sunderman *et al*, 1981). [The Working Group noted that only one dose was used, which was not toxic to the fetuses.]

(xi) *Implantation into subcutaneously implanted tracheal grafts*

Rat: Groups of 30 and 32 female Fischer 344 rats, ten weeks of age, received five gelatin pellets containing 1 or 3 mg nickel subsulfide in heterotopic tracheal transplants inserted under the dorsal skin. At the lower dose level, tumours developed in 9/60 tracheas (six carcinomas and three sarcomas); at the higher dose level, tumours developed in 45/64 tracheas (one carcinoma and 44 sarcomas). No tumour developed in 20 control transplanted tracheas. The high dose resulted in necrosis of the epithelium and thus favoured the development of sarcomas (Yarita & Nettesheim, 1978).

(xii) *Intramuscular, subcutaneous or intra-articular injection or injection into retroperitoneal fat*

Rat: In a study designed to determine the types of sarcoma that develop from various mesenchymal tissue components, groups of 20 male Fischer 344 rats, seven to eight weeks of age, received injections of 5 mg nickel subsulfide either intramuscularly, subcutaneously, into the intra-articular space or into retroperitoneal fat. Control groups of ten rats each were injected with 0.5 mL aqueous procaine penicillin G vehicle. The incidences and types of sarcoma that developed in the experimental groups were: intramuscular, 19/20 (all rhabdomyosarcomas); subcutaneous, 18/19 (ten malignant fibrous histiocytomas, five rhabdomyosarcomas, three fibrosarcomas or unclassified); intra-articular, 16/19 (eight rhabdomyosarcomas, three malignant fibrous histiocytomas, five fibrosarcomas or unclassified); and retroperitoneal fat, 9/20 (five malignant fibrous histiocytomas, three rhabdomyosarcomas, one fibrosarcoma or unclassified). Controls did not develop tumours (Shibata *et al.*, 1989).

(xiii) *Administration with known carcinogens*

Rat: Groups of 30 male Fischer rats, eight to nine weeks of age, received intramuscular injections in both thighs of either 10 mg nickel subsulfide, 10 mg benzo[*a*]pyrene or 20 mg nickel subsulfide plus 10 mg benzo[*a*]pyrene in penicillin G procaine suspension, or vehicle alone. All treated rats developed sarcomas; rhabdomyosarcomas occurred in 24/30 given 10 mg nickel subsulfide, 4/30 given benzo[*a*]pyrene and 28/30 given 20 mg nickel subsulfide plus benzo[*a*]pyrene. No sarcoma occurred in controls (Maenza *et al.*, 1971).

Groups of 13, 13 and 12 male Wistar rats, weighing approximately 200 g, received single intratracheal injections of 5 mg nickel subsulfide,2 mg benzo[*a*]pyrene or 5 mg nickel subsulfide plus 2 mg benzo[*a*]pyrene and were observed for 15 months. One rat from each group developed a tumour, consisting of one hepatoma, one retroperitoneal tumour and one squamous-cell carcinoma of the lung, respectively. Significant differences were seen in the incidence of preneoplastic lesions (peribronchial adenomatoid proliferation and bronchial squamous metaplasia), the occurrence decreasing in the order: nickel subsulfide plus benzo[*a*]pyrene > benzo[*a*]pyrene > nickel subsulfide (Kasprzak *et al*., 1973).

(*d*) *Nickel salts*

(i) *Intramuscular administration*

Rat: A group of 32 male and female Wistar rats, two to three months of age, received an injection of 5 mg nickel sulfate hexahydrate in one or both thigh muscles (54 injected sites). Thirteen rats survived until the end of the experiment at 603 days.

No local tumour was found at the site of injection. No vehicle control was used (Gilman, 1962).

In a study reported as an abstract, sheep fat pellets, each containing 7 mg of either nickel sulfate, nickel chloride, nickel acetate, anhydrous nickel acetate, nickel carbonate or nickel ammonium sulfate, were given as three intramuscular implants [interval unspecified] into groups of 35 Bethesda black [NIH black] rats. Animals were observed for 18 months. Six tumours developed in the nickel carbonate group; single tumours developed in the nickel acetate and nickel sulfate groups. No tumour developed in any of the other groups or in 35 controls (Payne, 1964).

In a study comparing the in-vitro solubility and carcinogenicity of several nickel compounds, nickel fluoride and nickel sulfate were suspended in penicillin G procaine and injected intramuscularly [dose unspecified] into groups of 20 Fischer rats [sex and age unspecified]. The incidence of local sarcomas was 3/18 (17%; 3/36 sites) with nickel fluoride and 0/20 with nickel sulfate. Seventeen of 20 (85%) rats given nickel subsulfide as a positive control developed local sarcomas. No tumour developed in 20 rats injected with nickel sulfide [presumed to be amorphous] (Gilman, 1966). [The Working Group noted that no concurrent vehicle control was used and that the length of observation was not specified.]

A group of 20 male Wistar rats, weighing 200-220 g, received 15 intramuscular injections of 20 μL of a 0.2 M solution of nickel sulfate (4.4 μmol [0.26 mg]/injection of nickel; total dose, 66 μmol [4 mg]/rat nickel) every other day during one month. Further groups of 20 male rats received injections of nickel subsulfide (total dose, 40 μmol [7.1 mg nickel]; positive control) or sodium sulfate (15 injections of 20 μL of a 0.2 M solution; negative control). Nickel subsulfide induced local tumours in 16/20 rats; no tumour developed in nickel sulfate- or sodium sulfate-treated rats (Kasprzak *et al.*, 1983).

One local sarcoma was found in 16 male Fischer 344 rats, two to three months old, given an intramuscular injection of nickel chromate into the right thigh as 14 mg/rat nickel. Ten rats survived two years (Sunderman, 1984).

(ii) *Intraperitoneal administration*

Mouse: In a screening assay for lung adenomas in strain A mice, groups of ten male and ten female Strong strain A mice, six to eight weeks old, received intraperitoneal injections of nickel acetate in 0.85% physiological saline (total doses, 72, 180 and 360 mg/kg bw) three times a week for 24 weeks and were observed for 30 weeks, at which time all survivors were autopsied. Further groups of mice received a single intraperitoneal injection of 20 mg urethane (positive control), 24 injections of saline only or remained untreated. The incidences of lung tumours were: saline control, 37% (0.42 tumours/animal); untreated control, 31% (0.28 tumours/animal); positive control, 100% (21.6 tumours/animal); 72 mg

nickel acetate, 44% (0.67 tumours/animal); 180 mg nickel acetate, 50% (0.71 tumours/-animal); and 360 mg nickel acetate, 63% (1.26 tumours/animal). The difference in response between the group given 360 mg nickel acetate and the negative control group was significant ($p < 0.01$). Five adenocarcinomas of the lung were observed in the nickel-treated mice compared to none in controls (Stoner *et al.*, 1976).

In the same type of screening assay, 30 male and female Strong strain A mice, six to eight weeks of age, received intraperitoneal injections of 10.7 mg/kg bw nickel acetate tetrahydrate (maximal tolerated dose; 0.04 mmol [2.4 mg]/kg bw nickel) three times a week for 24 weeks. A control group received injections of 0.9% saline under the same schedule. Animals were autopsied 30 weeks after the first injection. Of the nickel-treated group, 24/30 animals survived to 30 weeks and had an average of 1.50 lung adenomas/animal, whereas 25/30 controls had an average of 0.32 lung adenoma/animal ($p < 0.05$) (Poirier *et al.*, 1984).

Rat: In a study described earlier (p. 322), groups of female Wistar rats were given repeated intraperitoneal injections of 1 mg of each of four soluble nickel salts. The dose schedule and tumour responses at 30 months are shown in Table 23. The tumours were either mesotheliomas or sarcomas (tumours of the uterus were not included) (Pott *et al.*, 1989, 1992). [The Working Group noted that administration of nickel sulfate and nickel chloride by intramuscular injection has not been shown to induce tumours in rats. They suggest that in this instance the repeated small intraperitoneal doses permitted repeated exposure of potential target cells. Repeated intramuscular injections would result in nickel coming into contact with different cells at each injection. The Group also noted that the results at 30 months were reported only as an extended abstract.]

(iii) *Administration with known carcinogens*

Rat: Groups of 12 rats [strain, sex and age unspecified] received a single subcutaneous injection of 9 mg/mL dinitrosopiperazine in aqueous Tween 80. The following day, one group received topical insertion into the nasopharynx of 0.02 mL of a 0.5% solution of nickel sulfate in 4% aqueous gelatin once a week for seven weeks. A further group was held for six days and then administered 1 mL of aqueous 1% nickel sulfate solution in the drinking-water for six weeks. Additional groups of 12 rats received treatment with dinitrosopiperazine, nickel sulfate solution or nickel sulfate in gelatin only. Survival at 371 days was lower in the group treated with dinitropiperazine plus nickel sulfate solution in the drinking-water than in the group given the nitrosamine or the nickel sulfate solution alone. Two nasopharyngeal tu-mours (one squamous-cell carcinoma, one fibrosarcoma) occurred in the group treated with dinitropiperazine plus nickel sulfate in drinking-water and two (one papilloma, one early carcinoma) in the group treated with dinitropiperazine plus

Table 23. Tumour responses of rats to intraperitoneal injection of soluble nickel salts[a]

Compound	Total dose (mg, as Ni)	Schedule	Incidence of abdominal tumours
Nickel chloride.$6H_2O$	50	50 × 1 mg	4/32 [$p < 0.05$]
Nickel sulfate.$7H_2O$	50	50 × 1 mg	6/30 [$p < 0.05$]
Nickel acetate.$4H_2O$	25	25 × 1 mg	3/35
	50	50 × 1 mg	5/31 [$p < 0.05$ for trend]
Nickel carbonate	25	25 × 1 mg	1/35
Nickel hydroxide.$2H_2O$	50	50 × 1 mg	3/33
Saline		3 × 1 mL	1/33
		50 × 1 mL	0/34

[a]From Pott *et al.* (1989, 1992)

insertion of nickel sulfate in gelatin. No tumour occurred in the other groups. The authors concluded that 'probably nickel has a promoting action in the induction of nasopharyngeal carcinoma in rats following dinitrosopiperazine initiation' (Ou *et al.*, 1980). [The Working Group noted the small number of animals used and the poor survival.]

As reported in an abstract, in an extension of the study by Ou *et al.* (1980), five of 22 rats given an initiating injection of dinitrosopiperazine developed carcinomas following oral administration of nickel sulfate in gelatin. Two of the carcinomas were of the nasopharynx, two of the nasal cavity and one of the hard palate. No tumour developed in rats [numbers unspecified] treated with dinitrosopiperazine plus aqueous nickel sulfate, with nickel sulfate in gelatin alone or with dinitrosopiperazine alone (Liu *et al*., 1983). [The Working Group noted the small number of animals used and the poor survival.]

As reported in an abstract, a group of 13 female rats [strain and age unspecified] received a single subcutaneous injection of 9 mg dinitrosopiperazine on day 18 of gestation. Pups of treated dams were fed 0.05 mL of 0.05% nickel sulfate beginning at four weeks of age every day for one month. The dose of nickel sulfate was increased by 0.1 mL per month for a further five months, by which time 5/21 pups had developed carcinomas of the nasal cavity. In a group of untreated pups of treated dams, 3/11 rats developed tumours (one nasopharyngeal squamous-cell carcinoma, one neurofibrosarcoma of the peritoneal cavity and one granulosa-thecal-cell carcinoma of the ovary). Groups given nickel sulfate and untreated control groups of seven pups each did not develop tumours. None of the pregnant rats that had been injected with dinitrosopiperazine alone developed tumours (Ou *et al.*, 1983).

Groups of 15 male Fischer 344 rats, seven weeks old, were administered 500 mg/L *N*-nitrosoethylhydroxyethylamine (NEHEA) in the drinking-water for two weeks. Thereafter, rats received drinking-water alone or drinking-water containing 600 mg/L nickel chloride hexahydrate for 25 weeks, when the study was terminated. The incidence of renal-cell tumours in the group receiving NEHEA and nickel chloride (8/15) was significantly higher ($p < 0.05$) than that in controls given NEHEA alone (2/15) or nickel chloride alone (0/15) (Kurokawa *et al.*, 1985). Nickel chloride did not show promoting activity in livers of Fischer 344 rats after initiation with *N*-nitrosodiethylamine, in gastric tissue of Wistar rats after initiation with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, in the pancreas of Syrian golden hamsters following initiation with *N*-nitrosobis(2-oxy-propyl)amine or in skin of SENCAR mice initiated with 7,12-dimethylbenz[*a*]anthracene. The authors concluded that nickel chloride is a promoter in renal carcinogenesis in rats (Hayashi *et al.*, 1984; Kurokawa *et al.*, 1985).

(*e*) *Other nickel compounds*

(i) *Inhalation*

Rat: Groups of 64 or 32 male Wistar rats, weighing 200-250 g, were exposed by inhalation for 30 min to 30 or 60 mg/m^3 nickel carbonyl vapourized from a solution in 50:50 ethanol:diethyl ether, respectively, three times a week for 52 weeks. Another group of 80 rats was exposed once to 250 mg/m^3 nickel carbonyl. All treated animals had died by 30 months. One lung carcinoma appeared in each of the first two groups, and two pulmonary carcinomas developed in the last group. No pulmonary tumour occurred among 41 vehicle-treated control rats (Sunderman *et al.*, 1957, 1959). A further group of 285 rats was exposed for 30 min to 600 mg/m^3 nickel carbonyl; 214 died from acute toxicity. One lung adenocarcinoma was observed in the remaining 71 animals. Similar exposure to nickel carbonyl followed by intraperitoneal injection of sodium diethyl dithiocarbamate, an antidote, resulted in survival of all 60 treated rats and the development of a single anaplastic lung carcinoma. Minimal time to observation of lung tumours in these groups was in excess of 24 months. No lung carcinoma was observed in a group of 32 controls (Sunderman & Donnelly, 1965).

A group of five non-inbred rats [sex and age unspecified] was exposed by inhalation to 70 mg/m^3 nickel refinery dust (containing 11.3% metallic nickel, 58.3% nickel sulfide [identity unspecified], 1.7% nickel monoxide and 0.2% water-soluble nickel [composition of sample unclear]) for 5 h per day on five days per week for six months. Seventeen months after the start of treatment, one of five rats developed a squamous-cell carcinoma of the lung. No tumour developed among 47 untreated controls (Saknyn & Blokhin, 1978). [The Working Group noted the small number of animals used.]

Hamster: Groups of 102 male Syrian golden outbred LAK:LVG hamsters, two months old, were exposed by inhalation to concentrations of 17 or 70 mg/m^3 nickel-enriched fly ash from the addition of nickel acetate to pulverized coal before combustion (nickel content, 6%) for 6 h per day on five days per week for 20 months. Further groups were exposed to 70 mg/m^3 fly ash containing 0.3% nickel, or were sham-exposed. Five animals from each group were autopsied at four-month intervals up to 16 months, and all survivors were sacrificed at 20 months. No significant difference in mortality rate or bodyweight was observed between the groups. There were 14, 16, 16 and seven benign and malignant tumours in the sham-exposed, fly ash, low-dose and high-dose nickel-enriched fly ash groups, respectively. The only two malignant pulmonary neoplasms (one adenocarcinoma, one mesothelioma) occurred in the group receiving fly ash enriched with the high dose of nickel (Wehner *et al.*, 1981, 1984).

(ii) *Intratracheal instillation*

Rat: A group of 26 white non-inbred rats [sex and age unspecified] received a single intratracheal instillation of 20-40 mg aerosol dust (64.7% nickel monoxide (black), 0.13% nickel sulfide, 0.18% metallic nickel) in 0.6 mL saline. One squamous-cell carcinoma of the lung had developed by 17 months. No tumour developed among a group of 47 controls (Saknyn & Blokhin, 1978). [The Working Group noted that it was not stated whether the controls were untreated or received the vehicle alone.]

(iii) *Intramuscular administration*

Mouse: A group of 40 female Swiss mice, two to three months of age, received an intramuscular injection in each thigh of 10 mg of a nickel refinery dust (57% nickel subsulfide, 20% nickel sulfate hexahydrate, 6.3% nickel monoxide) suspended in penicillin G procaine. Of the 36 mice that survived more than 90 days, 20 developed a total of 23 local sarcomas, with an average latent period of 46 weeks. No tumour occurred among 48 control mice injected with the vehicle alone (Gilman & Ruckerbauer, 1962).

Rat: A group of 35 male and female hooded rats, two to three months of age, received an intramuscular injection in each thigh of 20 mg of a nickel refinery dust (57% nickel subsulfide, 20% nickel sulfate hexahydrate, 6.3% nickel oxide) suspended in penicillin G procaine. Of the 27 rats that survived more than 90 days, 19 developed local sarcomas. Another group of 31 male and female rats received injections of the same refinery dust after repeated washing in distilled water; 20/28 of the rats that survived more than 90 days developed local tumours at one or other of the injection sites. No tumour occurred among 30 control rats injected with the vehicle alone (Gilman & Ruckerbauer, 1962).

Groups of 25 male and 25 female Fischer 344 rats [age unspecified] received 12 intramuscular injections of 12 or 25 mg nickelocene in trioctanoin. Tumour incidences were 18/50 and 21/50, respectively. No local tumour occurred in a group of 25 male and 25 female controls (Furst & Schlauder, 1971).

Groups of 15-30 male Fischer 344 rats, approximately eight weeks old, received a single intramuscular injection of 14 mg nickel as one of four nickel arsenides, nickel antimonide, nickel telluride, nickel sinter matte (Ni_4FeS_4; positive control), nickel titanate or ferronickel alloy ($NiFe_{1\cdot6}$; negative controls) in 0.3 mL glycerol:water (1:1; v/v) into the exterior thigh. The compounds were > 99.9% pure and were ground down to a median particle size of < 2 μm. Rats that died within two months of the injection were excluded from the experiment; remaining animals were observed for two years. Median survival ranged from 32 weeks (positive controls) to over 100 weeks (negative controls). The incidences of local tumours in the groups were: nickel sinter matte, 15/15; nickel sulfarsenide, 14/16; nickel arsenide hexagonal, 17/20; nickel antimonide, 17/29; nickel telluride, 14/26; and nickel arsenide tetragonal, 8/16. No tumour was observed in the groups treated with nickel arsenide, ferronickel alloy or nickel titanate nor in a vehicle control group. Median latency for tumour induction ranged from 16 weeks (positive controls) to 33 weeks (nickel arsenide tetragonal-treated group). The incidence of tumours induced by the test compounds was significantly greater than that in the vehicle control group ($p < 0.001$); 67% of all the sarcomas were rhabdomyosarcomas, 11% fibrosarcomas, 15% osteosarcomas and 5% undifferentiated sarcomas. Metastases occurred in 57% of tumour-bearing rats (Sunderman & McCully, 1983).

In a continuation of these tests, nickel selenide, nickel subselenide and nickel monoxide (positive control; see p. 327) were tested using the same experimental techniques. Nickel selenide and nickel subselenide induced significant increases in the incidence of local tumours (8/16 and 21/23, respectively; $p < 0.001$); the positive control group had 14/15 tumours. Metastases occurred in 38 and 86%, respectively, of tumour-bearing rats in the selenium-treated groups and in 29% of positive controls. Approximately 50% of the tumours were rhabdomyosarcomas (Sunderman, 1984).

Hamster: Groups of 25 male and 25 female hamsters, three to four weeks old, received eight monthly injections of 5 mg nickelocene in 0.2 mL trioctanoin into the right thigh. No tumour was induced. A group of survivors from another test [age unspecified] received a single intramuscular injection of 25 mg nickelocene in trioctanoin; fibrosarcomas occurred in 1/13 females and 3/16 males. No tumour occurred in 25 male or 25 female vehicle controls (Furst & Schlauder, 1971).

(iv) *Intraperitoneal administration*

Rat: Groups of 16 and 23 non-inbred albino rats [sex and age unspecified] received a single intraperitoneal injection of 90-150 mg of one of two refinery dusts: the first contained 11.3% metallic nickel, 58.3% nickel sulfide, 1.7% nickel monoxide and 0.2% water-soluble nickel; the second contained 2.9% metallic nickel, 26.8% nickel sulfide, 6.8% nickel monoxide and 0.07% water-soluble nickel. Each was given in 1.5 mL physiological saline. Three local sarcomas developed within six to 15 months in animal treated with the first dust, and three local sarcomas developed within nine to 11 months in animals treated with the second dust. No tumour was observed in 47 control rats (Saknyn & Blokhin, 1978). [The Working Group noted that it was not specified whether control rats were untreated or were treated with the vehicle.]

(v) *Intravenous administration*

Rat: A group of 61 male and 60 female Sprague-Dawley rats, eight to nine weeks of age, received six injections of 9 mg/kg bw nickel carbonyl (as Ni) at two- to four-week intervals and were observed for life. Nineteen animals developed malignancies, six of which were undifferentiated sarcomas and three, fibrosarcomas at various sites; the other tumours were single carcinomas of the liver, kidney and mammary gland, one haemangioendothelioma, one undifferentiated leukaemia and five pulmonary lymphomas. Two pulmonary lymphomas developed in 15 male and 32 female sham-injected controls. The difference in total tumour incidence was significant ($p < 0.05$) (Lau *et al.*, 1972).

(vi) *Intrarenal administration*

Groups of male fischer rats [initial number unspecified], approximately eight weeks old, received intrarenal injections of 7 mg nickel as one of several nickel compounds in 0.1 or 0.2 mL saline solution or in glycerol:distilled water (1:1, v/v) in each pole of the right kidney and were observed for two years after treatment. The incidence of renal cancer was significantly elevated in the groups treated with nickel sulfarsenide (3/15 sarcomas) but not in those treated with nickel arsenide (1/20 renal-cell carcinoma), nickel selenide (1/12 sarcoma), nickel subselenide (2/23 sarcomas), nickel telluride (0/19), nickel subarsenides (tetragonal and hexagonal; 0/15 and 0/17), nickel antimonide (0/20) or nickel titanate (0/19). No local tumour developed in vehicle controls (Sunderman *et al.*, 1984b).

The experiments described in section 3.1 are summarized in Table 24.

Table 24. Summary of studies used to evaluate the carcinogenicity to experimental animals of metallic nickel and nickel compounds

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Metallic nickel powder and nickel alloys				
Cr/Ni stainless steel	Intratracheal	Hamster (60)	36 mg, no local tumour 108 mg, no local tumour	Muhle *et al.* (1990)
Metallic nickel powder	Inhalation	Mouse (20)	No lung tumour	Hueper (1958)
Metallic nickel powder	Inhalation	Rat (160)	Benign lung neoplasms	Hueper (1958)
Metallic nickel powder (plus sulfur dioxide)	Inhalation	Rat (120)	0/46 lung tumour	Hueper & Payne (1962)
Metallic nickel powder	Inhalation	Guinea-pig (42)	1/23 intra-alveolar carcinoma, 1/23 metastasis of adenocarcinoma	Hueper (1958)
Metallic nickel powder	Intratracheal	Rat (80)	10. × 0.9 mg, 8/32 lung tumours [$p < 0.05$] 20 × 0.3 mg, 10/39 lung tumours [$p < 0.05$] Controls, 0/40 lung tumour	Pott *et al.* (1987)
Metallic nickel powder	Intratracheal	Hamster (100 per group)	10 mg, 1% local tumours 20 mg, 8% local tumours 40 mg, 12% local tumours 4 × 20 mg, 10% local tumours	Ivankovic *et al.* (1987)
Metallic nickel powder	Intratracheal	Hamster (60)	1/56 lung tumour	Muhle *et al.* (1990)
Metallic nickel powder	Intrapleural	Rat (25)	4/12 local sarcomas *vs* 0/70 in controls [$p < 0.01$]	Hueper (1952)
Metallic nickel powder	Intrapleural	Rat (10)	2/10 mesotheliomas *vs* 0/20 in controls	Furst *et al.* (1973)
Metallic nickel powder	Subcutaneous	Rat (10)	5/10 local tumours	Mitchell *et al.* (1960)
Metallic nickel powder	Intramuscular	Rat (10)	10/10 local tumours *vs* 0 in controls	Heath & Daniel (1964)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Metallic nickel powder	Intramuscular	Rat (50)	38/50 local tumours *vs* 0 in controls	Furst & Schlauder (1971)
Metallic nickel powder	Intramuscular	Rat (20)	3.6 mg, 0/10 local tumours 14.4 mg, 2/9 local tumours Controls, 0/20 local tumours	Sunderman & Maenza (1976)
Metallic nickel powder	Intramuscular	Rat (20)	17/20 local tumours *vs* 0/56 in controls	Berry *et al.* (1984)
Metallic nickel powder	Intramuscular	Rat (20)	13/20 local tumours *vs* 0/44 in controls	Sunderman (1984)
Metallic nickel powder	Intramuscular	Rat (40)	14/30 local tumours *vs* 0/60 in controls	Judde *et al.* (1987)
Metallic nickel powder	Intramuscular	Hamster (50)	2/50 local tumours *vs* 0/50 in controls	Furst & Schlauder (1971)
Metallic nickel powder	Intraperitoneal	Rat	30–50% local tumours *vs* none in controls	Furst & Cassetta (1973)
Metallic nickel powder	Intraperitoneal	Rat (50)	46/48 abdominal tumours	Pott *et al.* (1987)
Metallic nickel powder	Intraperitoneal	Rat	6 mg, 4/34 local tumours 2×6 mg, 5/34 local tumours 25×1 mg, 25/35 local tumours	Pott *et al.* (1990)
Metallic nickel powder	Intravenous	Mouse (25)	No tumour	Hueper (1955)
Metallic nickel powder	Intravenous	Rat (25)	7/25 local tumours	Hueper (1955)
Metallic nickel powder	Intrarenal	Rat (20)	No local tumour	Jasmin & Riopelle (1976)
Metallic nickel powder	Intrarenal	Rat	No local tumour	Sunderman *et al.* (1984b)
Metallic nickel powder	Subperiosteal	Rat (20)	11/20 local tumours	Berry *et al.* (1984)
Metallic nickel powder	Intrafemoral	Rat (20)	9/20 local tumours	Berry *et al.* (1984)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel alloy: 26.8%, Ni, 16.2% Cr, 39.2% Fe, 0.04% Co	Intratracheal	Hamster (100 per group)	10 mg, no local tumour 20 mg, no local tumour 40 mg, no local tumour 4×20 mg, no local tumour	Ivankovic *et al.* (1987)
Nickel alloy: 66.5%, Ni, 12.8% Cr, 6.5% Fe, 0.2% Co	Intratracheal	Hamster (100 per group)	10 mg, 1% local tumours 20 mg, 8% local tumours 40 mg, 12% local tumours 4×20 mg, 10% local tumours	Ivankovic *et al.* (1987)
Nickel–gallium alloy (60% Ni)	Subcutaneous	Rat (10)	9/10 local tumours	Mitchell *et al.* (1960)
Nickel–iron alloy ($NiFe_{1-8}$)	Intramuscular	Rat (16)	0/16 local tumours	Sunderman (1984)
Nickel–iron alloy ($NiFe_{1-8}$)	Intrarenal	Rat	1/14 renal cancers *vs* 0/46 controls	Sunderman *et al.* (1984b)
Nickel alloy (50% Ni)	Intraperitoneal	Rat	50 mg, 8/35 local tumours 3×50 mg, 13/35 local tumours	Pott *et al.* (1989, 1990)
Nickel alloy (29% Ni)	Intraperitoneal	Rat	50 mg, 2/33 local tumours 2×50 mg, 1/36 local tumours	Pott *et al.* (1989, 1990)
Nickel alloy (66% Ni)	Intraperitoneal	Rat	50 mg, 12/35 local tumours 3×50 mg, 22/33 local tumours	Pott *et al.* (1989, 1990)
Pentlandite	Intratracheal	Hamster (60)	1/60 local tumour	Muhle *et al.* (1990)
Nickel oxides and hydroxides				
Nickel monoxide (green)	Inhalation	Rat (6, 8)	8 mg/m³, 1/8 lung tumour 0.6 mg/m³, 0/6 lung tumour	Horie *et al.* (1985)
Nickel monoxide	Inhalation	Rat (40, 20)	0.06 mg/m³, no tumour 0.2 mg/m³, no tumour	Glaser *et al.* (1986)
Nickel monoxide	Inhalation	Hamster (51)	1/51 osteosarcoma	Wehner *et al.* (1975, 1979)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel monoxide	Intrapleural	Rat (32)	31/32 local tumours *vs* 0/32 in controls	Skaug *et al.* (1985)
Nickel monoxide	Intratracheal	Rat	10 × 5 mg, 10/37 lung tumours 10 × 15 mg, 12/38 lung tumours controls, 0/40	Pott *et al.* (1987)
Nickel monoxide	Intratracheal	Hamster (50)	1/49 lung tumours *vs* 4/50 in controls	Farrell & Davis (1974)
Nickel monoxide	Intramuscular	Mouse (50, 52)	33/50 and 23/52 local tumours	Gilman (1962)
Nickel monoxide	Intramuscular	Rat (32)	21/32 local tumorus	Gilman (1962)
Nickel monoxide	Intramuscular	Rat (20)	2/20 local tumours	Gilman (1966)
Nickel monoxide	Intramuscular	Rat (20)	No local tumour	Sosiński (1975)
Nickel monoxide	Intramuscular	Rat (15)	14/15 local tumours	Sunderman & McCully (1983)
Nickel monoxide	Intramuscular	Rat (20)	0/20 local tumour	Berry *et al.* (1984)
Nickel monoxide	Subperiosteal	Rat (20)	0/20 local tumour	Berry *et al.* (1984)
Nickel monoxide	Intraperitoneal	Rat (50)	46/47 local tumours	Pott *et al.* (1987)
Nickel monoxide	Intraperitoneal	Rat	25 mg, 12/34 local tumours 100 mg, 15/36 local tumours	Pott *et al.* (1989, 1990)
Nickel monoxide (green)	Intrarenal	Rat (12)	0/12 local tumour	Sunderman *et al.* (1984b)
Nickel hydroxide	Intramuscular	Rat	15/20 local tumours	Gilman (1966)
Nickel hydroxide	Intramuscular	Rat (3 x 20)	Dried gel: 5/19 local tumours Crystalline: 3/20 local tumours Colloidal: 0/13 local tumour	Kasprzak *et al.* (1983)
Nickel trioxide	Intramuscular	Rat (10)	0/10 local tumour	Judde *et al.* (1987)
Nickel trioxide	Intracerebral	Rat (20)	3/20 local tumours	Sosiński (1975)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel sulfides				
Nickel disulfide	Intramuscular	Rat	12/14 local tumours	Sunderman (1984)
Nickel disulfide	Intrarenal	Rat	2/10 local tumours	Sunderman *et al.* (1984b)
Nickel sulfide (amorphous)	Intramuscular	Rat (10 per group)	5.6 mg, no local tumour 22.4 mg, no local tumour	Sunderman & Maenza (1976)
β-Nickel sulfide	Intramuscular	Rat	14/14 local tumours	Sunderman (1984)
Nickel sulfide (amorphous)	Intramuscular	Rat	3/25 local tumours	Sunderman (1984)
Nickel sulfide	Intrarenal	Rat (18)	0/18 local tumour	Jasmin & Riopelle (1976)
β-Nickel sulfide	Intrarenal	Rat	8/14 local tumours	Sunderman *et al.* (1984b)
Nickel sulfide (amorphous)	Intrarenal	Rat	0/15 local tumour	Sunderman *et al.* (1984b)
Nickel subsulfide	Inhalation	Rat (226)	14/208 malignant lung tumours; 15/208 benign lung tumours	Ottolenghi *et al.* (1974)
Nickel subsulfide	Intratracheal	Mouse (100)	No increase in lung tumours	Fisher *et al.* (1986)
Nickel subsulfide	Intratracheal	Rat	0.94 mg: 7/47 lung tumours 1.88 mg: 13/45 lung tumours 3.75 mg: 12/40 lung tumours	Pott *et al.* (1987)
α-Nickel subsulfide	Intratracheal	Hamster (62)	0/62 lung tumour	Muhle *et al.* (1990)
Nickel subsulfide	Intrapleural	Rat (32)	28/32 local tumours	Skaug *et al.* (1985)
Nickel subsulfide	Subcutaneous	Mouse (20)	5 mg, 4/8 local tumours 10 mg, 7/8 local tumours	Oskarsson *et al.* (1979)
Nickel subsulfide	Subcutaneous	Rat (40 per group)	3.3 mg, 37/39 local tumours 10 mg, 37/40 local tumours	Mason (1972)
Nickel subsulfide	Subcutaneous	Rat (20)	18/19 local tumours	Shibata *et al.* (1989)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel subsulfide	Intramuscular	Mouse (45, 18)	Swiss, 27/45 local tumours C3H, 9/18 local tumours	Gilman (1962)
Nickel subsulfide	Intramuscular	Mice (20)	5 mg, 4/8 local tumours 10 mg, 4/8 local tumours	Oskarsson *et al.* (1979)
Nickel subsulfide	Intramuscular	Mouse (10, 10)	C57Bl6, 5/10 local tumours DBA/2, 6/10 local tumours	Sunderman (1983b)
Nickel subsulfide	Intramuscular	Rat (32)	25/28 local tumours	Gilman (1962)
Nickel subsulfide	Intramuscular	Rat (20)	10 mg powder, 19/20 local tumours 500 mg fragments, 5/7 local tumours 500 mg discs, 14/17 local tumours 10 mg diffusion chamber, 14/17 local tumours controls, 1/19 local tumour	Gilman & Herchen (1963)
Nickel subsulfide (disc)	Intramuscular	Rat (groups of 15)	4/10 local tumours with removal of disc after 64 days 7/10 local tumours with removal of disc after 128 days 10/10 local tumours with removal of disc after 206 days	Herchen & Gilman (1964)
Nickel subsulfide	Intramuscular	Rat (30, 27)	NIH black, 28/28 local tumours Hooded, 14/23 local tumours	Daniel (1966)
Nickel subsulfide	Intramuscular	Rat (40 per group)	3.3 mg, 38/39 local tumours 10 mg, 34/40 local tumours	Mason (1972)
Nickel subsulfide	Intramuscular	Rat (10 per group)	5 mg, 8/20 local tumours 20 mg, 9/9 local tumours	Sunderman & Maenza (1976)
Nickel subsulfide	Intramuscular	Rat (63,20)	Fischer, 59/63 local tumours Hooded, 11/20 local tumours	Yamashiro *et al.* (1980)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel subsulfide	Intramuscular	Rats (groups of 30)	0.6 mg, 7/30 local tumours 1.2 mg, 23/30 local tumours 2.5 mg, 28/30 local tumours 5 mg, 29/30 local tumours	Sunderman *et al.* (1976)
Nickel subsulfide	Intramuscular	Rat	0.63 mg, 7/29 local tumours 20 mg, 9/9 local tumours	Sunderman (1981)
α-Nickel subsulfide	Intramuscular	Rat	9/9 local tumours	Sunderman (1984)
Nickel subsulfide	Intramuscular	Rat (20)	10/20 local tumours	Berry *et al.* (1984)
Nickel subsulfide	Intramuscular	Rat (100)	2/100 local tumours	Judde *et al.* (1987)
Nickel subsulfide	Intramuscular	Hamster (15, 17)	5 mg, 4/15 local tumours 10 mg, 12/17 local tumours controls, 0/14 local tumour	Sunderman (1983a)
Nickel subsulfide	Intramuscular	Rabbit	16 local tumours	Hildebrand & Biserte (1979a,b)
α-Nickel subsulfide	Intramuscular	Rabbit (4)	0/4 local tumour	Sunderman (1983a)
Nickel subsulfide	Intramuscular	Rat (20)	19/20 local tumours	Shibata *et al.* (1989)
α-Nickel subsulfide	Topical	Hamster (6–7, 13–15)	54 mg total, 0/6 local tumour; 108 mg total, 0/7 local tumour; 540 mg total, 0/15 local tumour; 1080 mg total, 0/13 local tumour	Sunderman (1983b)
Nickel subsulfide	Intraperitoneal	Rat (37)	9/37 local tumours	Gilman (1966)
Nickel subsulfide	Intraperitoneal	Rat (50)	27/42 local tumours	Pott *et al.* (1987)
Nickel subsulfide	Intraperitoneal	Rat	6 mg, 20/36 local tumours 12 mg, 23/35 local tumours 25 mg, 25/34 local tumours	Pott *et al.* (1989, 1990)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel subsulfide	Subperiosteal	Rat (20)	0/20 local tumour	Berry *et al.* (1984)
Nickel subsulfide	Intrafemoral	Rat (20)	10/20 local tumours	Berry *et al.* (1984)
Nickel subsulfide	Intrarenal	Rat (16/24)	In glycerin, 7/16 local tumours In saline, 11/24 local tumours	Jasmin & Riopelle (1976)
α-Nickel subsulfide	Intrarenal	Rat (11–32)	Wistar Lewis, 7/11 local tumours NIH black, 6/12 local tumours Fischer 344, 9/32 local tumours Long–Evans, 0/12 local tumour	Sunderman *et al.* (1979a)
Nickel subsulfide	Intratesticular	Rat (19)	16/19 local tumours	Damjanov *et al.* (1978)
Nickel subsulfide	Intraocular	Rat (15)	14/15 local tumours	Albert *et al.* (1980); Sunderman (1983b)
Nickel subsulfide	Intraocular	Salamander (8)	7/8 local tumours	Okamoto (1987)
Nickel subsulfide	Transplacental	Rat (8)	No difference in tumour incidence	Sunderman *et al.* (1981)
Nickel subsulfide	Pellet implantation into subcutaneous implanted tracheal grafts	Rat (60, 64)	5 mg, 9/60 local tumours 15 mg, 45/64 local tumours	Yarita & Nettesheim (1978)
Nickel subsulfide	Intra-articular	Rat (20)	16/19 local tumours	Shibata *et al.* (1989)
Nickel subsulfide	Intra-fat	Rat (20)	9/20 local tumours	Shibata *et al.* (1989)
Nickel ferrosulfide	Intramuscular	Rat	15/15 local tumours	Sunderman (1984)
Nickel ferrosulfide	Intrarenal	Rat	1/12 local tumour	Sunderman *et al* (1984b)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel salts				
Basic nickel carbonate tetrahydrate	Intraperitoneal	Rat	25 mg, 1/35 lung tumours *vs* 1/33 in controls 50 mg, 3/33 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Nickel acetate	Intramuscular	Rat (35)	1/35 local tumour	Payne (1964)
Nickel acetate	Intraperitoneal	Mouse (3 x 20)	72 mg, 8/18 lung tumours 180 mg, 7/14 lung tumours 360 mg, 12/19 lung tumours	Stoner *et al.* (1976)
Nickel acetate tetrahydrate	Intraperitoneal	Mouse (30)	1.50 lung tumours/animal Controls, 0.32 lung tumours/animal	Poirier *et al.* (1984)
Nickel acetate tetrahydrate	Intraperitoneal	Rat	25 mg, 3/35 lung tumours *vs* 1/33 in controls 50 mg, 5/31 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Nickel ammonium sulfate	Intramuscular	Rat (35)	0/35 local tumour	Payne (1964)
Nickel carbonate	Intramuscular	Rat (35)	6/35 local tumours	Payne (1964)
Nickel chloride	Intramuscular	Rat (35)	0/35 local tumour	Payne (1964)
Nickel chloride hexahydrate	Intraperitoneal	Rat	4/32 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Nickel chromate	Intramuscular	Rat (16)	1/16 local tumour	Sunderman (1984)
Nickel fluoride	Intramuscular	Rat (20)	3/18 local tumours	Gilman (1966)
Nickel sulfate	Intramuscular	Rat (35)	1/35 local tumour	Payne (1964)
Nickel sulfate	Intramuscular	Rat (20)	0/20 local tumour	Gilman (1966)
Nickel sulfate	Intramuscular	Rat (20)	0/20 local tumour	Kasprzak *et al.* (1983)
Nickel sulfate hexahydrate	Intramuscular	Rat (32)	0/32 local tumour	Gilman (1962)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel sulfate heptahydrate	Intraperitoneal	Rat	6/30 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Other nickel compounds				
Ferronickel alloy	Intramuscular	Rat	No local tumour	Sunderman & McCully (1983)
Nickel antimonide	Intramuscular	Rat	17/29 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel antimonide	Intrarenal	Rat	0/20 local tumour	Sunderman *et al.* (1984b)
Nickel arsenide	Intramuscular	Rat	No local tumour	Sunderman & McCully (1983)
Nickel arsenide	Intrarenal	Rat	1/20 local tumour	Sunderman *et al.* (1984b)
Nickel arsenide hexagonal	Intramuscular	Rat	17/20 *vs* 0/40 controls ($p < 0.05$)	Sunderman & McCully (1983)
Nickel arsenide hexagonal	Intrarenal	Rat	0/17 local tumour	Sunderman *et al.* (1984b)
Nickel arsenide tetragonal	Intramuscular	Rat	8/16 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel arsenide tetragonal	Intrarenal	Rat	0/15 local tumour	Sunderman *et al.* (1984b)
Nickel carbonyl	Inhalation	Rat (64, 32, 80)	30 mg/m^3 for 32 weeks: 1/64 pulmonary tumour 60 mg/m^3 for 32 weeks: 1/32 pulmonary tumour 250 mg/m^3 once: 1/80 pulmonary tumour	Sunderman *et al.* (1957, 1959)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel carbonyl	Inhalation	Rat	1/71 lung tumour *vs* 0/32 control	Sunderman & Donnelly (1965)
Nickel carbonyl	Intravenous	Rat (121)	19/120 lung tumours	Lau *et al.* (1972)
Nickel-enriched fly ash	Inhalation	Hamster (102)	No significant difference	Wehner *et al.* (1981, 1984)
Nickelocene	Intramuscular	Rat (50)	144 mg, 18/50 local tumours 300 mg, 21/50 local tumours	Furst & Schlauder (1971)
Nickelocene	Intramuscular	Hamster (50)	8×5 mg, 0/50 local tumour 25 mg, 4/29 local tumours	Furst & Schlauder (1971)
Nickel monoxide dust	Intratracheal	Rat (26)	1/26 lung tumour *vs* 0/47 control	Saknyn & Blokhin (1978)
Nickel selenide	Intramuscular	Rat	8/16 local tumours	Sunderman (1984)
Nickel selenide	Intramuscular	Rat	1/12 local tumour *vs* 0/79 control	Sunderman *et al.* (1984b)
Nickel subselenide	Intramuscular	Rat	21/23 local tumours	Sunderman (1984)
Nickel subselenide	Intrarenal	Rat	2/23 local tumours *vs* 0/79 control	Sunderman *et al.* (1984b)
Nickel sulfarsenide	Intramuscular	Rat	14/16 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel sulfarsenide	Intrarenal	Rat	3/15 local tumours *vs* 0/79 control	Sunderman *et al* (1984b)
Nickel telluride	Intramuscular	Rat	14/26 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel telluride	Intrarenal	Rat	0/19 local tumour	Sunderman *et al.* (1984b)
Nickel titanate	Intramuscular	Rat	No local tumour	Sunderman & McCully (1983)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel titanate	Intrarenal	Rat	0/19 local tumour	Sunderman *et al.* (1984b)
Refinery dust	Inhalation	Rat (5)	1/5 lung tumour *vs* 0/47 control	Saknyn & Blokhin (1978)
Refinery dust	Intramuscular	Mouse (40)	20/36 local tumours *vs* 0/48 control ($p < 0.01$)	Gilman & Ruckerbauer (1962)
Refinery dust	Intramuscular	Rat (35)	Dust, 19/27 local tumours Washed dust, 20/28 local tumours Controls, 0/30 local tumour	Gilman & Ruckerbauer (1962)
Refinery dust	Intraperitoneal	Rat (16, 23)	Dust 1, 3/16 local tumours Dust 2, 3/23 local tumours Controls, 0/47 local tumour	Saknyn & Blokhin (1978)

3.2 Other relevant data in experimental systems

(*a*) *Absorption, distribution, excretion and metabolism*

The results of studies on absorption, distribution, excretion, and metabolism of nickel compounds have been reviewed and/or summarized in several publications (National Research Council, 1975; Sunderman, 1977; Kasprzak, 1978; Bencko, 1983; Mushak, 1984; Sarkar, 1984; Fairhurst & Illing, 1987; Kasprzak, 1987; Sunderman, 1988; Maibach & Menné, 1989).

(i) *Nickel oxides and hydroxides*

Male Wistar rats were exposed to 0.4-70 mg/m^3 (0.6-4-μm particles) nickel monoxide aerosols for 6-7 h per day on five days per week for a maximum of three months. The clearance rate of nickel monoxide from the lung after a one-month exposure to 0.6-8 mg/m^3 (1.2-μm particles) was estimated to be about 100 μg per year. The exposure did not increase background nickel levels in organs other than the lung (Kodama *et al.*, 1985).

Electron microscopic examination of the lungs of male Wistar rats exposed to nickel monoxide aerosols (0.6-8 mg/m^3; 1.2- or 2.2-μm particles) for a total of 140-216 h showed that the particles were trapped mainly by alveolar macrophages. One year after termination of exposure, the particles were distributed in the alveoli, hilar lymphoid apparatus and terminal bronchioli. Some nickel monoxide particles were present within the lysosomes of macrophages (Horie *et al.*, 1985).

Female Wistar rats were given a single intratracheal injection of black nickel monoxide, prepared by heating nickel hydroxide at 250°C for 45 min (final product containing a mixture of nickel monoxide and nickel hydroxide; > 90% to insoluble in water; particles, 3.7 μm or less in diameter) in a normal saline suspension (100 nmol [7.5 μg] nickel monoxide in 0.2 mL). The highest concentrations of nickel were seen in the lungs and mediastinal lymph nodes, followed by the heart, femur, duodenum, kidney, pancreas, ovaries, spleen, blood and other tissues. Following injection, the concentration of nickel in the lung decreased at a much slower rate than in other tissues. By the third day after injection of nickel monoxide, about 17% of the nickel was excreted with the faeces and about 16% in the urine. By 90 days, about 60% of the dose of nickel had been excreted. half of it in the urine. The overall pattern indicates a partial transfer of nickel from lung to the mediastinal lymph nodes and slow solubilization of this product in tissue fluids (English *et al.*, 1981).

(ii) *Nickel subsulfide*

After intratracheal instillation of 11.7 μg α-^{63}Ni-nickel subsulfide powder (1-66-μm particles) in a normal saline suspension to male strain A/J mice, 38% was cleared from the lungs with a half-time of 1.2 days, while 42% was cleared with a half-time of 12.4 days;

10% of the dose was retained in the lung 35 days after instillation. The highest amounts of nickel were found in the kidney, followed by blood > liver > femur up to seven days; at 35 days, levels were greatest in kidney, followed by femur > liver > blood; maximal levels occurred 4 h after dosing and decreased rapidly thereafter with biological half-times similar to those in the lung. The urine was the primary excretion pathway; after 35 days, 100% of the nickel dose was recovered in the excreta, 60% of which was in urine (Valentine & Fisher, 1984).

The cumulative eight-week urinary excretion of nickel following intramuscular injection of ^{63}Ni-nickel subsulfide to male Fischer rats (1.2 mg/rat, 1.4 μm-particles) was 67%, while faecal excretion during that time was only 7% of the dose. The residual nickel contents at the injection site at 22 and 31 weeks after injection were 13-17% and 13-14% of the dose, respectively. The kinetics of nickel disappearance were described by a three-compartmental model, with pool sizes of 60, 27 and 11% of the dose and half-times of 14, 60 and indefinite number of days, respectively (Sunderman *et al.*, 1976).

α-Nickel subsulfide particles labelled with ^{63}Ni and ^{35}S injected intramuscularly into Fischer rats (Kasprzak, 1974) or intramuscularly and subcutaneously into NMRI mice of each sex (Oskarsson *et al.*, 1979) persisted at the injection site for several months, with a gradual loss of both ^{63}Ni and ^{35}S. In mice, nickel subsulfide was transferred to regional lymph nodes and to the reticuloendothelial cells of the liver and spleen. The presence of ^{63}Ni in the kidney and ^{35}S in the cartilage indicated solubilization of the subsulfide from the site of injection during tumorigenesis. There was no excessive or specific localization of the solubilized ^{63}Ni or ^{35}S in the tumours or in metastases. Most of the radioactivity in the tumours appeared to be associated with dust particles.

Elevated concentrations of nickel were detected in fetuses after intramuscular administration of α-nickel subsulfide to Fischer rats on day 6 of gestation (Sunderman *et al.*, 1978a).

(iii) *Nickel salts*

Intratracheal instillation of nickel chloride (100 nmol[13 μg]/rat) to female Wistar rats resulted in a fast distribution of nickel throughout the body, followed by rapid clearance. During the first six days after injection, over 60% of the dose was excreted in the urine and approximately 5% in faeces; after 90 days, these amounts had increased only slightly to 64% and 6%, respectively (English *et al.*, 1981) Similar distribution and excretion patterns were observed after intratracheal injection of nickel chloride (1.27 μg/rat Ni) to male Sprague-Dawley rats (Carvalho & Ziemer, 1982).

Pulmonary clearance and excretion of nickel following intratracheal instillation of nickel sulfate at doses of 17, 190 or 1800 nmol [1, 11 or 106 μg] Ni per rat to Fischer 344 rats

appeared to depend on the dose. At periods up to four days after instillation, lungs, trachea, larynx, kidney and urinary bladder contained the highest concentrations of nickel. The half-time for urinary excretion (the predominant route of excretion) varied from 23 h for the lowest dose to 4.6 h for the highest. Faecal excretion accounted for 30% (17- and 190-nmol doses) and 13% (1800-nmol) of the dose. The long-term half-time of nickel clearance from the lung varied from 21 h at the highest dose to 36 h at the lowest dose (Medinsky *et al.*, 1987).

In male Sprague-Dawley rats exposed to nickel chloride aerosols (90 μg/m^3 Ni; 0.7-0.9-μm particles) for 2 h per day for 14 days, the nickel burden in the lung reached a steady level after five days. The maximal clearance velocity was calculated to be 34.6 ng/g.h. These data support the hypothesis of a saturable clearance mechanism for 'soluble nickel' in the lung (Menzel *et al.*, 1987).

After intratracheal administration of 'nickel carbonate' (0.05 mg/mouse Ni) to female Swiss albino mice, most of the dose was eliminated in the urine in about 12 days (Furst & Al-Mahrouq, 1981). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

After a single intravenous injection of 10 μg nickel as ^{63}Ni-nickel chloride per mouse (albino or brown mice [strains not specified], including pregnant mice), whole-body autoradiography at 30 min showed that nickel persisted in the blood, kidney, urinary bladder, lung, eye and hair follicles; at three weeks, nickel persisted in the lung, central nervous system, kidneys, hair follicles and skin (Bergman *et al.*, 1980). In C57Bl mice, nickel was also localized in the epithelium of the forestomach; in the kidney, it was present in the cortex at sites that probably corresponded to the distal convoluted tubules. Nickel was retained much longer in the lung than in other tissues (Oskarsson & Tjälve, 1979a).

A single intravenous injection of 1 mg/kg bw ^{33}Ni-nickel chloride to male Sprague-Dawley rats resulted in rapid urinary excretion of 87% of the dose in the first day after injection and 90% after four days. Faecal excretion was much lower, up to a total of approximately 3% of the dose after four days (Sunderman & Selin, 1968). Lung and spleen were ranked after kidney as nickel-accumulating organs in Sprague-Dawley rats given an intraperitoneal injection of 82 μg/kg bw ^{63}Ni-nickel chloride (Sarkar, 1980).

The kinetics of nickel metabolism in rats and rabbits after a single intravenous injection of ^{63}Ni-nickel chloride followed a two-compartmental mathematical model, with first-order kinetics of nickel elimination from plasma with half-times of 6 and 50 h for rats and 8 and 83 h for rabbits, respectively, for the two compartments (Onkelinx *et al.*, 1973).

Following a single intraperitoneal injection of ^{63}Ni-nickel chloride to BALB/c mice (100 μCi/mouse), nickel was found to remain in the lung much longer than in any other tissue

(Herlant-Peers *et al.*, 1982). Preferential accumulation of nickel in the lung was also observed in Fischer 344 rats following daily subcutaneous injections of 62.5 or 125 μmol [8.1 or 16.3 mg]/kg bw nickel chloride for up to six weeks (Knight *et al.*, 1988). In contrast, multiple intraperitoneal injections of nickel acetate to male Swiss albino mice (0.5, 0.75 or 1.0 mg/mouse; 10, 20 or 30 daily injections each) resulted in preferential accumulation of nickel in the thymus (Feroz *et al.*, 1976).

Daily oral administration of 2.5 mg nickel sulfate per rat [strain unspecified] for 30 days resulted in accumulation of nickel in trachea > nasopharynx > skull > oesophagus > intestine > skin > liver = spleen > stomach > kidney > lung = brain > heart (Jiachen *et al.*, 1986).

Nickel was taken up from the lumen of male Sprague-Dawley rat jejunum *in vitro* at a rate proportional to the concentration of ^{63}Ni-nickel chloride in the perfusate up to 20 μM [1.2 mg] Ni. At higher concentrations (6 and 12 mg Ni), apparent saturation was approached. Nickel was not retained by the mucosa and showed a very low affinity for metallothionein (Foulkes & McMullen, 1986).

Dermal absorption of 2 or 40 μCi ^{63}Ni-nickel chloride was observed in guinea-pigs. After 1 h, nickel had accumulated in highly keratinized areas, the stratum corneum and hair shafts. Following exposure for 4-48 h, nickel also accumulated in basal and suprabasal epidermal cells. After 4 h, nickel appeared in blood and urine (Lloyd, 1980).

It has been demonstrated in several studies that nickel chloride crosses the placenta in mice (Jacobsen *et al.*, 1978; Lu *et al.*, 1979; Olsen & Jonsen, 1979; Lu *et al.*, 1981; Jasim & Tjälve, 1986) and rats (Sunderman *et al.*, 1977; Mas *et al.*, 1986).

(iv) *Other nickel compounds*

In NMRI mice, high levels of nickel were found in the respiratory tract, brain, spinal cord, heart, diaphragm, adrenal cortex, brown fat, kidney and urinary bladder 5 min to 24 h following inhalation of ^{63}Ni- and ^{14}C-nickel carbonyl at 3.05 g/m^3 Ni for 10 min (Oskarsson & Tjälve. 1979b).

After exposure of rats to nickel carbonyl by inhalation, increased levels of nickel were found predominantly in microsomal and supernatant fractions of the lung and in the microsomal fraction of the liver (Sunderman & Sunderman, 1963).

After an intravenous injection of nickel carbonyl as 22 mg/kg bw Ni to Sprague-Dawley rats, most of the subcellular nickel in liver and lung was bound to supernatant fractions, followed by nuclei and debris, mitochondria and microsomes (Sunderman & Selin, 1968).

Twenty-four hours after an intravenous injection of ^{63}Ni-nickel carbonyl (0.9 mg/kg bw Ni) to NMRI mice, nickel was found to be associated with both particulate and soluble cellular constituents of the lung, liver and kidneys. Radioactivity was detected in the gel

chromatograms of cytosols from lung, kidney and blood serum of treated mice in the void volume and salt volume (Oskarsson & Tjälve, 1979c).

Following intravenous injection of 50 μL/kg bw nickel carbonyl (22 μg/kg bw Ni) to Sprague-Dawley rats, over 38% of the dose was exhaled during 6 h after injection and none after that time. Average total urinary excretion of nickel over four days was 31% (23% within the first 12 h), whereas total faecal excretion was 2.4% and biliary excretion was 0.2%. Total average excretion of nickel in four days was 72%. Most of the remaining nickel carbonyl underwent intracellular decomposition and oxidation to nickel[II] and carbon monoxide. Twenty-four hours after the injection, nickel injected as nickel carbonyl was distributed among organs and tissues, with the highest concentration in lung (Sunderman & Selin, 1968; Kasprzak & Sunderman, 1969).

(*b*) *Dissolution and cellular uptake*

(i) *Metallic nickel and nickel alloys*

Slow dissolution and elimination of finely powdered nickel metal from the muscle injection site was observed in rats. In the local rhabdomyosarcomas that developed, nickel was recovered in the nuclear fraction and mitochondria; little or no nickel was found in the microsomes (Heath & Webb, 1967). The nuclear fraction of nickel is preferentially bound to nucleoli (Webb *et al.*, 1972).

Slow dissolution of metallic nickel occurred when nickel metal powder was incubated at 37°C with horse serum or sterile homogenates of rat muscle, liver, heart or kidney prepared in Tyrode solution. The solubilization may have involved oxygen uptake and was faster for a freshly reduced powder than for an older commercial powder; over 97% of the dissolved nickel became bound to diffusible components of the tissue homogenates (mostly histidine, followed by nucleotides, nucleosides and free bases) (Weinzierl & Webb, 1972).

(ii) *Nickel oxides and hydroxides*

The dissolution half-times of six differently prepared samples of nickel oxide and four samples of nickel-copper oxides in water were longer than 11 years. However, in rat serum and renal cytosol, the half-time dropped to about one year for a low-temperature nickel oxide and to 2.7-7.2 years for three nickel-copper oxides, the rest retaining the > 11-year value. Two preparations of nickel oxide obtained at temperatures ≤735°C and all four nickel-copper oxides appeared to be phagocytized by C3H/10T½ cells more actively than the other nickel oxides (Sunderman *et al.*, 1987).

Kasprzak *et al.* (1983) found the half-times for two preparations of nickel hydroxide (air-dried colloidal and crystalline) in an 0.1 M ammonium acetate buffer of pH 7.4 to be 56

h and 225 h, respectively. Corresponding values in an artificial lung fluid were 360 h and 1870 h, respectively.

(iii) *Nickel sulfides*

The dissolution rate of α-nickel subsulfide depends on the particle size, the presence of oxygen and the dissolving medium (Gilman & Herchen, 1963; Kasprzak & Sunderman, 1977; Dewally & Hildebrand, 1980; Lee *et al.*, 1982).

Both in vivo and in cell-free systems *in vitro*, α-nickel subsulfide reacts with oxygen to yield insoluble crystalline β-nickel sulfide and soluble nickel[II] derivatives; β-nickel sulfide also dissolves through oxidation of its sulfur moiety (Kasprzak & Sunderman, 1977; Oskarsson *et al.*, 1979; Dewally & Hildebrand, 1980). It has been suggested that the transformation of nickel subsulfide into β-nickel sulfide under anaerobic conditions in the muscle might be due to reaction with sulfur from sulfhydryl groups in the host organism (Dewally & Hildebrand, 1980).

Particles of crystalline nickel sulfides, α-nickel subsulfide and β-nickel sulfide (< 5 μm in diameter, 1-20 μg/mL) were phagocytized by cultured Syrian hamster embryo cells and Chinese hamster CHO cells, while particles of amorphous nickel sulfide were taken up only sparingly by the cells. Pretreatment of Syrian hamster embryo cells with benzo[*a*]pyrene enhanced the uptake of nickel subsulfide. The half-life of the engulfed particles was about 40 h in Syrian hamster cells; they disappeared from the cells through solubilization, and solubilized nickel was detected in the nuclear fraction (Costa & Mollenhauer, 1980a,b; Costa *et al.*, 1981a).

α-Nickel subsulfide and β-nickel sulfide were also incorporated into human embryonic L132 pulmonary cells in culture. β-Nickel sulfide was present within large intracellular vesicles; nickel subsulfide was generally bound to the membranes of intracellular vesicles, to lysosomal structures and to the outer cell membrane (Hildebrand *et al.*, 1985, 1986).

The soluble nickel derived from nickel subsulfide and β-nickel sulfide intracellularly undergoes subcellular distribution that differs from that following entry of nickel from outside the cells (Harnett *et al.*, 1982; Sen & Costa, 1986a). Treatment of cultured Chinese hamster CHO cells with β-nickel sulfide (10 μg/mL, three-day incubation) resulted in binding of nickel to DNA and RNA at a level 300-2000 times higher and to protein at a level 15 times higher than after similar treatment with nickel chloride (Harnett *et al.*, 1982). Cellular uptake of β-nickel sulfide facilitates a specific interaction of nickel with the heterochromatic long arm of the X chromosome of Chinese hamster CHO cells (Sen & Costa, 1986a). Lee *et al.* (1982) found that soluble nickel derived from nickel subsulfide forms an exceptionally stable ternary protein-nickel-DNA complex *in vitro* in the presence of DNA and rat liver microsomes.

(iv) *Nickel salts*

Soluble nickel retained in the tissues of mice becomes bound to particulate and soluble cellular constituents, the distribution depending on the tissue. In lung and liver of NMRI mice, nickel was bound predominantly to a high-molecular-weight protein; in the kidney, it was bound mainly to low-molecular-weight ultrafiltrable ligands. No nickel was bound to metallothionein or superoxide dismutase (Oskarsson & Tjälve, 1979c).

Several nickel-binding proteins were found in lung and liver cytosol of BALB/c mice that were different after incorporation *in vivo* and *in vitro*. The composition and structures of these proteins were not identified (Herlant-Peers *et al.*, 1982).

Intracellular nickel concentrations in the lungs of strain A mice given intraperitoneal injections of nickel acetate were highest in the microsomes, followed by mitochondria, cytosol and nuclei (Kasprzak, 1987).

In blood serum, nickel was sequestered mainly by albumin, which had a high binding capacity for this metal in most species tested, except for dogs and pigs (Callan & Sunderman, 1973). Nickel in human serum is chelated by histidine, serum albumin or both in a ternary complex, although a small fraction is bound to a glycoprotein (Sarkar, 1980; Glennon & Sarkar, 1982).

Less nickel chloride was taken up by Chinese hamster CHO cells than insoluble nickel sulfides; moreover, nickel incorporated from nickel chloride had a much higher affinity for cellular proteins than for DNA or RNA (Harnett *et al.*, 1982). A greater effect on the heterochromatic long arm of the X chromosome was observed when Chinese hamster CHO cells were exposed to nickel-albumin complexes encapsulated in liposomes than to nickel chloride alone (Sen & Costa, 1986a).

Cellular binding and uptake of nickel depend on the hydro- and lipophilic properties of the nickel complexes to which the cells are exposed. Nickel-complexing ligands, L-histidine, human serum albumin, D-penicillamine and ethylenediaminetetraacetic acid, which form hydrophilic nickel complexes, inhibited the uptake of nickel by rabbit alveolar macrophages, human B-lymphoblasts and human erythrocytes. The same ligands also sequestered nickel from nickel-preloaded cells. Diethyldithiocarbamate, however, which forms a lipophilic nickel complex, enhanced the cellular uptake of nickel and prevented its removal from nickel-preloaded cells. It also induced transfer of nickel in a cell lysate from the cytosol to the residual pellet (Nieboer *et al.*, 1984b). Sodium pyridinethione, which forms a lipophilic nickel complex, behaved similarly (Jasim & Tjälve, 1986).

Nickel applied to rat liver and kidney nuclei as nickel chloride bound in a dose-related manner to the chromatin and as to polynucleosomes and to the DNA molecule. In the nuclear chromatin. nickel was associated with both the DNA and histone and non-histone proteins; a ternary nickel-DNA-protein complex more stable than binary nickel-DNA

complexes was identified (Ciccarelli & Wetterhahn, 1985).

Calf thymus DNA appeared to have more than two types of binding site for nickel; DNA phosphate moieties were identified as having the highest affinity for nickel (Kasprzak *et al.*, 1986).

(v) *Other nickel compounds*

'Nickel carbonate' particles were actively phagocytized by human embryonal lung epithelial cells L132 in culture and showed an increased affinity for cytoplasmic and cell membranes (Hildebrand *et al.*, 1986). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

Following an intraperitoneal injection of 'nickel carbonate' to male Sprague-Dawley rats, nickel was found to be associated with liver and kidney nuclear DNA as early as 3 h after injection, with a further increase by 20 h. The nickel concentration in kidney DNA was five to six times higher than that in liver. Significant differences were found in the distribution of nickel between nucleic acids and associated proteins in DNA samples extracted from kidney and liver (Ciccarelli & Wetterhahn, 1984a,b). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

Sunderman *et al.* (1984b) determined dissolution half-times in rat serum and renal cytosol and phagocytic indices in peritoneal macrophages *in vitro* of various water-insoluble nickel derivatives, including nickel selenide, nickel subselenide, nickel telluride, nickel sulfarsenide, nickel arsenide, nickel arsenide tetragonal, nickel arsenide hexagonal, nickel antimonide, nickel ferrosulfide matte, a ferronickel alloy ($NiFe_{1\cdot6}$) and nickel titanate. No correlation was found between those two parameters and the carcinogenic activity of the tested compounds in the muscle of Fischer 344 rats.

(*c*) *Interactions*

Parenteral administration of soluble nickel salts induced changes in the tissue distribution of other metal ions (Whanger, 1973; Nielsen, 1980; Chmielnicka *et al.*, 1982; Nieboer *et al.*, 1984b; Nielsen *et al.*, 1984).

Several physiological divalent cations appeared to affect nickel metabolism. Thus, manganese decreased the proportion of ultrafiltrable nickel constituents of muscle homogenates; the gross muscle uptake and excretion of nickel were not affected. Metallic manganese dust also inhibited the dissolution rate of nickel subsulfide in rat serum, serum ultrafiltrate and water (Sunderman *et al.*, 1976). Manganese dust reduced the phagocytosis of nickel subsulfide particles by Syrian hamster embryo cells in vitro (Costa *et al.*, 1981a). Magnesium decreased the uptake of nickel by pulmonary nuclei and cytosol of strain A

mice and decreased nickel uptake by lung, kidney and liver of Fischer 344 rats (Kasprzak *et al.*, 1987). Both manganese and magnesium strongly antagonized the binding of nickel to the phosphate groups of calf thymus DNA *in vitro*, while copper, which did not inhibit nickel carcinogenesis, was a much weaker antagonist (Kasprzak *et al.*, 1986).

Nickel that accumulated in mouse tissues following administration of nickel carbonyl in vivo could be displaced from those tissues by treatment *in vitro* with other cations, including H^+, in proportion to their valence; Mg^{2+} and La^{3+} were the most effective (Oskarsson & Tjälve, 1979b).

Certain nickel[II]-peptide complexes in aqueous solution were found to react with ambient oxygen by a facile autocatalytic process in which nickel[III] intermediates played a major role. Such reactions may lead to degradation, e.g., decarboxylation, of the organic ligand (Bossu *et al.*, 1978). Nickel[III] was also identified in a nickel[II]-glycyl-glycyl-*n*-histidine complex, indicating possible redox effects of the nickel[III]/nickel[II] redox couple on that protein (Nieboer *et al.*, 1986).

(*d*) *Toxic effects*

The toxicity of nickel and its inorganic compounds has been reviewed (US Environmental Protection Agency, 1986; Fairhurst & Illing, 1987; World Health Organization, 1990), and the chemical basis of the biological reactivity of nickel has been discussed (Ciccarelli & Wetterhahn, 1984a; Nieboer *et al.*, 1984b,c).

(i) *Metallic nickel and nickel alloys*

The lungs of male rabbits exposed by inhalation to 1 mg/m^3 nickel metal dust (< 40 μm particles) for 6 h per day on five days per week for three and six months showed two- to three-fold increases in the volume density of alveolar type II cells. The six-month exposure caused focal pneumonia (Johansson *et al.*, 1981; Camner *et al.*, 1984).

Similar changes, resembling alveolar proteinosis, were observed in rabbits after exposure to nickel metal dust by inhalation for four weeks (Camner *et al.*, 1978). After three or six months of exposure at 1 mg/m^3, phagocytic activity *in vitro* was increased upon challenge by *Escherichia coli* (Johansson *et al.*, 1980).

A single intramuscular injection of 20 mg nickel metal dust to male WAG rats resulted in long-lasting suppression of natural killer cell activity in peripheral blood mononuclear cells. Between eight and 18 weeks after the nickel injection, the activity decreased to 50-60% of that in the control rats (Judde *et al.*, 1987).

(ii) *Nickel oxides*

Exposure of female Wistar rats by inhalation to nickel monoxide aerosols (generated at 550° C from nickel acetate) at concentrations of 200, 400 and 800 μg/m^3 for 24 h per day for 120 days resulted in a significant, dose-related reduction in growth rate, decreased kidney

and liver weights and erythrocyte count, decreased activity of serum alkaline phosphatase, increased wet lung weight and leukocyte count and increased mean erythrocyte cell volume (Weischer *et al*., 1980a,b).

Male Wistar rats exposed continuously to nickel monoxide (generated at 550°C from nickel acetate) aerosols at 50 μg/m^3 (median particle diameter, 0.35 μm) for 15 weeks showed no significant difference in the overall ability of the lungs to clear ferrous oxide up to day 7. After that time, lung clearance in nickel oxide-exposed rats decreased significantly. The half life of ferrous oxide clearance after day 6 was 58 days for control rats and 520 days for nickel oxide-exposed rats; in excised lungs, the values were 56 and 74 days, respectively (Oberdoerster & Hochrainer, 1980).

An increase in lung weight (six-fold) and alveolar proteinosis were observed in male Wistar rats that died during life-time exposure to an aerosol of nickel monoxide (produced by pyrolysis of nickel acetate [probably at 550°C] [particle size unspecified]) at 60 or 200 μg/m^3, 23 h per day, seven days per week. With longer exposures, marked accumulation of macrophages and focal septal fibrosis were also observed (Takenaka *et al.*, 1985).

No significant histopathological change was found in male Wistar rats exposed to green nickel oxide (0.6 μm particles) for up to 12 months at 0.3 or 1.2 mg/m^3, 7 h per day on five days per week (Tanaka *et al.*, 1988).

No mortality was observed following exposure by inhalation of Fischer 344/N rats and B6C3F$_1$, mice to nickel monoxide (formed at 1350°C; 3 μm particles) at 0.9-24 mg/m^3 Ni for 6 h/day on five days per week for 12 days. Lung inflammation and hyperplasia of alveolar macrophages occurred primarily at the highest exposure concentration in both species; generally, the lung lesions in mice were less severe than those in rats. Atrophy of the olfactory epithelium was seen only in two rats at the highest dose, while atrophy of the thymus and hyperplasia of the lymph nodes were seen in both rats and mice exposed to the highest concentrations (Dunnick *et al.*, 1988).

In Syrian golden hamsters, life-time inhalation of 53 mg/m^3 nickel monoxide ([unspecified] 0.3 μm particles) for 7 h per day resulted in emphysema in animals that died early in the experiment. Other lung effects included interstitial pneumonitis and diffuse granulomatous pneumonia, fibrosis of alveolar septa, bronchiolar (basal-cell) hyperplasia, bronchiolization of alveolar epithelium, squamous metaplasia and emphysema and/or atelectasia of various degrees (Wehner *et al.*, 1975).

The median lethal concentration for rat macrophages exposed *in vitro* to green nickel monoxide exceeded 12 μmol (708 μg)/mL Ni. The LC_{50} for canine macrophages was 3.9 μmol (230 μg)/mL Ni as nickel monoxide for 20 h. Nickel monoxide was far less toxic to macrophages than nickel sulfate, nickel chloride or nickel subsulfide (Benson *et al.*, 1986a).

The toxicity of six different preparations of nickel monoxide calcined at temperatures of <650-1045°C and four mixed nickel-copper oxides was tested *in vitro* on alveolar macrophages of beagle dogs, Fischer 344 rats and $B6C3F_1$ mice. Nickel oxides were less toxic to the macrophages than were the nickel-copper oxides; the toxicity of the nickel-copper oxides increased with increasing copper content. Generally, dog macrophages were more sensitive to the oxides than mouse and rat macrophages (Benson *et al.*, 1988a).

The ability of the same oxides to stimulate erythropoiesis in Fischer 344 rats correlated well with their cell transforming ability in Syrian hamster embryo cells (see also genetic and related effects; Sunderman *et al.*, 1987).

(iii) *Nickel sulfides*

The LD_{50} after a single instillation in $B6C3F_1$ mice of nickel subsulfide (particle size, <2 μm) in a normal saline suspension was 4 mg/kg bw (Fisher *et al.*, 1986).

Acute toxic effects of nickel subsulfide (1.8 μm particles) administered intratracheally to male BALB/c mice (12 μg/mouse) included pulmonary haemorrhaging, most evident three days after exposure. The number of polymorphonuclear cells in the pulmonary lavage fluid was increased, whereas the number of macrophages tended to decrease below the control values later (20 h to seven days) after the exposure (Finch *et al.*, 1987).

Alveolitis was observed in Fischer 344 rats following intratracheal instillation of nickel subsulfide as a saline/gelatin suspension (3.2-320 μg/kg bw). The effects closely resembled those of nickel chloride and nickel sulfate at comparable doses of nickel. Pulmonary lesions also included type II cell hyperplasia with epithelialization of alveoli and, in some animals, fibroplasia of the pulmonary interstitium (Benson *et al.*, 1986b).

Chronic active inflammation, fibrosis and alveolar macrophage hyperplasia were observed in Fischer 344 rats and $B6C3F_1$ mice exposed by inhalation to nickel subsulfide (low-temperature form) for 13 weeks (6 h per day, five days per week; 0.11-1.8 mg/m^3 Ni). The toxicity of nickel subsulfide to the lung resembled that of nickel sulfate hexahydrate, and both were more toxic than nickel oxide. Rats were more sensitive than mice (Dunnick *et al.*, 1989).

Administration of nickel subsulfide to female rats as a single intrarenal injection caused pronounced erythrocytosis (Jasmin & Riopelle, 1976; Oskarsson *et al.*, 1981). A single intrarenal injection of nickel subsulfide to male rats also caused an increase in renal haem oxygenase activity; no correlation between the induction of haem oxygenase and erythrocytosis was observed (Sunderman *et al.*, 1983a). Administration of nickel sulfide [probably amorphous] in glycerine or saline into each pole of the kidney of female rats did not induce renal erythropoietic activity (Jasmin & Riopelle, 1976).

Under comparable exposure *in vitro*, beagle dog alveolar macrophages were more sensitive to the toxicity of nickel subsulfide than were those of Fischer 344 rats. Nickel subsulfide appeared to be much more toxic to the macrophages of both species than nickel chloride, nickel sulfate or nickel monoxide (Benson *et al.*, 1986a).

Nickel subsulfide incubated with calf thymus histones in the presence of molecular oxygen caused random polymerization of those proteins; this effect was not produced by soluble nickel acetate (Kasprzak & Bare, 1989).

(iv) *Nickel salts*

The oral LD_{50} of nickel acetate was 350 mg/kg bw in rats and 420 mg/kg bw in mice; the intraperitoneal LD_{50} was 23 mg/kg bw in rats (National Research Council, 1975). The LD_{50} of nickel acetate in ICR mice after an intraperitoneal injection was 97 mg/kg bw in females and 89 mg/kg bw in males at days 3 and 5 for three-week-old animals and 39-54 mg/kg bw in nine- or 14-week-old animals of either sex (Hogan, 1985). With nickel chloride, intraperitoneal LD_{50} values of 6-9.3 mg/kg bw Ni were reported for female Wistar rats (Mas *et al.*, 1985), 11 mg/kg bw rats and 48 mg/kg bw for mice (National Research Council, 1975).

Exposure of $B6C3F_1$, mice and Fischer 344/N rats to nickel sulfate hexahydrate by inhalation for 6 h per day for 12 days (five days per week plus two consecutive days; 0.8-13 mg/m^3 Ni; 2 μm particles) caused death of all mice at concentrations of ≥1.6 mg/m^3 and of some rats at concentrations of 13 mg/m^3. Lesions of the lung and nasal cavity were observed in both mice and rats after exposure to 0.8 mg/m^3 nickel or more; these included necrotizing pneumonia, chronic inflammation and degeneration of the bronchiolar epithelium, atrophy of the olfactory epithelium, and hyperplasia of the bronchial and mediastinal lymph nodes (Benson *et al.*, 1988b; Dunnick *et al.*, 1988).

A single intratracheal instillation of nickel chloride hexahydrate or nickel sulfate hexahydrate to Fischer 344/Cr1 rats (0.01, 0.1 or 1.0 μmol [0.59, 5.9 or 59 μg Ni/rat) caused alveolitis and affected the activities of several enzymes measured in the pulmonary lavage fluid (Benson *et al.*, 1985, 1986b).

Rabbits were exposed to nickel chloride (0.2-0.3 mg/m^3 Ni) for 6 h per day on five days per week for one to eight months. Nodular accumulation of macrophages was seen in lung tissue, and the volume density of alveolar type II cells was elevated. The phagocytic activity of macrophages was normal after one month of exposure but was decreased after three months (Camner *et al.*, 1984; Lundborg & Camner, 1984; Camner *et al.*, 1985).

Exposure of Syrian golden hamsters to a nickel chloride aerosol (100-275 μg/m^3 Ni; <2-μm particles) for 2 h per day for one or two days resulted in a dose-related decrease in the ciliary activity of the tracheal epithelium and in mucosal degeneration (Adalis *et al.*, 1978).

A single intramuscular injection of nickel chloride (18.3 mg/kg bw) to male CBA/J mice caused significant involution of the thymus within two days. Significant reduction in the mitogen-stimulated responses of B and T lymphocytes *in vitro* as well as significant suppression of the primary antibody response (T-cell-dependent) to sheep red blood cells were observed after the treatment. Natural killer cell activity was also suppressed. The immunosuppressive effects of nickel chloride lasted for a few days. The activity of peritoneal macrophages was not affected (Smialowicz *et al.*, 1984, 1985).

Following a single intramuscular injection of 10-20 mg/kg bw nickel chloride into Fischer 344 rats, the activity of natural killer cells was transiently suppressed for three days. In contrast to mice, rats showed no significant difference in the lymphoproliferative responses of splenocytes to B and T mitogens from those of controls (Smialowicz *et al.*, 1987).

Intramuscular injection of nickel chloride (20 mg/kg bw Ni) to Fischer 344 rats 4 h before death inhibited thymidine uptake into kidney DNA (Hui & Sunderman, 1980). An immediate, significant decrease, followed by a transient sharp increase of thymidine incorporation into pulmonary DNA was observed in strain A mice following intraperitoneal administration of nickel acetate (Kasprzak & Poirier, 1985).

After 90 daily intraperitoneal injections of nickel sulfate (3 mg/kg bw Ni) to male albino rats, focal necrosis of the proximal convoluted tubules in the kidneys and marked cellularity around periportal areas and necrotic areas in the liver were observed. Bile-duct proliferation and Kupffer-cell hyperplasia were also evident, and degenerative changes were observed in a few seminiferous tubules and in the inner wall of the myocardium (Mathur *et al.*, 1977a).

Subcutaneous injection of up to 0.75 mmol [98 mg]/kg bw nickel chloride to male Fischer 344 rats increased lipid peroxidation in the liver, kidney and lung in a dose-related manner (Sunderman *et al.*, 1985b).

Renal, hepatic, pulmonary and brain haem oxygenase activity was induced after subcutaneous injection of 15 mg/kg bw nickel chloride to male Fischer 344 rats. Induction of haem oxygenase was also observed in the kidneys of male BL6 mice, male Syrian golden hamsters and male guinea-pigs killed 17 h after subcutaneous injection of 0.25 mmol [32 mg]/kg bw nickel chloride (Sunderman *et al.*, 1983a).

The skin of male albino rats was painted once daily for up to 30 days with 0.25 mL nickel sulfate hexahydrate solution in normal saline (40, 60 and 100 mg/kg bw Ni). The 30-day painting caused atrophy in some areas and acanthosis in other areas of the epidermis, disorder in the arrangement of epidermal cells and hyperkeratinization. Liver damage, including focal necrosis, was seen in histological studies (Mathur *et al.*, 1977b).

The toxicity of nickel sulfate and nickel chloride to alveolar macrophages from beagle dogs and Fischer 344 rats *in vitro* was intermediate to that of nickel subsulfide and nickel monoxide (median lethal concentrations, 0.30-0.36 μmol [17.7-21.2 μg] and 3.1-3.6 μmol [183-212 μg]/mL Ni for dog and rat macrophages, respectively) (Benson *et al.*, 1986a). Macrophages lavaged from rabbit lungs and incubated for two days with 3-24 μg/mL Ni as nickel chloride showed a decrease of up to 50% in lysozyme activity with increasing concentrations of nickel (Lundborg *et al.*, 1987).

Although nickel salts inhibit the proliferation of normal mammalian cells in culture, nickel sulfate hexahydrate increased proliferation of some lymphoblastoid cell lines carrying the Epstein-Barr virus (Wu *et al.*, 1986).

Exposure of Syrian hamster embryo cells to nickel chloride or nickel sulfate at a concentration of 10 μmol [600 μg]/L Ni or more enhanced nucleoside excretion (Uziel *et al.*, 1986).

Nickel chloride inhibited the transcription of calf thymus DNA and phage T4 DNA with *Eschenchia coli* RNA polymerase in a concentration-dependent manner (0.01-10 mM [0.6-600 mg] Ni). It also stimulated RNA chain initiation at very low concentrations (maximal at 0.6 mg), followed by a progressive decrease in initiation at concentrations that significantly inhibited overall transcription (Niyogi *et al.*, 1981).

(v) *Other nickel compounds*

Animals exposed to nickel carbonyl by inhalation developed pulmonary oedema within 1 h. LC_{50} values (30-min exposure) reported include 67 mg/m^3 for mice, 240 mg/m^3 for rats and 190 mg/m^3 for cats (National Research Council, 1975). Even after administration by other routes, the lung is the main target organ (Hackett & Sunderman, 1969); the LD_{50} for rats was 65 mg/kg, 61 mg/kg and 38 mg/kg after intravenous, subcutaneous and intraperitoneal administration, respectively (National Research Council, 1975).

Male Wistar rats exposed by inhalation to 0.03-0.06 mg/L nickel carbonyl for 90 min three times a week for 52 weeks developed extensive inflammatory lesions in the lung, contiguous pericarditis and suppurative lesions of the thoracic walls. Squamous-cell metaplasia was present in bronchiectatic walls of several rats (Sunderman *et al.*, 1957).

Exposure of female Fischer 344 rats by inhalation to 1.2-6.4 μmol [0.2-1.1 mg]/L nickel carbonyl for 15 min caused acute hyperglycaemia (Horak *et al.*, 1978). Urinary excretion of proteins and amino acids indicated nephrotoxicity (Horak & Sunderman, 1980).

After exposure of rats to 0.6 mg/L nickel carbonyl by inhalation, RNA derived from the lung showed alterations in the phase transition curve, indicating disruption of hydrogen bonds (Sunderman, 1963). Nickel carbonyl administered intravenously at an LD_{50} dose of

20 mg/kg bw nickel to Sprague-Dawley rats inhibited cortisone-induced hepatic tryptophan pyrrolase (Sunderman, 1967), orotic acid incorporation into liver RNA *in vivo* and *in vitro* (Beach & Sunderman, 1969, 1970) and incorporation of leucine into liver and lung protein (Witschi, 1972). Intravenous administration of nickel carbonyl to Fischer 344 rats (20 mg/kg bw nickel) caused a significant decrease in thymidine incorporation into liver and kidney DNA 4 h later (Hui & Sunderman, 1980).

The toxicity of 'nickel carbonate' to human embryo pulmonary epithelium L132 cells in culture did not differ significantly from that of nickel chloride at the same 25-150 μM concentration range applied (Hildebrand *et al.*, 1986). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

A highly significant correlation was found between carcinogenic potential and the incidence of erythrocytosis for various water-insoluble nickel compounds, including nickel selenide, nickel subselenide, nickel telluride, nickel sulfarsenide, nickel arsenide, nickel arsenide tetragonal, nickel arsenide hexagonal, nickel antimonide, nickel ferrosulfide matte, a ferronickel alloy ($NiFe_{1\cdot6}$) and nickel titanate (Sunderman *et al.*, 1984b).

Dusts of nickel-converter mattes (58% nickel sulfide, 11% metallic nickel, 2% nickel monoxide, 1% copper, 0.5% cobalt, 0.2% soluble nickel salts), a nickel concentrate (67% total nickel, 57% nickel sulfide) and two nickel-copper mattes (27-33% nickel sulfides, ~3% metallic nickel, 23-36% copper) were administered to white rats and mice by inhalation or by intragastric, intratracheal or intraperitoneal routes and onto the skin. The intratracheal LD_{50} was 200-210 mg/kg bw for the mattes and 220 mg/kg for the nickel concentrate. The intraperitoneal LD_{50} varied from 940 mg/kg bw for the nickel concentrate to 1000 mg/kg bw for the nickel-copper mattes and 1100 mg/kg bw for the nickel matte. Mice and rats were almost equally sensitive. Chronic exposure of rats and mice by inhalation to the same dusts caused bronchitis, perivasculitis, bronchopneumonia and fibrosis. Haemorrhagic foci and atrophy were observed in the kidneys (Saknyn *et al.*, 1976).

(*e*) *Effects on reproduction and prenatal toxicity*

The embryotoxicity and genotoxicity of nickel, both directly to the mammalian embryo and indirectly through maternal injury, have been reviewed (Léonard & Jacquet, 1984).

(i) *Metallic nickel and nickel alloys*

Treatment of chick embryo myoblasts with 20-40 μg nickel powder per litre of culture fluid prevented normal differentiation of cells, with only a few mitoses seen after five days' incubation. Reduction of cell division was coupled with cell degeneration, resulting in

small colony size. At concentrations of 80 μg/L nickel, extensive degeneration of the cultures and complete suppression of mitosis occurred within five days (Daniel *et al.*, 1974).

(ii) *Nickel sulfides*

Nickel subsulfide (80 mg/kg bw Ni) administered intramuscularly to Fischer rats on day 6 of gestation reduced the mean number of live pups per dam. No anomaly was found, and no evidence of maternal toxicity was reported (Sunderman *et al.*, 1978a). In another study, intrarenal injection of nickel subsulfide (30 mg/kg bw Ni) to female rats prior to breeding produced intense erythrocytosis in pregnant dams but not in the pups, which had reduced blood haematocrits at two weeks (Sunderman *et al.*, 1983b).

Both rats and mice administered 5 or 10 mg/m^3 nickel subsulfide aerosols by inhalation for 12 days developed degeneration of testicular germinal epithelium (Benson *et al.*, 1987).

(iii) *Nickel salts*

Studies on the teratogenic effects of nickel chloride in chick embryos have produced conflicting results, perhaps due to differences in dose and route of administration. Cardiac anomalies (Gilani, 1982), exencephaly and distorted skeletal development (Gilani & Marano, 1980) have been reported, whereas some authors found no nickel-induced anomaly (Ridgway & Karnofsky, 1952; Anwer & Mehrotra, 1986).

Embryo cultures from BALB/c mice were used to determine the mechanism of preimplantation loss of embryos derived from matings three and four weeks after treatment of males with 40 or 56 mg/kg bw nickel nitrate. Treated and control animals were allowed to mate with superovulated females and the number of cleaved eggs and the development of embryos to blastocysts and implantations were counted. Neither the fertilizing capacity of spermatozoa nor the development of cultured embryos was influenced by a dose of 40 mg/kg bw. A dose of 56 mg/kg bw significantly reduced the fertilization rate but did not affect the development of two-cell embryos. The results suggest that preimplantation loss after exposure to nickel is due to toxic effects on spermatids and spermatogonia rather than to zygotic death (Jacquet & Mayence, 1982).

Following daily intragastric administration of 25 mg/kg bw nickel sulfate to male white rats over a period of 120 days, severe lesions in germ-cell development in the testis were observed (Waltscheva *et al.*, 1972). Rats administered nickel sulfate by inhalation for 12 days developed testicular degeneration (Benson *et al.*, 1988b).

Groups of three to five male albino rats received subcutaneous injections of 0.04 mmol [6.2 mg]/kg bw nickel sulfate either as a single dose or as daily doses for up to 30 days.

Treatment interfered to some degree with spermatogenesis, but this was temporary, and the testes ultimately recovered (Hoey, 1966).

Preimplantation embryos from NMRI mice (two- and four- to eight-cell stages) were cultured with nickel chloride hexahydrate; 10 μM (2.5 mg) adversely affected the development of day 2 embryos (two-cell stage), whereas 300 μM (71.3 mg) were required to affect day 3 embryos (eight-cell stage) (Storeng & Jonsen, 1980). In order to compare the effects of nickel chloride hexahydrate on mouse embryos treated *in vivo* by intraperitoneal injection during the preimplantation period, a single injection of 20 mg/kg bw nickel chloride was given to groups of female mice on day 1, 2, 3, 4, 5 or 6 of gestation. On day 19 of gestation, the implantation frequency in females treated on day 1 was much lower than that of controls. The litters of the control group were larger, and significantly so, among mice treated on days 1, 3 and 5 of gestation; the body weight of fetuses was also decreased on day 19. Nickel chloride may thus adversely affect mouse embryos during the passage through the oviduct, with subsequent effects after implantation. Data on maternal effects were not presented (Storeng & Jonsen, 1981).

Long-Evans rats born in a laboratory especially designed to avoid environmental contamination from trace metals were administered nickel [salt unspecified] at 5 mg/L in the drinking-water in five pairs. About one-third of the offspring in the first generation were runts, and one maternal death occurred. In the second generation, there were 10% young deaths with only 5% runts and, in the third generation, 21% young deaths with 6% runts. Thus, the size of the litters decreased somewhat with each generation and, with some failures in breeding, the number of rats was reduced (Schroeder & Mitchener, 1971). A subsequent study, reported in an abstract, found similar effects on reproduction through two generations of rats following administration of 500 mg/L nickel chloride in drinking-water. There was no decrease in maternal weight gain or other maternal effect (Kimmel *et al.*, 1986).

Nickel chloride was administered in the drinking-water to female rats at a concentration of 0.1 or 0.01 mg/L Ni for seven months and then during pregnancy. Embryonic mortality was 57% among nine rats exposed to the higher concentration, compared to 34% among eight controls. At the lower concentration no such difference was observed (Nadeenko *et al.*, 1979).

Nickel chloride (1.2-6.9 mg/kg bw Ni) was administered intraperitoneally to pregnant ICR mice on single days between days 7-11 of gestation. Increased resorption, decreased fetal weight, delayed skeletal ossification and a high incidence of malformations were observed in a dose-related fashion on gestation day 18. The malformations consisted of acephaly, exencephaly, cerebral hernia, open eyelids, cleft palate, micromelia, ankylosis of the extremities, club foot and other skeletal abnormalities. Five of 27, 6/25 and 7/24 dams

receiving 4.6 mg/kg bw or more died within 72 h after injection on days 9, 10 and 11 (Lu *et al.*, 1979).

Fischer rats were administered nickel chloride (16 mg/kg bw Ni) intramuscularly on day 8 of gestation. The body weight of fetuses on day 20 of gestation and of weanlings four to eight weeks after birth were reduced. No congenital anomaly was found in fetuses from nickel-treated dams, or in rats that received ten intramuscular injections of 2 mg/kg bw Ni as nickel chloride twice daily from day 6 to day 10 of gestation (Sunderman *et al.*, 1978a).

Groups of pregnant Wistar rats were given nickel chloride (1, 2 or 4 mg/kg bw Ni) by intraperitoneal injection on days 8, 12 and 16 of pregnancy and were sacrificed on day 20. More malformations occurred when nickel was administered during organogenesis than after, and their occurrence was maximal at dose levels that were toxic to dams. The abnormalities included hydrocephalus, haemorrhage, hydronephrosis, skeletal retardation and one heart defect (Mas *et al.*, 1985).

(iv) *Other nickel compounds*

Nickel carbonyl (11 mg/kg bw Ni) was injected intravenously into pregnant Fischer rats on day 7 of gestation. On day 20, fetal mortality was increased, the body weight of live pups was decreased and there was a 16% incidence of fetal malformations, including anophthalmia, microphthalmia, cystic lungs and hydronephrosis. No information was given regarding maternal toxicity (Sunderman *et al.*, 1983b).

Fischer rats were exposed on day 7 or 8 of gestation by inhalation to nickel carbonyl at concentrations of 80, 160 or 360 mg/m^3 for 15 min. Ophthalmic anomalies (anophthalmia and microphthalmia) were observed in 86/511 fetuses from 62 pregnancies; they were most prevalent at the highest dose level and were not observed when the compound was given on day 9 of gestation (Sunderman *et al.*, 1979b). In another experiment, pregnant rats exposed to 60 or 120 mg/m^3 nickel carbonyl by inhalation for 15 min on day 8 of gestation also had a high incidence of ocular anomalies. Maternal toxicity was not reported (Sunderman *et al.*, 1978b).

Groups of pregnant hamsters were administered 60 mg/m^3 nickel carbonyl by inhalation for 15 min on days 4, 5, 6, 7 or 8 of gestation. Dams were sacrificed on day 15 and the fetuses examined for malformation. Exposure on days 4 and 5 of gestation resulted in malformations in about 5.5% of the progeny, which included cystic lung, exencephaly, fused rib, anophthalmia, cleft palate and haemorrhage into the serous cavities. Nine of 14 dams lived until day 16 of gestation. Haemorrhages were not observed in controls. Among the fetuses of dams exposed to nickel carbonyl on day 6 or 7 of gestation, one fetus had fused ribs and two had hydronephrosis. For pregnancies allowed to reach full-term, there was no significant difference on the day of delivery between pups from nickel carbonyl-exposed litters and controls. Neonatal mortality was increased (Sunderman *et al.*, 1980).

(*f*) *Genetic and related effects*

Many reviews of the genetic effects of nickel compounds have been published (Heck & Costa, 1982; Christie & Costa, 1984; Costa & Heck, 1984; Hansen & Stern, 1984; Reith & Brøgger, 1984; Costa & Heck, 1986; Fairhurst & Illing, 1987; Sunderman, 1989).

The genotoxic effects of different nickel compounds are divided into five categories: (i) those for metallic nickel; (ii) those for nickel oxides and hydroxides; (iii) those for crystalline nickel sulfide, crystalline nickel subsulfide and amorphous nickel sulfide; (iv) those for nickel chloride, nickel sulfate, nickel acetate and nickel nitrate; and (v) those for nickel carbonate, nickelocene, nickel potassium cyanide and nickel subselenide. The studies on these compounds are summarized in Appendix 1 in this volume.

(i) *Metallic nickel*

Nickel powder was reported not to induce chromosomal aberrations in cultured human peripheral lymphocytes [details not given] (Paton & Allison, 1972).

Nickel powder ground to a mean particle size of 4-5 μm at concentrations of 5, 10 and 20 μg/mL caused a dose-dependent increase in morphological transformation of Syrian hamster embryo cells (Costa *et al.*, 1981b). At 20 μg/mL, nickel powder produced a 3% incidence of transformation, while crystalline nickel subsulfide and crystalline nickel sulfide (at 10-20 μg/mL) produced a 10-13% incidence of transformation and 5 and 10 μg/mL of amorphous nickel sulfide induced none. Nickel powder inhibited progression through S phase in Chinese hamster CHO cells, as measured by flow cytometry (Costa *et al.*, 1982).

Hansen and Stern (1984) reported that nickel powder transformed BHK 21 cells [see General Remarks for concern about this assay]. Proliferation in soft agar was used as the endpoint. At equally toxic doses, they found that nickel powder and crystalline nickel subsulfide had similar transforming activities; the toxicity of 200 μg/mL nickel powder was equal to that of 10 μg/mL nickel subsulfide.

(ii) *Nickel oxides*

Nickel monoxide and nickel trioxide in distilled water gave negative results in the *Bacillus subtilis* rec^+/rec^- assay for differential toxicity at concentrations ranging from 5 to 50 mM (Kanematsu *et al.*, 1980). [The Working Group noted that since particulate nickel compounds such as these are relatively insoluble and their entry into mammalian cells requires phagocytosis (Costa & Mollenhauer, 1980a,b,c), it is unlikely that they were able to enter the bacteria.]

Chromosomal aberrations were not induced in human peripheral lymphocytes by treatment *in vitro* with nickel monoxide [details not given] (Paton & Allison, 1972).

Nickel monoxide and nickel trioxide transformed Syrian hamster embryo cells at concentrations of 5-20 μg/mL. The activity of the trioxide was about twice that of the monoxide, similar to that of metallic nickel and about 20% that of crystalline nickel sulfide (Costa *et al.*, 1981a,b).

Nickel monoxide that was calcined at a low temperature had greater transforming activity in this system than nickel monoxide calcined at a high temperature at concentrations of 5 and 10 μg/mL and was equivalent to that of crystalline nickel sulfide. The cell-transforming activity of these nickel compounds was reported to correlate well with their ability to induce preneoplastic changes in rats (Sunderman *et al.*, 1987).

Syrian hamster BHK 21 cells were transformed by nickel monoxide and by a nickel oxide catalyst identified as $NiO_{1\cdot4}(3H_2O)$. At equally toxic doses, nickel monoxide had the same transforming activity as did nickel subsulfide. [See General Remarks for concern about this assay.] The nickel oxide catalyst, $NiO_{1\cdot4}$, had similar toxicity and transforming capacity as nickel subsulfide (Hansen & Stern, 1983, 1984).

The ability of 50 μM nickel monoxide to induce anchorage-independent growth in primary human diploid foreskin fibroblasts was similar to that of 10 μM nickel subsulfide or nickel acetate. The absolute numbers of anchorage-independent colonies induced al these doses were 26 with nickel monoxide, 67 with nickel subsulfide, 79 with nickel sulfide (10 μM) and about 42 with nickel acetate, compared with none in cultures of untreated cells. The frequency of anchorage-independent growth induced by nickel monoxide was about three-fold less than with nickel subsulfide, but was equivalent to that obtained with nickel acetate. The transformed cells had 33- to 429-fold higher plating efficiency in agar than the parental cells; anchorage-independence was stable for eight passages only (Biedermann & Landolph (1987).

Nickel oxide inhibited progression through S phase in Chinese hamster CHO cells, as measured by flow cytometry (Costa *et al.*, 1982).

(iii) *Nickel sulfides (crystalline nickel sulfide, crystalline nickel subsulfide and amorphous nickel sulfide)*

Crystalline nickel sulfide and nickel subsulfide were actively phagocytized by cells at an early stage following their addition to tissue cultures. Phagocytosis was dependent upon the calcium concentration in the medium (Abbracchio *et al.*, 1982a) and particle size (particles > 5-6 μm were much less actively taken up and much less toxic than smaller particles) (Costa & Mollenhauer, 1980a,b,c). Particles are taken up in areas of active cell ruffling,

internalized and moved about the cell in a saltatory motion; lysosomes repeatedly interact with the particles, which are contained in the perinuclear region and sometimes inside cytoplasmic vacuoles, where they slowly dissolve, releasing nickel ions (Evans *et al.*, 1982). Interaction between lysosomes and nickel sulfide particles may result in exposure of the particles to the acidic content of the lysosomes, and this interaction may accelerate intracellular dissolution of crystalline nickel sulfide to ionic nickel (Abbracchio *et al.*, 1982a). In contrast, amorphous nickel sulfide and nickel particles were not significantly taken up by cells *in vitro* (Costa *et al*, 1981a). Crystalline nickel sulfide particles differ from amorphous particles in that they have a negative surface charge, as shown using Z-potential measurements and binding of the particles to filter-paper discs offering different charges (Abbracchio *et al.*, 1982b). Alteration of the positive charge of amorphous nickel sulfide particles by treatment with lithium aluminium hydride results in activation of phagocytosis (Abbracchio *et al.*, 1982b; Costa, 1983).

Crystalline nickel sulfide was actively phagocytized by the protozoan *Paramaecium tetraurelia* and induced lethal genetic damage in parent cells. The activity of nickel subsulfide was more consistent than that of nickel sulfide, but both compounds produced higher mutagenic activities than glass beads, used as a control. The concentrations used ranged from 0.5 to 54 μg/mL; both compounds showed greatest mutagenicity at 0.5 μg/mL, as higher levels were toxic (Smith-Sonneborn *et al.*, 1983).

Crystalline nickel subsulfide at 5, 10 and 50 μg/mL inhibited DNA synthesis in the rat liver epithelial cell line T51B (Swierenga & McLean, 1985). Nickel subsulfide inhibited progression through S phase in Chinese hamster CHO cells, as measured by flow cytometry (Costa *et al.*. 1982).

Crystalline nickel sulfide and nickel subsulfide were active in inducing DNA damage in cultured mammalian cells. Crystalline nickel sulfide induced DNA strand breaks in rat primary hepatocytes (Sina *et al*, 1983) and, at 1-20 μg/mL, single-strand breaks in tritium-labelled DNA in cultured Chinese hamster ovary cells, as determined using alkaline sucrose gradients (Robison & Costa, 1982). Using the same technique, Robison *et al.* (1982) showed that crystalline nickel subsulfide also induced strand breaks, whereas amorphous nickel sulfide, which is not phagocytized by cells, did not. As observed with alkaline elution analysis, crystalline nickel sulfide induced two major types of lesion — single-strand breaks and DNA protein cross-links (Costa *et al.*, 1982; Patierno & Costa, 1985). Treatment of primary Syrian hamster embryo cells with crystalline nickel subsulfide at 10 μg/mL and Chinese hamster CHO cells with crystalline nickel sulfide at 1-5 μg/mL induced DNA repair, as determined by analysis with caesium chloride gradients. Amorphous nickel sulfide had no effect in either cell type (Robison *et al.*, 1983).

Crystalline nickel subsulfide and amorphous nickel sulfide induced a weak mutation response at the *hprt* (6-thioguanine and 8-azaguanine resistance) locus in Chinese hamster ovary cells (Costa *et al.*, 1980).

Mutation to 8-azaguanine resistance was induced in a cultured rat liver epithelial cell line T51B treated with particulate crystalline nickel subsulfide at concentrations ranging from 5 to 50 μg/mL. At noncytotoxic doses, the mutagenic activity was four-fold above background, and at cytotoxic doses it was 20-fold above background. The mutagenic activity of dissolved products of these particles (at 12.5-20 μg/mL) was about two-fold above background at noncytotoxic doses and 20-fold above background at cytotoxic doses. Neither dissolved nor particulate nickel subsulfide at 2-27 μg/mL induced unscheduled DNA synthesis in rat primary hepatocytes (Swierenga & McLean, 1985). Nickel subsulfide, however, was reported to inhibit unscheduled DNA synthesis induced in primary rat hepatocytes by methyl methane sulfonate [details not given] (Swierenga & McLean, 1985). Concentrations of 0.5-10 μM nickel subsulfide did not induce 8-azaguanine or 6-thioguanine resistance in primary human fibroblasts (Biedermann & Landolph, 1987).

Crystalline nickel sulfide (0.1-0.8 μg/cm^2) was mutagenic in monolayer cultures in Chinese hamster V79 cells in which the endogenous *hprt* gene had been inactivated by a mutation and a single copy of a bacterial *gpt* gene had been inserted (Christie *et al.*, 1992).

The frequency of sister chromatid exchange was increased in cultured human lymphocytes treated with nickel subsulfide at 1-10 μg/mL (Saxholm *et al.*, 1981).

Chromosomal aberrations were induced in cultured mouse mammary carcinoma Fm3A cells following treatment with 4-8 $\times$ 10^{-4} M crystalline nickel sulfide dissolved in medium and filtered. The early chromosomal aberrations consisted of gaps; following reincubation in control medium after treatment, gaps, breaks, exchanges and other types of aberration were observed (Nishimura & Umeda, 1979; Umeda & Nishimura, 1979). [The Working Group noted that the chemical form of nickel used in this study is not known.]

Treatment of Chinese hamster ovary cells with crystalline nickel sulfide at 5-20 μg/mL for 6-48 h produced a dose- and time-dependent increase in the frequency of chromosomal aberrations, which were selective for heterochromatin and included mostly gaps and breaks, with some exchanges and dicentrics (Sen & Costa, 1985). Crystalline nickel sulfide at 1-10 μg/mL also increased the frequency of sister chromatid exchange in a dose-dependent fashion, selectively in heterochromatic regions, in both Chinese hamster ovary cells (Sen & Costa, 1986b) and mouse C3H/10T½ cells (Sen *et al.*, 1987).

A dose-dependent increase in the frequency of morphological transformation was induced in primary Syrian hamster embryo cells by treatment with crystalline nickel subsulfide at 1-5 μg/mL for nine days (DiPaolo & Casto, 1979) and by either crystalline nickel sulfide or nickel subsulfide at 0.1-10 μg/mL for 48 h (Costa *et al.*, 1979; Costa, 1980; Costa & Mollenhauer, 1980a,b,c; Costa *et al.*, 1981a,b, 1982). At the same dose range, amorphous nickel sulfide had no effect. Clones derived from the transformed cells had greater plating efficiency, saturation densities and proliferation rates than normal cells; they also had more inducibility of ornithine decarboxylase, were able to proliferate in soft agar and were tumorigenic in nude mice.

C3H/10T½ cells were transformed at equal frequencies by crystalline nickel subsulfide at concentrations of 0.001, 0.01 and 0.1 μg/mL; at concentrations higher than 1 μg/mL, there was no transformation due to cell lysis or death. Transformed cells also showed long microvilli. They were not characterized for their ability to form tumours in nude mice or for anchorage-independent growth (Saxholm *et al.*, 1981). [The Working Group questioned the induction of transformation by concentrations of crystalline nickel subsulfide as low as 0.001 μg/mL.]

Crystalline nickel subsulfide induced transformed properties in rat liver epithelial T51B cells that were related to cytokeratin lesions. Solutions prepared as leachates of nickel subsulfide (containing about 300 μg/mL Ni) induced large juxtanuclear cytokeratin aggregates within 24 h of exposure, which persisted after removal of the compounds and were passed on to daughter cells. After long-term exposure to 2.5 μg/mL crystalline nickel subsulfide (dissolution products), these lesions were related to concomitant induction of differentiation and transformation markers, loss of density dependence, ability to grow in calcium-deficient medium and increased growth rates. Altered cells formed differentiated benign tumours in nude mice (Swierenga *et al.*, 1989).

Crystalline nickel subsulfide at 5-20 μg/mL induced transformation to anchor-age-independence of Syrian hamster BHK 21 cells (Hansen & Stern, 1983). [See General Remarks for concern about this assay.]

Human skin fibroblasts transformed by crystalline nickel subsulfide to anchorage-independent growth had a much higher plating efficiency than normal cells. The phenotype was stable for eight passages (Biedermann & Landolph, 1987).

Crystalline nickel sulfide, but not amorphous nickel sulfide, at doses of 1-20 μg/mL, inhibited the polyriboinosinic-polyribocytidylic acid-stimulated production of α/β interferon in mouse embryo fibroblasts (Sonnenfeld *et al.*, 1983).

Heterochromatic abnormalities were seen in early-passage cultures of cells from crystalline nickel sulfide-induced, mouse rhabdomyosarcomas (Christie *et al.*, 1988).

(iv) *Nickel salts (nickel chloride, nickel sulfate, nickel nitrate and nickel acetate)*

Nickel acetate induced γ prophage in *Escherichia coli* $WP2_S$, with a maximal effect at 0.04 mM (Rossmann *et al.*, 1984). Nickel sulfate at 300 μg/mL did not induce forward mutations in T4 phage (Corbett *et al.*, 1970).

Nickel chloride at 1-10 mM decreased the fidelity of DNA polymerase using a poly (c) template (Sirover & Loeb, 1976, 1977). Nickel acetate inhibited DNA synthesis in mouse mammary carcinoma Fm3A cells (Nishimura & Umeda, 1979).

Nickel chloride at 200-1000 μM induced a genotoxic response in a differential killing assay using *E. coli* WP2 (wild-type) and the repair-deficient derivative WP67 (*uvr*A$^-$, *pol*A$^-$) and CM871 (*uvr*A$^-$, *rec*A$^-$, *lex*A$^-$) (Tweats *et al.*, 1981). De Flora *et al.* (1984) reported negative results with nickel chloride, nickel nitrate and nickel acetate using the same strains in a liquid micromethod test procedure, with and without an exogenous metabolic system.

Nickel chloride did not induce differential toxicity in *B. subtilis* H17 *rec*$^+$ (*arg*$^-$, *trp*$^-$) or M45 *rec*$^-$ (*arg*$^-$, *trp*$^-$) at 5-500 mM (Nishioka, 1975; Kanematsu *et al.*, 1980). No mutagenicity was induced by nickel chloride at 0.1-100 mM in *S. typhimurium* LT_2 or TA100 (Tso & Fung, 1981), by nickel chloride, nickel acetate or nickel nitrate in *S. typhimurium* TA1535, TA1537, TA1538, TA97, TA98 or TA100 (De Flora *et al.*, 1984) or by nickel chloride or nickel sulfate in *S. typhimurium* TA1535, TA1537, TA1538, TA98 or TA100, when trimethylphosphate was substituted for *ortho*- phosphate to allow nickel to be soluble in the media (Arlauskas *et al.*, 1985). Even when substantial quantities of nickel were demonstrated to enter the bacteria, there was still no mutagenic response in *S. typhimurium* strains TA1535, TA1538, TA1975 or TA1978 (0.5-2 mM) (Biggart & Costa, 1986).

Pikálek and Nečásek (1983), however, demonstrated mutagenic activity of nickel chloride at 0.5-10 μg/mL in homoserine-dependent *Corynebacterium* sp887, utilizing a fluctuation test. Dubins and LaVelle (1986) demonstrated co-mutagenesis of nickel chloride with alkylating agents in S. *typhimurium* strain TA100 and in *E. coli* strains $WP2^+$ and WP2 *uvrA*$^-$; Ogawa *et al.* (1987) demonstrated co-mutagenesis with 9-aminoacridine. Nickel acetate at up to 100 μM was not co-mutagenic with ultraviolet light in *E. coli* WP2 (Rossman & Molina, 1986). Soluble nickel salts have been shown to be negative in host-mediated assays, using *S. typhimurium* G46 in NMRI mice and *Serratia marcescens* A21 in mice, at concentrations of 50 mg/kg (Buselmaier *et al.*, 1972).

Nickel chloride at 3 and 10 mM for 24 h induced gene conversion in *Saccharomyces cerevisiae* D7 (Fukunaga *et al.*, 1982). It also induced petite mutations in 13 *S. cerevisiae* haploid strains (Egilsson *et al.*, 1979).

Negative results were obtained in the *Drosophila melanogaster* somatic eye colour (zeste mutation) test with nickel chloride at 0.21 mM (Rasmuson, 1985) and at 4.2 mM (Vogel, 1976) and with nickel nitrate at 0.14 mM (Rasmuson, 1985).

Nickel sulfate induced sex-linked recessive lethal mutations in *D. melanogaster* at concentrations of 200, 300 and 400 ppm and sex chromosomal loss at the highest concentration tested. The injection volume was not stated, but the LD_{50} was 400 ppm (Rodriguez-Arnaiz & Ramos, 1986). Nickel nitrate at 3.4-6.9 mM did not induce sex-linked recessive lethal mutations in *D. melanogaster* (Rasmuson, 1985).

Nickel chloride increased the frequency of strand breaks in Chinese hamster ovary cells at 1 and 10 μg/mL with 2-h exposure (Robison & Costa, 1982) and at 10-100 μM for 16 and 48 h, with a decrease in the average molecular weight of DNA from 7.2-5.7 $\times$ 10^{-7} Da (Robison *et al.*, 1982). Nickel chloride at 0.5-5 mM induced both single-strand breaks and DNA-protein cross-links in the same cell line. The extent of cross-linking was maximal during the late S phase of the cell cycle when heterochromatic DNA is replicated (Patierno & Costa, 1985; Patierno *et al*., 1985).

Nickel chloride at 0.05 mM for 30 min did not induce DNA strand breaks in human lymphocytes as evaluated by alkaline unwinding (McLean *et al.*, 1982). [The Working Group noted that the exposure period was very short and the dose very low.] Nickel sulfate at 250 μg/mL did not induce DNA single-strand breaks in human fibroblasts (Ag 1522) (Fornace, 1982).

Nickel chloride at 0.1-1 mM induced DNA repair synthesis in Chinese hamster ovary and primary Syrian hamster embryo cells, which have a very high degree of density inhibition of growth and very little background replication synthesis (Robison *et al.*, 1983, 1984). It inhibited DNA synthesis in primary rat embryo cells at 1.0 μg/mL (Basrur & Gilman, 1967) and in T51B rat liver epithelial cells (Swierenga & McLean, 1985).

Exposure of two human cell lines, HeLa and diploid embryonic fibroblasts, and of Chinese hamster V79 cells and L-A mouse fibroblasts to nickel chloride *in vitro* resulted in a dose-dependent depression of proliferation and mitotic rate. The effects on viability were accompanied by a reduction in DNA, protein and. to a lesser degree, RNA synthesis. Cells in G1 and early S phases were most sensitive (Škreb & Fischer, 1984). Nickel chloride also selectively blocked cell cycle progression in the S phase in Chinese hamster ovary cells (Harnett *et al*., 1982). Nickel chloride at 40-120 μM for one to several days of exposure prolonged S-phase in Chinese hamster ovary cells (Costa *et al.*, 1982).

Nickel chloride at 0.4 and 0.8 mM for 20 h induced 8-azaguanine-resistant mutations in Chinese hamster V79 cells, although 0.8 mM induced a very weak mutagenic response (Miyaki *et al.*, l979). Nickel chloride at 0.5-2.0 mM induced a dose-related increase in the frequency of mutation to 6-thioguanine resistance in Chinese hamster V79 cells. At 2 mM,

cell survival was 50% and the mutant fraction was 8.6-fold above background (Hartwig & Beyersmann, 1989). Trifluorothymidine-resistant mutants were induced in L5178Y $tk^{+/-}$ mouse lymphoma cells following exposure to nickel chloride at 0.17-0.71 mM for 3 h; dose-dependent two- to five-fold increases in mutation frequency were seen, survival ranging from 5 to 33.5% to (Amacher & Paillet, 1980).

Nickel sulfate at 0.1 mM induced a two-fold increase in the frequency of mutation to 6-thioguanine resistance over the background level in Chinese hamster V79 cells (G 12) containing a transfected bacterial *gpt* gene (Christie *et al.*, 1992). No gene mutation to ouabain resistance was seen, however, in primary Syrian hamster embryo cells exposed to 5 μg/mL nickel sulfate (Rivedal & Sanner, 1980).

As assessed in a mutation assay for the synthesis of P-$85^{gag\text{-}mos}$ viral proteins, nickel chloride at concentrations of 20-160 μM induced expression of the v-*mos* gene in MuSVts 110-infected rat kidney cells (6m2 cell line) (Biggart & Murphy, 1988).

Nickel chloride at 0.01-0.05 mM increased the incidence of sister chromatid exchange in Chinese hamster ovary cells (Sen *et al*., 1987). An increased frequency was also seen with nickel sulfate at 0.1 mM in the P33 $8D_1$ macrophage cell line (Andersen, 1983), at 0.13 mM in Chinese hamster Don cells (Ohno *et al.*, 1982), at 0.004-0.019 mM in Syrian hamster embryo cells (Larramendy *et al.*, 1981), at 0.75 µg/mL (0.003 mM) in Chinese hamster ovary cells (Deng & Ou, 1981) and at 0.01 mM in human lymphocytes (Andersen, 1983). Dose-dependent increases in the frequency of sister chromatid exchange were seen in human peripheral blood lymphocytes with nickel sulfate at 0.01 mM and 0.019 mM (Larramendy *et al.*, 1981), 0.0023-2.33 mM (Wulf, 1980) and 0.95-2.85 µM (Deng & Ou, 1981).

Nickel chloride induced chromosomal aberrations in Fm3A mouse mammary carcinoma cells (Nishimura & Umeda, 1979; Umeda & Nishimura, 1979). It also induced aberrations (primarily gaps, breaks and exchanges) in Chinese hamster ovary cells at 0.001-1 mM, preferentially in heterochromatic regions (Sen & Costa, 1985, 1986b; Sen *et al.*, 1987); and aberrations in Syrian hamster embryo cells at 0.019 mM (Larramendy *et al.*, 1981). Increased frequencies were also reported in Syrian hamster embryo cells (0.019 mM) and human peripheral blood lymphocytes (0.019 mM) exposed to nickel sulfate hexahydrate (Larramendy *et al.*, 1981) and in Fm3A mouse mammary carcinoma cells exposed to nickel acetate at 0.6 mM for 48 h (Umeda & Nishimura, 1979) or at 1 mM for 24 h (Nishimura & Umeda, 1979).

Nickel sulfate at 1.0 mM reduced average chromosomal length in human lymphocytes, indicating its ability to act as a powerful spindle inhibitor at concentrations just below lethal levels (Andersen, 1985).

Nickel sulfate hexahydrate and nickel chloride induced a concentration-dependent increase in morphological transformation of Syrian hamster embryo cells (Pienta *et al.*, 1977; DiPaolo & Casto, 1979 [2.5-10 µg/mL]; Zhang & Barrett, 1988). Nickel sulfate transformed these cells at 5 µg/mL (Rivedal & Sanner, 1980; Rivedal *et al.*, 1980; Rivedal & Sanner, 1981, 1983), and concentrations of 10-40 µg/mL (38-154 µM) nickel sulfate enhanced transformation of normal rat kidney cells infected with Molony murine sarcoma virus (Wilson & Khoobyarian, 1982).

Nickel acetate at 100-400 µg/mL transformed Syrian hamster BHK21 cells (Hansen & Stern, 1983) [See General Remarks for concern about this assay.]

Nickel acetate and nickel sulfate at 10 µM induced transformation to anchor-age-dependent growth of primary human foreskin fibroblasts (Biedermann & Landolph, 1987).

Continuous exposure of cultures of normal human bronchial epithelial cells to nickel sulfate at 5-20 µg/mL reduced colony-forming efficiency by 30-80%. After 40 days of incubation, 12 cell lines were derived which exhibited accelerated growth, aberrant squamous differentiation and loss of the requirement for epidermal growth factor for clonal growth. Aneuploidy was induced and marker chromosomes were found. However, none of these transformed cultures was anchorage-independent or produced tumours upon injection into athymic nude mice (Lechner *et al.*, 1984). Human fetal kidney cortex explants were exposed continuously to 5 µg/mL nickel sulfate. After 70-100 days, immortalized cell lines were obtained, with decreased serum dependence, increased plating efficiency, higher saturation density and ability to grow in soft agar. However, they were not tumorigenic (Tveito *et al.* 1989).

Nickel sulfate disrupted cell-to-cell communication in a dose-related manner in NIH3T3 cells from a base level of 98% at 0.5 mM to 2% at 5mM; cell viability was not affected by these concentrations (Miki *et al.*, 1987). [The Working Group noted that the method for determining cell viability was not described.]

Intraperitoneal injections of nickel sulfate at 15-30% of the LD_{50} to CBA mice *in vivo* suppressed DNA synthesis in hepatic epithelial cells and in the kidney (Amlacher & Rudolph, 1981). Nickel chloride given by intramuscular injection to rats at 20 mg/kg bw Ni inhibited DNA synthesis in the kidney (Hui & Sunderman, 1980).

Polychromatic erythrocytes were not induced in BALB/c mice after an intraperitoneal injection of 25 mg/kg bw nickel chloride or 56 mg/kg bw nickel nitrate (Deknudt & Léonard, 1982).

The frequency of chromosomal aberrations in bone-marrow cells and spermatogonia of male albino rats was not increased following intraperitoneal injections of 3 and 6 mg/kg bw nickel sulfate. Animals were sacrificed seven to 14 days after treatment (Mathur *et al.*, 1978).

Nickel chloride increased the frequency of chromosomal aberrations in bone-marrow cells of Chinese hamsters given intraperitoneal injections of concentrations that were 4-20% of the LD_{50} (Chorvatovičová, 1983) and of Swiss mice given intraperitoneal injections of 6, 12 or 24 mg/kg bw (Mohanty, 1987).

Dominant lethal mutations were not induced in BALB/c mice after an intraperitoneal injection of 12.5-100 mg/kg bw nickel chloride or 28-224 mg/kg bw nickel nitrate (Deknudt & Léonard, 1982).

(v) *Other nickel compounds*

DNA-protein cross-linking in the presence of the nickel[II]- and nickel[III]tetraglycine complexes and molecular oxygen was observed *in vitro* in calf thymus nucleohistone. The same complexes were also able to cause random polymerization of histones *in vitro* (Kasprzak & Bare, 1989).

Haworth *et al.* (1983) reported no mutation in *S. typhimurium* TA100, TA1535, TA1537 or TA98 following exposure to nickelocene at doses up to 666 µg/plate.

Nickel potassium cyanide at concentrations of 0.2-1.6 mM for 48 h increased the frequency of chromosomal aberrations in Fm3A mouse mammary carcinoma cells (Nishimura & Umeda, 1979; Umeda & Nishimura, 1979).

Crystalline nickel subselenide at 1-5 µg/mL inhibited cell progression through S phase, as seen with flow cytometry (Costa *et al.*, 1982). Concentrations of 5-20 µg/mL crystalline nickel subselenide transformed primary Syrian hamster embryo cells (Costa *et al.*, 1981a,b; Costa & Mallenhauer, 1980c).

Intravenous administration of nickel carbonyl to rats at 20 mg/kg bw Ni inhibited DNA synthesis in liver and kidney (Hui & Sunderman, 1980).

DNA-protein cross-links and single-strand breaks, as detected by alkaline elution, were found in rat kidney nuclei 20 h after intraperitoneal injection of 'nickel carbonate' at 10-40 mg/kg bw (Ciccarelli *et al.*, 1981). After 3 and 20 h, single-strand breaks were detected in lung and kidney nuclei, and both DNA-protein and DNA interstrand cross-links were found in kidney nuclei. No DNA damage was observed in liver or thymus gland nuclei (Ciccarelli & Wetterhahn, 1982). [The Working Group noted that the compound tested was probably basic nickel carbonate.]

3.3 Other relevant data in humans

(a) *Absorption, distribution, excretion and metabolism*

Recent reviews include those of Raithel and Schaller (1981), Sunderman *et al.* (1986a), the US Environmental Protection Agency (1986), Grandjean *et al.* (1988), Sunderman (1988) and the World Health Organization (1991).

A positive relation exists between air levels of nickel and serum/plasma concentrations of nickel after occupational exposure to various forms of nickel (see also Tables 11, 12, 13).

A considerable scattering of results was apparent, and the correlation was poor; a better correlation may be achieved in individual studies of well-defined exposure groups (Grandjean *et al.*, 1988). Sparingly soluble compounds may be retained in the lungs for long periods of time. Thus, even three to four years after cessation of exposure, nickel concentrations in plasma and urine were elevated in retired nickel workers exposed to sparingly soluble compounds in the roasting/smelting department of a nickel refinery (Boysen *et al.*, 1984). Respiratory uptake of nickel in welders is described in the monograph on welding.

Provided that pulmonary exposure to nickel can be excluded, the approximate fraction of nickel absorbed by the intestinal tract can be estimated from oral intake and faecal and urinary nickel elimination (Horak & Sunderman, 1973). Cumulative urinary excretion in non-fasting volunteers given a single oral dose of 5.6 mg Ni as nickel sulfate hexahydrate indicated an intestinal absorption of 1-5% (Christensen & Lagesson, 1981; Sunderman, 1988). After ingestion of nickel sulfate during fasting, 4-20% of the dose was excreted in the urine within 24 h (Cronin *et al.*, 1980). Compartmental analysis of nickel levels in serum, urine and faeces in a study of intestinal absorption of nickel sulfate by human volunteers showed that an average of about 27% was absorbed when ingested as an aqueous solution after 12 h of fasting, while 0.7%was absorbed when the nickel was ingested with scrambled eggs (Sunderman *et al.*, 1989b). Ingestion of food items with a high natural nickel content resulted in a urinary excretion corresponding to about 1% Of the amount ingested (Nielsen *et al.*, 1987). The bioavailability of nickel can be reduced by various dietary constituents and beverages. Drugs may influence intestinal nickel absorption. Ethylenediaminetetraacetic acid very efficiently prevented intestinal absorption of nickel (Solomons *et al.*, 1982); and, as reported in an abstract, disulfiram increased the intestinal absorption of nickel, probably by forming a lipophilic complex between its metabolite diethyldithiocarbamate and nickel (Hopfer *et al.*, 1984).

After intestinal absorption of nickel ingested as nickel sulfate hexahydrate in lactose by eight volunteers, most of the nickel present in blood was in serum; nickel concentrations in serum and blood showed a very high positive correlation (r = 0.99) (Christensen & Lagesson, 1981). In patients with chronic renal failure, a high nickel concentration was found in serum but no significant increase was observed in lymphocytes (Wills *et al.*, 1985). However, in nickel refinery workers, plasma nickel concentrations were lower than those in whole blood, and about 63% appeared to be contained in the buffy coat (Barton *et al.*, 1980).

As reported in an abstract, nickel levels in intercellular fluid were significantly lower in a group of nickel-allergic patients than in controls, possibly due to cell binding or uptake (Bonde *et al.*, 1987). This finding may be related to the observation that incubation with nickel subsulfide *in vitro* caused considerable binding of nickel to the cell membrane of

T-lymphocytes from nickel-sensitized patients but to very few cells from nonsensitized persons (Hildebrand *et al.*, 1987).

The lungs contain the highest concentration of nickel in humans with no known occupational nickel exposure; lower levels occur in the kidneys, liver and other tissues (Sumino *et al.*, 1975; Rezuke *et al.*, 1987). One study documented high levels in the thyroid and adrenals (Rezuke *et al.*, 1987) and another in bone (Sumino *et al.*, 1975). The pulmonary burden of nickel appears to increase with age (Kollmeier *et al.*, 1987), although this correlation was not confirmed in another study (Raithel *et al.*, 1988). The upper areas of the lungs and the right middle lobe contained higher nickel concentrations than the rest of the lung (Raithel *et al.*, 1988), and high concentrations were found in hilar lymph nodes (Rezuke *et al.*, 1987).

Lung tissue from three of four random cases of bronchial carcinoma from an area with particularly high local emissions of chromium and nickel contained increased concentrations of nickel and chromium (Kollmeier *et al.*, 1987), while no such tendency was seen in ten other cases with no known occupational exposure to nickel (Turhan *et al.*, 1985).

High nickel concentrations were found in biopsies of nasal mucosa from both active and retired workers from the Kristiansand, Norway, nickel refinery, particularly in workers from the roasting/smelting department. After retirement, increased nickel levels persisted for at least ten years, with slow release at a half-time of 3.5 years (Torjussen & Andersen, 1979). Biopsies from two nasal carcinomas in nickel refinery workers contained nickel concentrations similar to those seen in biopsies from workers without cancer (Torjussen *et al.*, 1978). Lung tissue obtained at autopsy of workers from the roasting and smelting department of the Norwegian nickel refinery contained higher nickel concentrations (geometric mean, 148 μg/g dry weight; n = 15) than tissue from workers from the electrolysis department (geometric mean, 16 μg/g; n = 24); nickel concentrations in lung tissue were not higher in workers who had died from lung cancer than in workers who had died of other causes (Andersen & Svenes, 1989).

In cases of nickel carbonyl poisoning, the highest nickel concentrations have been recorded in the lungs, with lower levels in kidneys, liver and brain (National Research Council, 1975).

The half-time of nickel in serum was 11 h (one-compartment model during the first 32 h) in eight volunteers after ingestion of 5.6 mg nickel sulfate hexahydrate in lactose; serum nickel concentration and urinary nickel excretion showed a highly positive correlation (r = 0.98) (Christensen & Lagesson, 1981). Possibly due to delayed absorption of inhaled nickel, somewhat longer half-times were reported for nickel concentrations in plasma and urine (20-34 h and 17-39 h, respectively) in nickel platers (Tossavainen *et al.*, 1980), glass

workers (30-50 h in urine) (Raithel *et al*., 1982; Sunderman *et al.*, 1986a) and welders (53 h in urine) (Zober *et al.*, 1984). Ten subjects who had accidentally ingested soluble nickel compounds and were treated the following day with intravenous fluids to induce diuresis, showed an average elimination half-time of 27 h, while the half-time was twice as high in untreated subjects with lower serum nickel concentrations (Sunderman *et al.*, 1988b).

Urinary excretion of nickel is frequently used to survey workers exposed to inorganic nickel compounds (Aitio, 1984; Sunderman *et al.*, 1986a; Grandjean *et al.*, 1988). The best indicator of current exposure to soluble nickel compounds is a 24-h urine sample (Sunderman *et al.*, 1986a). In cases of nickel carbonyl intoxication, urinary nickel level is an important diagnostic and therapeutic guide (Sunderman & Sunderman, 1958; Adams, 1980), but its use in biological monitoring of exposure to nickel carbonyl has not been evaluated in detail.

Systemically absorbed nickel may be excreted through sweat (Christensen *et al.*, 1979). Faecal excretion includes non-absorbed nickel and nickel secreted into the gastrointestinal tract (World Health Organization, 1991). Saliva contains nickel concentrations similar to those seen in plasma (Catalanatto & Sunderman, 1977). Secretin-stimulated pancreatic juice was reported to contain an average of 1.09 nmol [64 μg]/mL nickel, corresponding to a total nickel secretion of about 1.64-2.18 μmol [96-128 μg] per day at a pancreatic secretion rate of 1.5-2 L/day (Ishihara *et al.*, 1987). Bile obtained at autopsy contained an average nickel concentration of 2.3 μg/L, suggesting daily biliary excretion of about 2-5 μg (Rezuke *et al.*, 1987). A biliary nickel concentration of 62 μg/g was recorded at autopsy of a small girl who had swallowed about 15 g nickel sulfate crystals (Daldrup *et al.*, 1983); since biliary excretion in this case would correspond to about 0.l% of the dose, it was considered that this route of excretion would be of minimal importance in acute intoxication (Rezuke *et al.*, 1987). Nickel-exposed battery production workers showed high faecal nickel excretion, probably owing to direct oral intake of nickel (e.g., via contamination of food from exposed surfaces); faecal nickel content (24 μg/g dry weight) was correlated with the amount present in air (18 $\mu g/m^3$) (Hassler *et al.*, 1983).

Nickel was found in cord blood from full-term infants at 3 μg/L (McNeely *et al.*, 1971). Tissue levels at 22-43 weeks of gestation were similar to those seen in adults (Casey & Robinson, 1978).

(*b*) *Toxic effects*

Nickel is an essential nutrient in several species, but no essential biochemical function has been established in humans. Recent reviews of nickel toxicity in humans include those of Raithel and Schaller (1981), the US Environmental Protection Agency (1986), Sunderman (1988) and the World Health Organization (1991).

Acute symptoms reported in 23 patients exposed to severe nickel contamination during haemodialysis included nausea, vomiting, weakness, headache and palpitations; the

symptoms disappeared rapidly upon cessation of dialysis (Webster *et al.*, 1980). Twenty workers who accidentally ingested water contaminated with nickel sulfate and chloride hexahydrates at doses estimated at 0.5-2.5 g Ni developed nausea, abdominal pain or discomfort, giddiness, lassitude, headache, diarrhoea vomiting, coughing and shortness of breath; no related sequela was observed on physical examination, and all individuals were asymptomatic within three days (Sunderman *et al.*, 1988b). In a study of fasting human volunteers, one subject who ingested nickel sulfate (as 50 μg/kg bw Ni) in water developed a transient hemianopsia at the time of peak nickel concentration in serum (Sunderman *et al.*, 1989b). One fatal case of oral intoxication with nickel sulfate has been reported (Daldrup *et al.*, 1983).

Biochemical indications of nephrotoxicity, mainly with tubular dysfunction, have been observed in nickel electrolysis workers (Sunderman & Horak, 1981). Increased haemoglobin and reticulocyte counts were reported in ten subjects three to eight days after they had accidentally ingested 0.5-2.5 g Ni as nickel sulfate and chloride hexahydrates in contaminated drinking-water (Sunderman *et al.*, 1988b).

Nickel is a common skin allergen — in recent studies, the most frequent cause of allergic contact dermatitis in women and one of the most common in men; about 10-15% of the female population and 1-2% of males show allergic responses to nickel challenge (Peltonen, 1979; Menné *et al.*, 1982). Nickel ions are considered to be exclusively responsible for the immunological effects of nickel (Wahlberg, 1976). Sensitization appears to occur mainly in young persons, usually due to non-occupational skin exposures to nickel alloys (Menné *et al*., 1982). Subsequent provocation of hand eczema may be caused by occupational exposures, especially to nickel-containing fluids and solutions (Rystedt & Fischer, 1983). Oral intake of low doses of nickel may provoke contact dermatitis in sensitized individuals (Veien *et al.*, 1985). Inflammatory reactions to nickel-containing prostheses and implants may occur in nickel-sensitive individuals (Lyell *et al.*, 1978).

Several cases of nickel-associated asthma have been described (Cirla *et al.*, 1985). Case reports suggest that inhalation of nickel dusts may result in chronic respiratory diseases (asthma, bronchitis and pneumoconiosis) (Sunderman, 1988). [The Working Group was unable to determine the causal significance of nickel in this regard.]

Nickel carbonyl is the most acutely toxic nickel compound. Symptoms following nickel carbonyl intoxication occur in two stages, separated by an almost symptom-free interval which usually lasts for several hours. Initially, the major symptoms are nausea, headache, vertigo, upper airway irritation and substernal pain, followed by interstitial pneumonitis with dyspnoea and cyanosis. Prostration, pulmonary oedema, kidney toxicity, adrenal insufficiency and death may occur in severe cases (Sunderman & Kincaid, 1954; Vuopala *et al.*, 1970; Sunderman, 1977).

Frequent clinical findings included fever with leukocytosis, electrocardiographic abnormalities suggestive of myocarditis and chest X-ray changes (Zhicheng, 1986). Hyperglycaemia has also been reported (Sunderman, 1977). Neurasthenic signs and weakness may persist in survivors for up to six months (Zhicheng, 1986).

(*c*) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(*d*) *Genetic and related effects*

Cytogenetic studies have been performed using peripheral blood lymphocytes from electroplating and nickel refining plant workers; they are summarized in Appendix 1 to this volume.

Waksvik and Boysen (1982) found elevated levels of chromosomal aberrations (mainly gaps; $p < 0.003$), but not of sister chromatid exchanges, in two groups of nickel refinery workers. One group of nine workers engaged in crushing/roasting/smelting processes and exposed mainly to nickel monoxide and nickel subsulfide for an average of 21.2 years (range, 3-33 years) at an air nickel content of 0.5 mg/m^3 (range, 0.1-1.0 mg/m^3) and with a mean plasma nickel level of 4.2 µg/L had 11.9% of metaphases with gaps. Another group of workers, engaged in electrolysis, who were exposed mainly to nickel chloride and nickel sulfate for an average of 25.5 years (range, 8-31 years) at an air nickel content of 0.2 mg/m^3 (range, 0.1-0.5 mg/m^3) and with a mean plasma level of 5.2 µg/L, had 18.3% of metaphases with gaps[1]. Mean control values of 3.7% of metaphases with gaps were seen in seven office workers in the same plant with plasma nickel levels of 1 µg/L, who were matched for age and sex. All subjects were nonsmokers and nonalcohol consumers, were free from overt viral disease, were not known to have cancer and had not received therapeutic radiation; none was a regular drug user and the groups were uniform as to previous exposure to diagnostic X-rays.

Waksvik *et al.* (1984) investigated nine ex-workers from the same plant who had been retired for an average of eight years who had had similar types of exposure to more than 1 mg/m^3 atmospheric nickel for 25 years or more; they were selected from among a group of workers known to have nasal dysplasia and who still had plasma nickel levels of 2 µg/L plasma. These retired workers showed some retention of gaps ($p < 0.05$) and an increased frequency of chromatid breaks to 4.1% of metaphases *versus* 0.5% ($p < 0.001$) in 11 unexposed retired workers controlled for age, life style and medication status. All subjects were of similar socioeconomic status and had not had X-rays or overt viral disease recently;

[1]The exposures of these workers were clarified in an erratum to the original article, published subsequently (*Mutat. Res*., *104*, 395 (1982)).

none smoked or drank alcohol. Four exposed and nine unexposed subjects were on medication but not with drugs known to influence chromosomal parameters.

Deng *et al.* (1983, 1988) studied the frequencies of sister chromatid exchange and chromosomal aberrations in lymphocytes from seven electroplating workers exposed to nickel. Air nickel concentrations were 0.0053-0.094 mg/m^3 (mean, 0.024 mg/m^3). Control subjects were ten administrative workers from the same plant matched for age and sex; the groups were uniform as to socioeconomic status, and none of the subjects smoked or used alcohol, had overt viral disease, had recently been exposed to X-rays or was taking medication known to have chromosomal effects. The exposed workers had an increased frequency of sister chromatid exchange (7.50 ± 2.19 (SEM) *versus* 6.06 ± 2.30 (SEM); $p < 0.05$). [The Working Group noted that this is a small difference between groups.] The frequency of chromosomal aberrations (gaps, breaks and fragments) was increased from 0.8% of metaphases in controls to 4.3% in nickel platers.

The frequencies of sister chromatid exchange and chromosomal aberrations were studied in workers in a nickel carbonyl production plant. The subjects were divided into four groups: exposed, exposed smokers, controls and control smokers. Controls were ex-employees. None of the subjects had a history of serious illness; none was receiving irradiation or was infected by viruses at the time of blood sampling. No significant difference in the frequency of chromosomal breaks or gaps was observed between the different groups, and there was no statistically significant difference in the frequency of sister chromatid exchange between unexposed and nickel-exposed workers (Decheng *et al.*, 1987). [The Working Group noted that several discrepancies in the description of this study make it difficult to evaluate.]

Studies of mutagenicity and chromosomal effects in humans are summarized in Table 25.

3.4 Epidemiological studies of carcinogenicity to humans

(a) Introduction

The report of the International Committee on Nickel Carcinogenesis in Man (ICNCM) (1990) presents updated results on nine cohort studies and one case-control study of nickel workers, one of which was previously unpublished. The industries include mining, smelting, refining and high-nickel alloy manufacture and one industry in which pure nickel powder was used. The report adds to or supersedes previous publications on most of these cohorts, as various new analyses are included, some cohorts have been enlarged, and follow-up has been extended. Nickel species were divided into four categories: metallic nickel, oxidic nickel, soluble nickel and sulfidic nickel (including nickel subsulfide). Soluble nickel was

Table 25. Cytogenetic studies of people exposed occupationally to nickel and nickel compounds

Occupational exposure	Reported principal components	Mean reported dose (range)	Sister chromatid exchange	Chromosomal aberrations	Reference
Crushing, roasting, smelting	Nickel monoxide, nickel subsulfide	Air: 0.5 (0.1–1.0) mg/m³ Exposure: 21.2 (3–33) years	None	Only gaps	Waksvik & Boysen (1982)
Electrolysis	Nickel chloride, nickel sulfate	Air: 0.2 (0.1–0.5) mg/m³ Exposure: 25.2 (8–31) years	None	Mainly gaps	Waksvik & Boysen (2982)
Crushing, roasting, smelting and/or electrolysis	Nickel monoxide, nickel subsulfide, nickel chloride, nickel sulfate	Air: 1 mg/m³ Exposure: >25 years	None	Gaps and breaks in retired workers	Waksvik *et al.* (1984)
Nickel carbonyl production	Nickel carbonyl	Exposure: 7971 h	None	None	Decheng *et al.* (1987)
Electroplating	Nickel and chromium compounds	Air: 0.0053–0.094 mg/m³ Exposure: 2–27 years	Small increase	Mainly gaps, but also breaks and fragments	Deng *et al.* (1983, 1988)

defined as consisting 'primarily of nickel sulfate and nickel chloride but may in some estimates include the less soluble nickel carbonate and nickel hydroxide'.

The historical estimates of exposure cited in the reviews of the following studies were not based on contemporary measurements. Furthermore, total airborne nickel was estimated first, and this estimate was then divided into estimates for four nickel species (metallic, oxidic, sulfidic and soluble), as defined in the report of the committee (ICNCM, 1990). The procedures for dividing the exposure estimates are described in section 2 of this monograph (pp. 297-298). Because of the inherent error and uncertainties in the procedures for estimating exposures, the estimated concentrations of nickel species in workplaces in the ICNCM analysis must be interpreted as broad ranges indicating only estimates of the order of magnitude of the actual exposures.

In order to facilitate the interpretation of the epidemiological findings on mortality from lung cancer and nasal cancer, selected estimates of exposure are presented in Tables 26, 27 and 28 (pp. 402-404) for some of the plants and subcohorts. The exposure estimates presented in the tables should be used only to make qualitative comparisons of exposure among departments within a plant and should not be used to make comparisons of exposure estimates among plants, for the reasons given above.

(*b*) *Nickel mining, smelting and refining*

(*i*) *INCO Ontario, Canada (mining, smelting and refining)*[1]

Follow-up of all sinter plant workers and of all men employed at the Ontario division of INCO for at least six months and who had worked (or been a pensioner) between 1 January 1950 and 31 December 1976 (total number of men, 54 509) was extended to the end of 1984 by record linkage to the Canadian Mortality Data Base (ICNCM, 1990). Sinter plant workers included men who had worked in two different sinter plants in the Sudbury area (the Coniston and Copper Cliff sinter plants) and in the leaching, calcining and sintering department at the Port Colborne nickel refinery. In the Coniston sinter plant, sulfidic nickel ore concentrates were partially oxidized at 600°C (Roberts *et al.*, 1984) on sinter machines to remove about one-third of the sulfur and to agglomerate the fine material for smelting in a blast furnace. In the Copper Cliff sinter plant, nickel subsulfide was oxidized to nickel oxide at very high temperatures (1650°C). The leaching, calcining and sintering department

[1]There are some discrepancies between the figures cited here and those reported by Roberts *et al.* (1989a,b), but the differences are not substantial.

produced black and green nickel oxides from nickel subsulfide by a series of leaching and calcining operations. The department also included a sinter plant like that at Copper Cliff. Employment records for men employed in the department did not allow them to be assigned to individual leaching, calcining or sintering operations. Mortality up to the end of 1976 in this cohort of about 55 000 men was described by Roberts *et al.* (1984); an earlier study of 495 men employed at the Copper Cliff sinter plant was reported by Chovil *et al.* (1981). The nickel species to which men were exposed in dusty sintering operations were primarily oxidic and sulfidic nickel, and possibly soluble nickel at lower levels (see Table 26). High concentrations of nickel compounds were estimated in the Copper Cliff sinter plant, which ranged from 25-60 mg/m^3 Ni as nickel oxide and 15-35 mg/m^3 Ni as nickel subsulfide, with up to 4 mg/m^3 Ni soluble nickel as anhydrous nickel sulfate between 1948 and 1954. Among the 3769 sinter plant workers, there were 148 lung cancer deaths (standardized mortality ratio (SMR), 261; 95% confidence interval (CI), 220-306) and 25 nasal cancer deaths (SMR, 5073; 95% CI, 3282-7489). Among the 50 977 nonsinter workers in the cohort, there were 547 lung cancer deaths (SMR, 110; 95% CI, 101-120) and six nasal cancer deaths (SMR, 142; 95% CI, 52-309). The only other site for which cancer mortality was significantly elevated was the buccal cavity and pharynx (12 deaths in sinter plant workers: SMR, 211; 95% CI, 109-369; 35 deaths in other workers: SMR, 71; 95% CI, 49-99). The sinter plant workers had little or no excess risk during the first 15 years after starting work (no nasal cancer death; five lung cancer deaths; SMR, 158 [95% CI, 51-370]), and their subsequent relative risk increased with increasing duration of employment. There were also statistically significant excesses of mortality from lung cancer in men employed for 25 or more years in the Sudbury area, both in mining (129 deaths; SMR, 134 [95% CI, 112-159]) and in copper refining (24 deaths; SMR, 207 [95% CI, 133-308]). In the electrolysis department of the Port Colborne plant, workers were estimated to be exposed to low concentrations of metallic, oxidic, sulfidic and soluble nickel. Seven nasal cancer deaths occurred (SMR, 5385; 95% CI, 2165-11 094) in men who had spent over 15 years in the electrolysis department at Port Colborne; all seven had spent some time in the leaching, sintering and calcining area at the Sudbury site, although two had spent only three and seven months, respectively. Lung cancer mortality among workers in the electrolysis department with no exposure in leaching, calcining and sintering, but with 15 or more years since first exposure, gave an SMR of 88 (19 deaths; 95% CI, 53-137). There was a marked difference in the ratio of lung to nasal cancer excess between the Copper Cliff sinter plant and the Port Colborne leaching, calcining and sintering plant: 7:1 at Copper Cliff (63 observed lung cancers, minus 20.5 expected, *versus* six nasal cancers) and only about 2:1 at Port Colborne (72 observed lung cancers, minus 30.0 expected, *versus* 19 nasal cancers).

(ii) *Falconbridge, Ontario, Canada (mining and smelting)*

A cohort of 11594 men employed at Falconbridge, Ontario, between 1950 and 1976, with at least six months' service, was previously followed up to the end of 1976 (Shannon *et al.*, 1984a,b). Follow-up has now been extended to the end of 1985 by record linkage to the Canadian Mortality Data Base (ICNCM, 1990). Expected numbers were calculated from Ontario provincial death rates. One death was due to nasal cancer, compared with 0.77 expected. The only cause of death showing a statistically significant excess in the overall analysis was lung cancer (114 deaths; SMR, 135; 95% CI, 111-162). Subdivision of the total cohort by duration of exposure in different areas and latency revealed no SMR for lung cancer that differed significantly from this moderate overall excess, but the highest SMRs occurred in men who had spent more than five years in the mines (46 deaths; SMR, 158; 95% CI, 116-211) or in the smelter (15 deaths; SMR, 163; 95% CI, 91-269). Men who had worked in the smelter are reported to have had low levels of exposure to pentlandite and pyrrhotite, sulfidic nickel, oxidic nickel and some exposure to nickel sulfate. Estimated total exposures to nickel in all areas of the facility were below 1 mg/m^3 Ni (ICNCM, 1990).

(iii) *INCO, Clydach, South Wales, UK (refining)*

The excess of lung and nasal sinus cancer among workers in the INCO refinery in Clydach, South Wales, which opened in 1902, was recognized over 50 years ago (Bridge, 1933). The first formal analyses of cancer mortality were carried out by Hill in 1939 and published by Morgan (1958), who identified calcining, furnaces and copper sulfate extraction as the most hazardous processes. Subsequent reports indicated that the risk had been greatly reduced by 1925 or 1930 (Doll, 1958; Doll *et al.*, 1970, 1977; Cuckle *et al.*, 1980); trends in risk with age at first exposure, period of first exposure and latency were analysed (Doll *et al.*, 1970; Peto *et al.*, 1984; Kaldor *et al.*, 1986). The cohort of 845 men employed prior to 1945 studied by Doll *et al.* (1970) has now been extended to include 2521 men employed for at least five years between 1902 and 1969, and followed up to the end of 1984 (ICNCM, 1990). Among 1348 men first employed before 1930 there were 172 lung cancer deaths (SMR, 393; 95% CI, 336-456) and 74 nasal cancer deaths (SMR, 21 120; 95% CI, 16 584-26 514); the highest risks were associated with calcining, furnaces and copper sulfate production. The calcining and furnace areas had high estimated levels of oxidic, sulfidic and metallic nickel (see Table 27). Until the late 1930s, the oxidic nickel consisted of nickel-copper oxide. Men in the copper plant were exposed to very high concentrations of nickel-copper oxide; they were also exposed to soluble nickel: the extraction of copper from the calcine involved the handling of large volumes of solutions containing 60 g/L nickel as nickel sulfate. Until 1923, arsenic present in sulfuric acid is believed to have accumulated at significant levels in several process departments, mainly as nickel arsenides. The only other

significantly elevated risks were an excess of five lung cancer deaths (SMR, 333; 95% CI, 108-776) and four nasal cancer deaths (SMR, 36 363; 95% CI, 9891-93 089) in men employed before 1930 with less than one year in calcining, furnace or copper sulfate but over five years in hydrometallurgy, an area in which exposure to soluble nickel was similar to that in other high-risk areas and exposures to oxidic nickel were an order of magnitude lower than in other high-risk areas, with negligible exposure to sulfidic nickel (see Table 27); and in the small subgroup of nickel plant cleaners (12 lung cancer deaths; SMR, 784 [95% CI, 402-1361]), who were highly exposed to metallic nickel (5 mg/m^3 Ni), oxidic nickel (6 mg/m^3 Ni) and sulfidic nickel (> 10 mg/m^3 Ni), with negligible exposure to soluble nickel (ICNCM, 1990). A notable anomaly in the data for the whole refinery was the marked reduction in nasal cancer but not lung cancer mortality, when comparing men first exposed before 1920 and those first exposed between 1920 and 1925 (Peto *et al.*, 1984). The risk, although greatly reduced, may not have been entirely eliminated by 1930, as there were 44 lung cancers (SMR, 125 [95% CI, 91-168]) and one nasal cancer (SMR, 526 [95% CI, 13-3028]) among the 1173 later employees.

(iv) *Falconbridge, Kristiansand, Norway (refining)*

The cohort of 3250 men reported by ICNCM (1990) is restricted to men first employed in 1946-69 with at least one year's service and followed until the end of 1984. For each work area, average concentrations for the four categories of nickel (sulfidic nickel, metallic nickel, oxidic nickel and soluble nickel) were estimated as four ranges for three periods (1946-67, 1968-77 and 1978-84). The four ranges and the arithmetic average computed for each range were: low (0.3 mg/m^3), medium (1.3 mg/m^3), high (5 mg/m^3) and very high (10 mg/m^3). There were 77 lung cancer deaths (SMR, 262; 95% CI, 207-327), three nasal cancer deaths (SMR, 453; 95% CI, 93-1324) and a further four incident cases of nasal cancer. Five of the nasal cancer cases had spent their entire employment in the roasting, smelting and calcining department, where oxidic nickel was estimated to have been the predominant exposure, with lesser amounts of sulfidic and metallic nickel. Before 1953, arsenic was present in the feed materials, and significant contamination with nickel arsenides is believed to have occurred at various steps of the process. The remaining two cases were in electrolysis workers who were exposed mainly to soluble nickel (nickel sulfate until 1953 and nickel sulfate and nickel chloride solutions thereafter) and nickel-copper oxides. No other type of cancer occurred significantly in excess. Among men first employed after 1955, there have been 13 lung cancer deaths (SMR, 173 [95% CI, 92-296]) and no nasal cancer (0.2 expected). Several comparisons were made assuming 15 years' latency. The highest risk for lung cancer was seen among a group of workers who had worked in the electrolysis department but never in roasting and smelting (30 deaths; SMR, 385; 95% CI, 259-549). In

the group of workers who had worked in roasting and smelting but never in the electrolysis department, 14 lung cancer deaths were seen (SMR, 225; 95% CI, 122-377) (see also Table 28). In those who had spent no time in either of these departments, the SMR was 187 (six cases [95% CI, 68-406]). Although exposure to soluble nickel in the roasting, calcining and smelting department was initially estimated to be negligible, it was noted that soluble nickel was certainly present in the Kristiansand roasting department in larger amounts than had been allowed for, and to some extent in all smelter and calcining plants (ICNCM, 1990).

The overlapping cohort reported by Pedersen *et al.* (1973) and Magnus *et al.* (1982) included 2247 men employed for at least three years from when the plant began operation in 1910. Results for cancers diagnosed up to 1979 were presented by Magnus *et al.* (1982). There were 82 lung cancers [standardized incidence ratio (SIR), 373; 95% CI, 296-463] and 21 nasal cancers (SIR, 2630 [95% CI, 1625-4013]). Of the nasal cancers, eight occurred in men involved in roasting-smelting, eight in electrolysis workers, two in workers in other specified processes and three in administration, service and unspecified workers. The incidence of no other type of cancer was significantly elevated overall, although there were four laryngeal cancers (SIR, 670) among roasting and smelting workers. An analysis of lung cancer incidence in relation to smoking suggested an additive rather than a synergistic effect. Adjustment for national trends in lung cancer rates, assuming an additive effect of nickel exposure, suggested little or no reduction in lung cancer risk between men first employed in 1930-39 and those first employed in 1950-59. This contrasts with the marked reduction in nasal cancer risk.

(v) *Hanna Mining and Nickel Smelting, Oregon, USA*

A total of 1510 men who had worked for at least six months between 1953, when the plant opened, and 1977 were followed up to the end of 1983 (ICNCM, 1990). Expected numbers of deaths were those for the state of Oregon. A statistically significant excess of lung cancer was observed among men with less than one year of exposure (seven deaths; SMR, 265 [95% CI, 107-546]) but not in men with longer exposure (20 deaths; SMR, 127 [95% CI, 77-196]) or in the subgroup who had worked in areas with potentially high exposures (smelting, ‘skull plant’, refining and ferrosilicon plant; seven deaths; SMR, 113; 95% CI, 45-233). There was no nasal cancer, and no excess of other cancers (21 deaths; SMR, 65 [95% CI, 41-100]). Average airborne concentrations were estimated to have been 1 mg/m^3 Ni or less, even in areas with potentially high exposure, and in most areas were below 0.1 mg/m^3 Ni. The principal nickel compounds to which workers were exposed were nickel-containing silicate ore and iron-nickel oxide, with very little soluble nickel and no sulfidic nickel.

(vi) *Societé Le Nickel, New Caledonia (mining and smelting)*

Approximately 25% of the adult male population of New Caledonia has worked in nickel mines (silicate-oxide nickel ores) or smelters. Since the local rates for cancer of the lung and upper respiratory tract are higher than those in neighbouring islands, a small hospital-based case-control study was conducted (Lessard *et al.*, 1978). Of the 68 cases identified in 1970-74, 29 cases and 22/109 controls had been exposed to nickel, giving an age- and smoking-adjusted relative risk (RR) of 3.0. [The Working Group noted that control subjects were selected from among patients seen in the laboratory of one hospital, while cases were identified through a variety of sources. Selection bias could have contributed to the apparent excess risk.]

Another study showed no difference in the incidence of lung cancer (RR, 0.9, not significant) or of upper respiratory tract cancer (RR, 1.4; not significant) between nickel workers and the general population. In a case-control study conducted among the nickel workers, no association was found between cancers at these sites and exposure to total dust, nickeliferous dust, raw ore or calcined ore (Goldberg *et al.*, 1987). Subsequent analyses (Goldberg *et al.*, 1992) provided little evidence that people with lung and upper respiratory tract cancer had had greater exposure to nickel than controls. Exposure was principally to silicate oxides, complex oxides, sulfides, metallic iron-nickel alloy and soluble nickel. The estimated total airborne nickel concentration in the facility was estimated to be low (<2 mg/m^3 Ni) (ICNCM, 1990).

(vii) *Other studies of mining, smelting and refining*

Several studies have been published in which the results were not described in sufficient detail for evaluation. Saknyn and Shabynina (1970, 1973) reported elevated lung cancer mortality among process workers in four nickel smelters in the USSR (SMRs, 200, 280, 380, 400 [no observed numbers given]). Electrolysis workers, exposed mainly to nickel sulfate and nickel chloride, were reported to be at particularly high risk for lung cancer (SMR, 820); excesses of stomach cancer and soft-tissue sarcoma were also observed. Tatarskaya (1965, 1967) reported an excess of nasal cancer among electrolysis workers in the USSR.

Olejár *et al.* (1982) reported a marginal excess of lung cancer (based on eight cases) among workers in a Czechoslovak refinery.

One nasal sinus cancer and one lung cancer occurred among 129 men at the Outokumpu Oy refinery in Finland, but expected numbers were not calculated. Workers were exposed primarily to soluble nickel; the highest measurement recorded was 1.1 mg/m^3 Ni (ICNCM, 1990).

Egedahl and Rice (1984) found no excess risk among workers in a refinery in Alberta, Canada, but there were only two cases of lung cancer in the cohort (SIR, 83 [95% CI, 10-301]).

(*c*) *Nickel alloy and stainless-steel production*

(i) *Huntington Alloys (INCO), W. Virginia (refining and manufacture of high-nickel alloys)*

A cohort of 3208 men with at least one year's service before 1947 was followed up to the end of 1977 (Enterline & Marsh, 1982) and then to the end of 1984 (ICNCM, 1990). Workers were exposed to metallic, oxidic, sulfidic and soluble nickel at low levels, except in the calcining department where high levels of sulfidic nickel (4000 mg/m^3 Ni) were present. Average airborne exposures were estimated to have been below 1 mg/m^3 Ni in all areas except calcining. On the basis of the ICNCM report (1990), there was no significant overall excess of lung cancer (91 deaths; SMR, 97 [95% CI, 80-121]). There was a nonsignificant excess among men first employed before 1947 (when calcining ceased) with 30 or more years' service (40 deaths; SMR, 124; 95% CI, 88-169). The group who had worked in calcining for five or more years was too small for useful analysis (two lung cancers; SMR, 100; 95% CI, 12-361). Four deaths from nasal cancer occurred in the whole cohort, all in persons employed before 1948; two were coded on death certificates as nasal cancer (expected, 0.9) and two were classified on the death certificates as bone cancer. Two had not worked in calcining and three had never been exposed to nickel sulfides; one had also worked as a heel finisher in a shoe factory. There was no excess mortality from nonrespiratory cancers.

(ii) *Henry Wiggin, UK (high-nickel alloy plant)*

Mortality up to 1978 in a cohort of 1925 men employed for at least five years in a plant that opened in 1953 was reported by Cox *et al*., (1981). Follow-up has now been extended to April 1985 for 1907 men (ICNCM, 1990). Average exposures from 1975 on rarely exceeded 1 mg/m^3 Ni in any area, with an overall average of the order of 0.5 mg/m^3 Ni. Measurements taken since 1975 were stated probably to be underestimates of the level of exposure to oxidic and metallic nickel of workers in earlier periods. Soluble nickel was reported to constitute 14-49% of total nickel in various departments (Cox *et al.*, 1981). Thirty deaths were due to lung cancer (SMR, 98; 95% CI, 57-121), including 13 deaths among men employed for ten years or more in areas where they were exposed to nickel (SMR, 91; 95% CI, 57-149). Subdivision by duration of exposure or latency produced no evidence of increased lung cancer risk, and there was no nasal cancer. An excess of soft-tissue sarcoma was found, based on two cases (SMR, 769; 95% CI, 92-2769) (ICNCM, 1990).

(iii) *Twelve high-nickel alloy plants in the USA*

Mortality up to the end of 1977 among 28 261 workers (90% male) employed for at least one year in 12 high-nickel alloy plants in the USA, and still working at some time between 1956 and 1960, was reported by Redmond (1984). There were 332 lung cancer deaths (SMR, 109 [95% CI, 98-122]) and two nasal sinus cancer deaths (SMR, 93 [95% CI, 12-358]). The excess of lung cancer was confined to men employed for five or more years in 'allocated services', most of whom were maintenance workers (197 deaths; SMR, 127 [95% CI, 110-146]). Excess mortality was observed from liver cancer (31 deaths; SMR, 182 [95% CI, 124-259]) in all men, and from cancer of the large intestine (SMR, 223 [95% CI, 122-375]) among non-white men. No data on exposure were available, but the authors noted that there may have been exposure to asbestos in these plants.

(iv) *Twenty-six nickel-chromium alloy foundries in the USA*

A proportionate mortality analysis of 851 deaths among men ever employed in 26 nickel-chromium alloy foundries in the USA in 1968-79 (Cornell & Landis, 1984) showed no statistically significant excess of lung cancer (60 deaths; proportionate mortality ratio (PMR, 105 [95% CI, 80-135]) or other cancers (103 deaths; PMR, 87 [95% CI, 71-106]) in comparison with US males. No death was due to nasal cancer.

Lung cancer mortality in a cohort of foundry workers was investigated by Fletcher and Ades (1984). The cohort consisted of men hired between 1946 and 1965 in nine steel foundries in the UK and employed for at least one year. The 10 250 members of the cohort were followed up until the end of 1978 and assigned to 25 occupational categories according to information from personnel officers. Lung cancer mortality for the subcohort of fettlers and grinders in the fettling shop was higher than expected on the basis of mortality rates for England and Wales (32 cases; SMR, 195; 95% CI, 134-276). [The Working Group noted that these workers may have been exposed to chromium- and nickel-containing dusts.]

(v) *Seven stainless-steel and low-nickel alloy production plants in the USA*

A proportionate mortality analysis of 3323 deaths among white males ever employed in areas with potential exposure to nickel in seven stainless-steel and low-nickel alloy production plants (Cornell, 1984) showed no excess of lung cancer (218 deaths; PMR, 97 [95% CI, 85-111]) or of other cancers (419 deaths; PMR 91 [95% CI, 83-100]). There was no death from nasal cancer.

(*d*) *Other industrial exposures to nickel*

(i) *Two nickel-cadmium battery factories in the UK*

Kipling and Waterhouse (1967) reported an excess of prostatic cancer based on four cases among 248 men exposed for one year or longer in a nickel-cadmium battery factory.

The cohort was enlarged to include 3025 workers (85% men) employed for at least one month (Sorahan & Waterhouse, 1983, 1985), and the most recent report included deaths up to the end of 1984 (Sorahan, 1987). Exposure categories were defined on the basis of exposure to cadmium. The authors commented that almost all jobs with high exposure to cadmium also entailed high exposure to nickel hydroxide, and there was also possible exposure to welding fumes (Sorahan & Waterhouse, 1983). The excess of prostatic cancer cases was confined to highly exposed workers, among whom there were eight cases (SIR, 402 [95% CI, 174-792]); in the remainder of the cohort there were seven (SIR, 78 [95% CI, 31-160]) (Sorahan & Waterhouse, 1985). An excess of cancer of the lung was seen (110 deaths; SMR, 130 [95% CI, 107-157]), and this showed a significant association with duration in 'high exposure' jobs, particularly among men first employed before 1947 (Sorahan, 1987).

(ii) *A nickel-cadmium battery factory in Sweden*

A total of 525 male workers in a Swedish nickel-cadmium battery factory employed for at least one year were followed up to 1980 (Andersson *et al.*, 1984). Six deaths were due to lung cancer (SMR, 120 [95% CI, 44-261]), four to prostatic cancer (SMR, 129 [95% CI, 35-330]) and one to nasopharyngeal cancer (SMR, > 1000). Cadmium levels prior to 1950 were said to have been about 1 mg/m^3 in some areas; nickel levels were reported as 'about five times higher', although no actual measurement was reported.

(iii) *A nickel and chromium plating factory in the UK*

A total of 2689 workers (48% male) employed in a nickel-chromium plating factory in the UK were followed to the end of 1983 by Sorahan *et al.* (1987). There was excess mortality from lung cancer (72 deaths; SMR, 150 [95% CI, 117-189]) and nasal cancer (three deaths; SMR, 1000 [95% CI, 206-2922]), but this was confined to workers whose initial employment had been as chrome bath platers, and the lung cancer excess was significantly related to duration of chrome bath work. An earlier study of 508 men employed only as nickel platers in the factory (Burges, 1980) showed no excess for any cancer except that of the stomach (eight deaths; SMR, 267); among men with more than one year's employment, the SMR for stomach cancer was 476 (adjusted for social class and region; four deaths [95% CI, 130-1219]). The SMR for lung cancer was 122 [95% CI, 59-224].

(iv) *A die-casting and electroplating plant in the USA*

A proportionate mortality analysis of 238 deaths (79% male) in workers employed for at least ten years in a die-casting and electroplating plant in the USA was reported by Silverstein *et al.* (1981). There was excess mortality from lung cancer (28 deaths; PMR 191 [95% CI, 127-276]) among white men, but not for cancer at any other site. The PMRs for lung cancer by duration of employment were 165 (<15 years) and 209 (≥15 years), and

those by latency were 178 (< 22.5 years) and 211 (≥ 22.5 years). The authors noted that the workers had been exposed to chromium[VI], polycyclic aromatic hydrocarbons and various compounds of nickel.

(v) *Oak Ridge gaseous diffusion plant, Tennessee, USA*

Fine pure nickel powder is used as barrier material in uranium enrichment by gaseous diffusion. A cohort of 814 white men employed at any time before 1954 in the production of this material was followed up from 1948 to 1972 by Godbold and Tompkins (1979). Exposure was thus entirely to metallic nickel. Follow-up was extended to the end of 1977 by Cragle *et al.* (1984), and mortality up to the end of 1982 was reported by ICNCM (1990). The median concentration of nickel was about 0.13 mg/m^3, but high concentrations occurred in some areas. About 300 of the 814 men had been employed for a total of less than two years. There was no excess of lung cancer, either overall (nine deaths; SMR, 54; 95% CI, 25-103) or among men employed for 15 years or longer (five deaths; SMR, 109 [95% CI, 35-254]), and mortality from other cancers was close to that expected (29 deaths; SMR, 96 [95% CI, 64-137]) for the whole cohort. No death from nasal cancer occurred, but only 0.22 were expected. [The Working Group noted that measurements made in 1948-63 (Godbold & Tompkins, 1979) suggest that the average exposure may have been to 0.5 mg/m^3 Ni.]

(vi) *Aircraft engine factory, Connecticut, USA*

Bernacki *et al.* (1978b) compared the employment histories of 42 men at an aircraft engine factory in the USA who had died of lung cancer with those of 84 age-matched men who had died of causes other than cancer. The proportion classified as nickel-exposed was identical (26%) among cases and controls. Atmospheric nickel concentrations in the past were believed to have been < 1 mg/m^3.

(*e*) *Other studies*

Several studies have been reported in which occupational histories of nasal cancer patients were sought by interview with patients or relatives, from medical or other records, or from death certificates. Acheson *et al.* (1981), in a study of 1602 cases diagnosed in England and Wales over a five-year period, found an excess (29 cases; SMR, 250 [95% CI, 167-359]) in furnace and foundry workers, which was partly (but not entirely) due to the inclusion of seven process workers from the INCO (Clydach) nickel refinery (see above). Hernberg *et al.* (1983) studied 287 cases diagnosed in Denmark, Finland or Sweden over a 3.5-year period. The association with exposure to nickel (12 cases, five matched controls among 167 matched case-control pairs who were interviewed; odds ratio, 2.4; 95% CI, 0.9-6.6) was not statistically significant. All except one of the nickel-exposed cases (a nickel refinery worker) had also been classified as having exposure to chromium (odds ratio, 2.7;

95% CI, 1.1-6.6), which was significantly associated with nasal cancer risk. Brinton *et al*. (1984) recorded exposure to nickel in only one (RR, 1.8; 95% CI, 0.1-27.6) of 160 cases and one of 290 controls in a hospital-based study between 1970 and 1980 in North Carolina and Virginia. Roush *et al.* (1980) examined exposure to nickel, cutting oils and wood dust in a case-control study based on all sinonasal cancer deaths in Connecticut in 1935-75. Job titles were obtained from deaths certificates and city directories and were classified according to estimated airborne exposures. Ten of 216 cases and 49 of 662 controls were classified as having been exposed to nickel (RR, 0.71; 95% CI, 0.4-1.5).

Gérin *et al.* (1984) reported significantly more frequent exposure to nickel among 246 Canadian lung cancer patients (29 exposed; odds ratio, 3.1; 95% CI, 1.9-5.0) than among patients with other cancers. All 29 cases had also been exposed to chromium, and 20 (69%) had been exposed to stainless-steel welding fumes. In a case-control study of 326 Danish laryngeal cancer patients, Olsen and Sabroe (1984) found a statistically significant association with exposure to nickel from alloys, battery chemicals and chemicals used in plastics production (RR, 1.7; 95% CI, 1.2-2.5; adjusted for age, tobacco and alcohol consumption and sex).

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin contact occur in nickel and nickel alloy production plants as well as in welding, electroplating, grinding and cutting operations. Airborne nickel levels in excess of 1 mg/m^3 have been found in nickel refining, in the production of nickel alloys and nickel salts, and in grinding and cutting of stainless-steel. In these industries, modern control technologies have markedly reduced exposures in recent years. Few data are available to estimate the levels of past exposures to total airborne nickel, and the concentrations of individual nickel compounds were not measured.

Occupational exposure has been shown to give rise to elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake. Non-occupational sources of nickel exposure include food, air and water, but the levels found are usually several orders of magnitude lower than those typically found in occupational situations.

Table 26. INCO Ontario (Canada) nickel refinery facilities – average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a]

Plant	Department	Estimated airborne concentration (mg/m^3 Ni)					Duration in department							
							Ever				≥5 years			
							Lung cancer		Nasal cancer		Lung cancer		Nasal cancer	
		Metallic nickel	Oxidic nickel	Sulfidic nickel	Soluble nickel	Total nickel	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Coniston	Sinter	Negl.[b]	0.1–0.5	1–5	Negl.	1–5	8	292 (126–576)	0	–	6	492 (181–1073)	0	–
Copper Cliff	Sinter													
1948–54		Negl.	25–60	15–35	<4	40–100	63	307 (238–396)	6	3617 (1327–7885)	33	789 (543–1109)	4	13 146 (3576–33 654)
1955–63		Negl.	5–25	3–15	<2	8–40								
Port Colborne	Leaching, calcining,													
1926–35	sintering	Negl.	20–40	10–20	<3	30–80	72	239 (187–302)	19	7776 (4681–12 144)	38	366 (259–502)	15	18 750 (10 500–30 537)
1936–45		Negl.	3–15	2–10	<3	5–25								
1946–58		Negl.	5–25	3–15	<3	8–40								
	Electrolysis	<0.5	<0.2	<0.5	<0.3	<1	19	88[d] (53–137)	0[c,d]	–	10[d,e]	89	0[c,d]	–

[a]From ICNCM (1990), estimated average airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department; standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]Negl., negligible exposure

[c]Two nasal cancer deaths occurred in men with >20 years in electrolysis and only short exposure (three months and seven months) in leaching, calcining and sintering

[d]Never worked in leaching, calcining and sintering

[e]Workers with ≥10 years in electrolysis

Table 27. MOND/INCO (Clydach, South Wales, UK) nickel refinery – average nickel exposure levels and cancer risks in 'high-risk' departments in workers with 15 or more years since first exposure[a]

Department	Estimated airborne concentration (mg/m^3 Ni)[b]				Duration in department							
					Ever				≥5 years			
					Lung cancer		Nasal cancer		Lung cancer		Nasal cancer	
	Metallic nickel	Oxidic nickel	Sulfidic nickel	Soluble nickel	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Furnaces, 1905–63	5.6	6.4	2.6	0.4	9	409	3	24 781	1	370	3	1000
Linear calciners, 1902–30; milling and grinding, 1902–36	5.3	18.8	6.8	0.8	16	725	7	44 509	12	1244	6	78 280
Copper plant, before 1937	–	13.1	0.4	1.1	17	317 (185–507)	5	13 912 (4507–32 415)	8	541 (233–1066)	2	14 541 (1759–52 493)
1938–60	–	0.4	0.01	0.01	–		–		–		–	
Hydrometallurgy 1902–79	0.5	0.9	0.05	1.3	7	196 (79–404)	4	18 779 (5108–48 074)	5	333 (108–776)	4	36 363 (9891–93 089)

[a]From ICNCM (1990); estimated average airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department. In each row, observations are restricted to men with < 1 year employment in other high-risk departments. Standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]The Working Group expressed reservations about the accuracy of these estimates, as discussed on p. 391.

Table 28. Falconbridge (Kristiansand, Norway) nickel refinery – average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a]

Department	Estimated airborne concentration (mg/m^3 Ni)				Duration in department							
	Metallic nickel	Oxidic nickel	Sulfidic nickel	Soluble nickel	Ever				≥5 years			
					Lung cancer		Nasal cancer[b]		Lung cancer		Nasal cancer[b]	
					Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Calcining, roasting, smelting; never in electrolysis	0.3–1.3	5.0–10.0	0.3	Negl.[c]	14	225 (122–377)	5	-	8	254 (109–500)	5	-
Electrolysis; never in calcining, roasting smelting	0.3–1.3	0.3–1.3	Negl.–1.3	1.3–5.0	30	385 (259–549)	2	-	19	476 (287–744)	2	-

[a]From ICNCM (1990); estimated average airborne concentrations of nickel species and mortality from or incidence of lung cancer and nasal cancer by department; standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]Three deaths and four incident cases

[c]Negl., negligible exposure

4.2 Experimental carcinogenicity data

Metallic nickel and nickel alloys

Metallic nickel was tested by inhalation exposure in mice, rats and guinea-pigs, by intratracheal instillation in rats, by intramuscular injection in rats and hamsters, and by intrapleural, subcutaneous, intraperitoneal and intrarenal injection in rats. The studies by inhalation exposure were inadequate for an assessment of carcinogenicity. After intratracheal instillation, it produced significant numbers of squamous-cell carcinomas and adenocarcinomas of the lung. Intrapleural injections induced sarcomas. Subcutaneous administration of metallic nickel pellets induced sarcomas in rats, intramuscular injection of nickel powder induced sarcomas in rats and hamsters, and intraperitoneal injections induced carcinomas and sarcomas. No significant increase in the incidence of local kidney tumours was seen following intrarenal injection.

Nickel alloys were tested by intramuscular, intraperitoneal and intrarenal injection and by subcutaneous implantation of pellets in rats. A ferronickel alloy did not induce local tumours after intramuscular or intrarenal injection. Two powdered nickel alloys induced malignant tumours following intraperitoneal injection, and one nickel alloy induced sarcomas following subcutaneous implantation in pellets.

Nickel oxides and hydroxides

Nickel monoxide was tested by inhalation exposure in rats and hamsters, by intratracheal instillation in rats, by intramuscular administration in two strains of mice and two strains of rats, and by intrapleural, intraperitoneal and intrarenal injection in rats. The two studies by inhalation exposure in rats were inadequate for an assessment of carcinogenicity; lung tumours were not induced in the study in hamsters. Intratracheal instillation resulted in a significant incidence of lung carcinomas. Local sarcomas were induced at high incidence after intrapleural, intramuscular and intraperitoneal injection. No renal tumour was seen following intrarenal injection.

Two studies in rats in which *nickel trioxide* was injected intramuscularly or intracerebrally were inadequate for evaluation.

In a study in which *nickel hydroxide* was tested in three physical states by intramuscular injection in rats, local sarcomas were induced by dry gel and crystalline forms. Local sarcomas were induced in one study in which nickel hydroxide was tested by intramuscular injection in rats.

Nickel sulfides

Nickel subsulfide was tested by inhalation exposure and by intratracheal instillation in rats, by subcutaneous injection to mice and rats, by intramuscular administration to mice,

rats, hamsters and rabbits, by intrapleural, intraperitoneal, intrarenal, intratesticular, intraocular and intra-articular administration in rats, by injection into retroperitoneal fat in rats, by implantation into rat heterotopic tracheal transplants and by administration to pregnant rats.

After exposure by inhalation, rats showed a significant increase in the incidence of benign and malignant lung tumours. Multiple intratracheal instillations resulted in malignant lung tumours (adenocarcinomas, squamous-cell carcinomas and mixed tumours).

A high incidence of local sarcomas was observed in rats after intrapleural administration. Subcutaneous injection induced sarcomas in mice and rhabdomyosarcomas and fibrous histiocytomas in rats. Nickel subsulfide has been shown consistently to induce local sarcomas following intramuscular administration, and dose-response relationships were demonstrated in rats and hamsters. The majority of the sarcomas induced were of myogenic origin, and the incidences of metastases were generally high. In rats, strain differences in tumour incidence and local tissue responses were seen. After intramuscular implantation of millipore diffusion chambers containing nickel subsulfide, a high incidence of local sarcomas was induced.

Mesotheliomas were included among the malignancies induced by intraperitoneal administration. Intrarenal injections resulted in a dose-related increase in the incidence of renal-cell neoplasms. A high incidence of sarcomas (including some rhabdomyosarcomas) was seen after intratesticular injection, and a high incidence of eye neoplasms (including retinoblastomas, melanomas and gliomas) after intraocular injection. Intra-articular injection induced sarcomas (including rhabdomyosarcomas and fibrous histiocytomas), and injection into retroperitoneal fat induced mainly fibrous histiocytomas. Implantation of pellets containing nickel subsulfide into rat heterotopic tracheal transplants induced both carcinomas and sarcomas; in the group given the highest dose, sarcomas predominated. The study in which pregnant rats were injected with nickel subsulfide early in gestation was inadequate for evaluation.

Nickel disulfide was tested by intramuscular and intrarenal injection in rats. High incidences of local tumours were induced.

Nickel monosulfide was tested by intramuscular and intrarenal injection in rats. The crystalline form induced local tumours, but the amorphous form did not.

Nickel ferrosulfide matte induced local sarcomas after administration by intramuscular injection in rats.

Nickel salts

Nickel sulfate was tested for carcinogenicity by intramuscular and intraperitoneal injection in rats. Repeated intramuscular injections did not induce local tumours; however,

intraperitoneal injections induced malignant tumours in the peritoneal cavity.

Nickel chloride was tested by repeated intraperitoneal injections in rats, inducing malignant tumours in the peritoneal cavity.

Nickel acetate was tested by intraperitoneal injection in mice and rats. After repeated intraperitoneal injections in rats, malignant tumours were induced in the peritoneal cavity. In strain A mice, lung adenocarcinomas were induced in one study and an increased incidence of pulmonary adenomas in two studies.

Studies in rats in which *nickel carbonate* was tested for carcinogenicity by intraperitoneal administration and *nickel fluoride* and *nickel chromate* by intramuscular injection could not be evaluated.

Other forms of nickel

Nickel carbonyl was tested for carcinogenicity by inhalation exposure and intravenous injection in rats. After inhalation exposure, a few lung carcinomas were observed two years after the initial treatment. Intravenous injection induced an increase in the overall incidence of neoplasms, which were located in several organs.

Nickelocene induced some local tumours in rats and hamsters following intramuscular injection.

One sample of *dust collected in nickel refineries*, containing nickel subsulfide and various proportions of nickel monoxide and nickel sulfate, induced sarcomas in mice and rats following intramuscular injection. Intraperitoneal administration of two samples of dust, containing unspecified nickel sulfides and various proportions of nickel oxide, soluble nickel and metallic nickel, induced sarcomas in rats. In a study in which hamsters were given prolonged exposure to a *nickel-enriched fly ash* by inhalation, the incidence of tumours was not increased.

Intramuscular administration to rats of *nickel sulfarsenide*, two *nickel arsenides*, *nickel antimonide*, *nickel telluride* and two *nickel selenides* induced significant increases in the incidence of local sarcomas, whereas administration of *nickel monoarsenide* and *nickel titanate* did not. None of these compounds increased the incidence of renal-cell tumours in rats after intrarenal injection.

4.3 Human carcinogenicity data

Increased risks for lung and nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand) and the UK (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant) and extraction of nickel salts from concentrated solution (hydrometallurgy) in the UK (see Table 26).

The substantial excess risk for lung and nasal cancer among Clydach hydrometallurgy workers seems likely to be due, at least partly, to their exposure to 'soluble nickel'. Their estimated exposures to other types of nickel (metallic, sulfidic and oxidic) were up to an order of rnagnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. Similarly, high risks for lung and nasal cancers were observed among electrolysis workers at Kristiansand. These men were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate was the only or predominant soluble nickel species present in these areas.

The highest risks for lung and nasal cancers were observed among calcining workers, who were heavily exposed to both sulfidic and oxidic nickel. A high lung cancer rate was also seen among nickel plant cleaners at Clydach, who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides cannot be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in calcining furnaces and nickel plant cleaners were also exposed to high levels of metallic nickel.

Among hard-rock sulfide nickel ore miners in Canada, there was some increase in lung cancer risk, but exposure to other substances could not be excluded. In studies of open-cast miners of silicate-oxide nickel ores in the USA and in New Caledonia, no significant increase in risk was seen, but the numbers of persons studied were small and the levels of exposure were reported to be low.

No significant excess of respiratory tract cancer was observed in three studies of workers in high-nickel alloy manufacture or in a small study of users of metallic nickel powder. No increase in risk for lung cancer was observed in one small group of nickel electroplaters in the UK with no exposure to chromium.

In a case-control study, an elevated risk for lung cancer was found among persons exposed to nickel together with chromium-containing materials.

The results of epidemiological studies of stainless-steel welders are consistent with the finding of excess mortality from lung cancer among other workers exposed to nickel compounds, but they do not contribute independently to the evaluation of nickel since welders are also exposed to other compounds. (See also the monograph on welding.)

4.4 Other relevant data

Nickel and nickel compounds are absorbed from the respiratory tract, and to a smaller extent from the gastrointestinal tract, depending on dissolution and cellular uptake. Absorbed nickel is excreted predominantly in the urine. Nickel tends to persist in the lungs of humans and of experimental animals, and increased concentrations are seen notably in

workers after inhalation of nickel. The nasal mucosa may retain nickel for many years.

Nickel carbonyl is the most acutely toxic nickel compound and causes severe damage to the respiratory system in experimental animals and in humans. Nickel causes contact dermatitis in humans. In experimental animals, adverse effects have also been documented in the respiratory system and in the kidney.

In four studies, the frequency of sister chromatid exchange did not appear to be increased in peripheral blood lymphocytes of nickel workers exposed during various processes. Enhanced frequencies of chromosomal gaps and/or anomalies were observed in single studies in peripheral blood lymphocytes of employees engaged in: (i) crushing, roasting and smelting (exposure mainly to nickel oxide and nickel subusulfide); (ii) electrolysis (exposure mainly to nickel chloride and nickel sulfate); and (iii) electroplating (exposure to nickel and chromium compounds). Enhanced frequencies were also seen in lymphocytes from retired workers who had previously been exposed in crushing, roasting and smelting and/or electrolysis.

Some nickel compounds have adverse effects on reproduction and prenatal development in rodents. Decreased fertility, reduction in the number of pups per litter and birth weight per pup, and a pattern of anomalies, including eye malformations, cystic lungs, hydronephrosis, cleft palate and skeletal deformities, have been demonstrated.

In one study, metallic nickel did not induce chromosomal aberrations in cultured human cells, but it transformed animal cells *in vitro*. Nickel oxides induced anchorage-independent growth in human cells *in vitro* and transformed cultured rodent cells; they did not induce chromosomal aberrations in cultured human cells in one study.

Crystalline nickel subsulfide induced anchorage-independent growth and increased the frequency of sister chromatid exchange but did not cause gene mutation in human cells *in vitro*. Crystalline nickel sulfide and subsulfide induced cell transformation, gene mutation and DNA damage in cultured mammalian cells; the sulfide also induced chromosomal aberrations and sister chromatid exchange. Amorphous nickel sulfide did not transform or produce DNA damage in cultured mammalian cells. In one study, crystalline nickel sulfide and crystalline nickel subsulfide produced DNA damage in *Paramoecium*.

Nickel chloride and nickel nitrate were inactive in assays *in vivo* for induction of dominant lethal mutation and micronuclei, and nickel sulfate did not induce chromosomal aberrations in bone-marrow cells; however, nickel chloride induced chromosomal aberrations in Chinese hamster and mouse bone-marrow cells.

Soluble nickel compounds were generally active in the assays of human and animal cells *in vitro* in which they were tested.

Nickel sulfate and nickel acetate induced anchorage-independent growth in human cells *in vitro*. Nickel sulfate increased the frequency of chromosomal aberrations in human cells, and nickel sulfate and nickel chloride increased the frequency of sister chromatid exchange. Nickel sulfate did not induce single-strand DNA breaks in human cells. Nickel sulfate and nickel chloride transformed cultured mammalian cells. Chromosomal aberrations were induced in mammalian cells by nickel chloride, nickel sulfate and nickel acetate, and sister chromatid exchange was induced by nickel chloride and nickel sulfate. Nickel chloride and nickel sulfate also induced gene mutation, and nickel chloride caused DNA damage in mammalian cells. In one study, nickel sulfate inhibited intercellular communication in cultured mammalian cells.

Nickel sulfate induced aneuploidy and gene mutation in a single study in *Drosophila*; nickel chloride and nickel nitrate did not cause gene mutation. Nickel chloride induced gene mutation and recombination in yeast.

In single studies, nickel acetate produced DNA damage in bacteria, while nickel nitrate did not; the results obtained with nickel chloride were inconclusive. In bacteria, neither nickel acetate, sulfate, chloride nor nitrate induced gene mutation.

Nickel carbonate induced DNA damage in rat kidney *in vivo*. Crystalline nickel subselenide transformed cultured mammalian cells, and nickel potassium cyanide increased the frequency of chromosomal aberrations. Nickelocene did not induce bacterial gene mutation. DNA damage was induced in calf thymus nucleohistone by nickel[III]-tetraglycine complexes.

4.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry.

There is *inadequate evidence* in humans for the carcinogenicity of metallic nickel and nickel alloys.

There is *sufficient evidence* in experimental animals for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides and crystalline nickel sulfides.

There is *limited evidence* in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides and nickel telluride.

[1]For descriptions of the italicized terms, see Preamble.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel trioxide, amorphous nickel sulfide and nickel titanate.

The Working Group made the overall evaluation on nickel compounds as a group on the basis of the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and several types of other relevant data, supported by the underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells.

Overall evaluation

Nickel compounds *are carcinogenic to humans (Group 1).*

Metallic nickel is *possibly carcinogenic to humans (Group 2B).*

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Summary Table of Genotoxicity Tests for Nickel (Metallic, Alloys, Compounds, and Occupational Exposures)

END PT.	TEST CODE	TEST SYSTEM	RESULTS[a] NM	RESULTS[a] M	DOSE[1] (LED OR KID)	REFERENCE
METALLIC NICKEL						
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	20.0000	COSTA *ET AL.* 1981b
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	200.0000	HANSEN & STERN 1984
C	CHL	CHROM ABERR, HUMAN LYMPHOCYTES *IN VITRO*	-	0	0.0000	PATON & ALLISON 1972
MILD STEEL WELDING (METAL INERT GAS)						
D	ECD	*E. COLI* POL A, DIFFERENTIAL TOX (SPOT)	-	-	0.0000	HEDENSTEDT *ET AL.* 1977
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	-	0.0000	HEDENSTEDT *ET AL.* 1977
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	-	4000.0000	MAXILD *ET AL.* 1978
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	-	10000.0000	ETIENNE *ET AL.* 1986
G	SA2	*S. TYPHIMURIUM* TA102, REVERSE MUTATION	-	-	10000.0000	ETIENNE *ET AL.* 1986
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	-	4000.0000	MAXILD *ET AL.* 1978
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	-	10000.0000	ETIENNE *ET AL.* 1986
G	SAS	*S. TYPHIMURIUM* (OTHER), REVERSE MUTATION	-	-	10000.0000	ETIENNE *ET AL.* 1986
S	SIC	SCE, CHINESE HAMSTER CELLS *IN VITRO*	-	0	750.0000	DE RAIT & BAKKER 1988
C	CIC	CHROM ABERR, CHINESE HAMSTER CELLS *IN VITRO*	-	0	1000.0000	ETIENNE *ET AL.* 1986
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	-	0	600.0000	HANSEN & STERN 1985
S	SVA	SCE, ANIMALS *IN VIVO*	-	0	26.0000	ETIENNE *ET AL.* 1986
C	CBA	CHROM ABERR, ANIMAL BONE MARROW *IN VIVO*	-	0	26.0000	ETIENNE *ET AL.* 1986
C	CLA	CHROM ABERR, ANIMAL *LEUKOCYTES IN VIVO*	-	0	26.0000	ETIENNE *ET AL.* 1986
NICKEL OXIDES						
D	BSD	*B. SUBTILIS REC*, DIFFERENTIAL TOXICITY[2]	-	0	1475.0000	KANEMATSU *ET AL.* 1980
D	BSD	*B. SUBTILIS REC*, DIFFERENTIAL TOXICITY[3]	-	0	2950.0000	KANEMATSU *ET AL.* 1980
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY[2]	+	0	16.0000	COSTA *ET AL.* 1981b
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY[3]	+	0	14.0000	COSTA *ET AL.* 1981b
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY[3]	+	0	7.9000	SUNDERMAN *ET AL.* 1987
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES[2]	+	0	30.0000	HANSEN & STERN 1983
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES[3]	+	0	4.0000	HANSEN & STERN 1983
C	CHL	CHROM ABERR, HUMAN LYMPHOCYTES *IN VITRO*[3]	-	0	0.0000	PATON & ALLISON 1972
T	THH	CELL TRANSFORMATION, HUMAN CELLS *IN VITRO*[3]	+	0	3.0000	BIEDERMANN & LANDOLPH 1987

[1]Doses are given as concentrations of the element, not the concentration of the compound.
[2]Nickel trioxide
[3]Nickel monoxide

[a] + positive
- negative

(+) weakly positive or limited study
(-) weakly negative or limited study

END PT.	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
NICKEL SULFIDES (AMORPH.)						
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	-	0	6.5000	COSTA *ET AL.* 1982
D	RIA	OTHER DNA REPAIR, ANIMAL CELLS *IN VITRO*	-	0	6.5000	ROBISON *ET AL.* 1983
G	GCO	MUTATION, CHO CELLS *IN VITRO*	(+)	0	1.0000	COSTA *ET AL.* 1980
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	-	0	3.2500	COSTA *ET AL.* 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	-	0	6.5000	COSTA & MOLLENHAUER 1980a
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	-	0	6.5000	COSTA *ET AL.* 1982

[1]Doses are given as concentrations of the element, not the concentration of the compound.

END PT.	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
NICKEL SULFIDES (CRYST.)						
C	PSC	*PARAMECIUM* SPECIES, CHROM ABERR	+	0	0.3000	SMITH--SONNEBORN *ET AL.* 1983
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	(+)	0	114.0000	SINA *ET AL.* 1983
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	6.5000	COSTA *ET AL.* 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	0.6500	ROBISON & COSTA 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	6.5000	PATIERNO & COSTA 1985
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	7.3000	ROBINSON *ET AL.* 1982
D	RIA	OTHER DNA REPAIR, ANIMAL CELLS *IN VITRO*	+	0	0.6500	ROBISON *ET AL.* 1993
G	G9H	MUTATION, CHL V79 CELLS, HPRT	+	0	4.9000	CHRISTIE *ET AL.* 1990
S	SIC	SCE, CHINESE HAMSTER CELLS *IN VITRO*	+	0	0.6500	SEN & COSTA 1986
C	CIC	CHROM ABERR, CHINESE HAMSTER CELLS *IN VITRO*	+	0	3.2000	SEN & COSTA 1985
C	CIM	CHROM ABERR, MOUSE CELLS *IN VITRO*	+	0	1.6000	SEN *ET AL.* 1987
C	CIT	CHROM ABERR, TRANSFORMED CELLS *IN VITRO*	+	0	38.0000	UMEDA & NISHIMURA 1979
C	CIT	CHROM ABERR, TRANSFORMED CELLS *IN VITRO*	+	0	24.0000	NISHIMURA & UMEDA 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	6.5000	COSTA *ET AL.* 1982
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	3.2500	COSTA & MOLLENHAUER 1980c
C	CVA	CHROM ABERR, OTHER ANIMAL CELLS *IN VIVO*	+	0	250.0000	CHRISTIE *ET AL.* 1988

[1]Doses are given as concentrations of the element, not the concentration of the compound.

END PT.	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
NICKEL SUBSULFIDES						
C	PSC	*PARAMECIUM* SPECIES, CHROM ABERR	+	0	0.4000	SMITH-SONNEBORN *ET AL.* 1983
D	RIA	OTHER DNA REPAIR, ANIMAL CELLS *IN VITRO*	+	0	7.3000	ROBISON *ET AL.* 1983
D	URP	UDS, RAT PRIMARY HEPATOCYTES	-	0	20.0000	SWIERENGA & MCLEAN 1985
G	GCO	MUTATION, CHO CELLS *IN VITRO*	(+)	0	1.1000	COSTA *ET AL.* 1980
G	GIA	MUTATION, OTHER ANIMAL CELLS *IN VITRO*	+	0	3.7000	SWIERENGA & MCLEAN 1985
T	TCM	CELL TRANSFORMATION, C3HIOT1/2 CELLS	+	0	0.0007	SAXHOLM *ET AL.* 1981
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	0.7300	DIPAOLO & CASTO 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	0.0730	COSTA *ET AL.* 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	0.7300	COSTA & MOLLENHAUER 1980a
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	3.7000	COSTA & MOLLENHAUER 1980c
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	3.7000	HAMEN & STERN 1983
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	1.8000	SWIERENGA *ET AL.* 1989
G	GIH	MUTATION, HUMAN CELLS *IN VITRO*	-	0	0.6000	BIEDERMANN & LANDOLPH 1987
S	SHL	SCE, HUMAN LYMPHOCYTES *IN VITRO*	+	0	0.7300	SAXHOLM *ET AL.* 1981
T	TIH	CELL TRANSFORMATION, HUMAN CELLS *IN VITRO*	+	0	0.6000	BIEDERMANN & LANDOLPH 1987
NICKEL CHLORIDE						
D	ERD	*E. COLI* REC, DIFFERENTIAL TOXICITY	-	-	567.0000	DE FLORA *ET AL.* 1984a
D	ERD	*E. COLI* REC, DIFFERENTIAL TOXICITY	+	0	90.0000	TWEATS *ET AL.* 1981
D	ERD	*E. COLI* REC, DIFFERENTIAL TOXICITY	-	0	0.0100	DUBINS & LA VELLE 1986
D	BSD	B. SURTILIS REC, DIFFERENTIAL TOXICITY	-	0	1475.0000	KANEMATSU *ET AL.* 1980
D	BSD	*B. SUBTILIS REC*, DIFFERENTIAL TOXICITY	-	0	147.5000	NISHIOKA 1975
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	0	587.0000	TSO & FUNG 1981
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SAO	S. TYPHIMURIUK TA100, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA2	*S. TYPHIMURIUM* TA102, REVERSE MUTATION	-	0	590.0000	BIGGART & COSTA 1986
G	SA5	*S. TYPHIMURIUM* TA1535, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA5	*S. TYPHIMURIUM* TA1535, REVERSE MUTATION	-	0	118.0000	BIGGART & COSTA 1986
G	SA5	*S. TYPHIMURIUM* TA1535, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA7	*S. TYPHIMURIUM* TA1537, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA7	*S. TYPHIMURIUM* TA1537, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA8	*S. TYPHIMURIUM* TA1538, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA8	*S. TYPHIMURIUM* TA1538, REVERSE MUTATION	-	0	118.0000	BIGGART & COSTA 1986
G	SA8	*S. TYPHIMURIUM* TA1538, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	0	0.0000	DE FLORA *ET AL.* 1984a
G	SAS	*S. TYPHIMURIUM* (OTHER), REVERSE MUTATION	-	0	590.0000	TSO & FUNG 1981

[1] Doses are given as concentrations of the element, not the concentration of the compound.

END PT.	TEST CODE	TEST SYSTEM	RESULTS NM	M	DOSE (LED OR HID)	REFERENCE
G	SAS	*S. TYPHIMURIUM* (OTHER), REVERSE MUTATION	-	0	118.0000	BIGGART & COSTA 1986
G	SAS	*S. TYPHIMURIUM* (OTHER), REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	EC2	*E. COLI* WP2, REVERSE MUTATION	-	0	4.5000	GREEN *ET AL.* 1976
R	SCG	S. CEREVISIAE, GENE CONVERSION	+	0	176.0000	FUKUNAGA *ET AL.* 1982
G	SCR	S. CEREVISIAE, REVERSE MUTATION	+	0	1535.0000	EGILSSON *ET AL.* 1979
G	DMM	*D. MELANOGASTER*, SOMATIC MUTAT/RECOMB	-	0	12.0000	RASMUSON 1985
G	DMX	*D. MELANOGASTER*, SEX-LINKED RECESSIVES	-	0	248.0000	VOGEL 1976
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	0.4500	ROBISON & COSTA 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	150.0000	PATIERNO & COSTA 1985
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	5.9000	ROBISON *ET AL.* 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS *IN VITRO*	+	0	59.0000	ROBISON *ET AL.* 1984
D	RIA	OTHER MA REPAIR, ANIMAL CELLS *IN VITRO*	+	0	5.9000	ROBISON *ET AL.* 1983
G	GCO	MUTATION, CHO CELLS *IN VITRO*	(+)	0	0.0000	HSIE *ET AL.* 1979
G	G9H	MUTATION, CHL V79 CELLS, HPRT	(+)	0	23.0000	MIYAKI *ET AL.* 1979
G	G9H	MUTATION, CHL V79 CELLS, HPRT	+	0	29.5000	HARTWIG & BEYERSMANN 1989
NICKEL CHLORIDE						
G	G5T	MUTATION, L5178Y CELLS, TK LOCUS	+	0	10.0000	AMACHER & PAILLET 1980
G	GIA	MUTATION, OTHER ANIMAL CELLS *IN VITRO*	+	0	2.4000	BIGGART & MURPHY 1988
G	GIA	MUTATION, OTHER ANIMAL CELLS *IN VITRO*	+	0	45.0000	SWIERENGA & MCLEAN 1985
S	SIC	SCE, CHINESE HAMSTER CELLS *IN VITRO*	+	0	8.0000	OHNO *ET AL.* 1982
S	SIC	SCE, CHINESE HAMSTER CELLS *IN VITRO*	+	0	0.6000	SEN & COSTA 1986
S	SIC	SCE, CHINESE HAMSTER CELLS *IN VITRO*	+	0	17.7000	HARTWIG & BEYERSMANN 1989
C	CIC	CHROM ABERR, CHINESE HAMSTER CELLS *IN VITRO*	+	0	0.6000	SEN & COSTA 1985
C	CIC	CHROM ABERR, CHINESE HAMSTER CELLS *IN VITRO*	+	0	6.0000	SEN *ET AL.* 1987
C	CIT	CHROM ABERR, TRANSFORMED CELLS *IN VITRO*	(+)	0	38.0000	UMEDA & NISHIMURA 1979
C	CIT	CHROM ABERR, TRANSFORMED CELLS *IN VITRO*	+	0	35.0000	NISHIMURA & UMEDA 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	2.2500	ZHANG & BARRETT 1988
D	DVA	DNA STRAND BREAKS, ANIMAL CELLS *IN VIVO*	+	0	44.4000	SAPAKOGLU *ET AL.* 1997
D	DIH	STRAND BREAKS/X-LINKS, HUMAN CELLS *IN VITRO*	?	0	3.0000	MCLEAN *ET AL.* 1982
S	SHL	SCE, HUMAN LYMPHOCYTES *IN VITRO*	+	0	0.6000	NEWMAN *ET AL.* 1982
H	HMK	HOST-MEDIATED ASSAY, MICROBIAL CELLS	-	0	23.0000	BUSELMAIER *ET AL.* 1972
M	MVM	MICRONUCLEUS TEST, MICE *IN VIVO*	-	0	11.0000	DEKNUDT & LEONARD 1982
C	CBA	CHROM ABERR, ANIMAL BONE MARROW *IN VIVO*	+	0	2.3000	CHORVATOVICOVA 1983
C	CRA	CHROM ABERR, ANIMAL BONE MARROW *IN VIVO*	+	0	2.7000	MOHANTY 1987
C	DIM	DOMINANT LETHAL TEST, MICE	-	0	46.0000	DEKNUDT & LEONARD 1982

[1]Doses are given as concentrations of the element, not the concentration of the compound.

END PT.	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
NICKEL SULFATE						
G	BPF	BACTERIOPHAGE, FORWARD MUTATION	-	0	114.0000	CORBETT *ET AL.* 1970
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA5	*S. TYPHIMURIUM* TA1535, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA7	*S. TYPHIMURIUM* TA1537, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA8	*S. TYPHIMURIUM* TA1538, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	0	0.0000	ARIAJUSKAS *ET AL.* 1985
G	EC2	*E. COLI* WP2, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS *ET AL.* 1985
G	DMX	*D. MELANOGASTER*, SEX-LINKED RECESSIVES	+	0	45.0000	RODRIGUEZ-ARNAIZ & RAMOS 1986
A	DMN	*D. MELANOGASTER*, ANEUPLOIDY	(+)	0	90.0000	RODRIGUEZ-ARNAIZ & RAMOS 1986
G	GIA	MUTATION, OTHER ANIMAL CELLS *IN VITRO*	-	0	1.0000	RIVEDAL & SANNER 1980
G	GIA	MUTATION, OTHER ANIMAL CELLS *IN VITRO*	(+)	0	6.0000	CHRISTIE *ET AL.* 1990
S	SIC	SCE, CHINESE HAMSTER CELLS *IN VITRO*	+	0	0.1700	DENG & QU 1981
S	SIC	SCE, CHINESE HAMSTER CELLS *IN VITRO*	+	0	8.0000	OHNO *ET AL.* 1982
S	SIM	SCE, MOUSE CELLS *IN VITRO*	+	0	6.0000	ANDERSEN 1983
S	SIS	SCE, SYRIAN HAMSTER CELLS *IN VITRO*	+	0	0.2000	LARRAMENDY *ET AL.* 1981
S	SIA	SCE, OTHER ANIMAL CELLS *IN VITRO*	(+)	0	6.0000	ANDERSEN 1983
C	CIS	CHROM ABERR, SYRIAN HAMSTER CELLS *IN VITRO*	+	0	1.0000	LARRAMENDY *ET AL.* 1981
T	TCS	CELL TRANSFORMATION,SHE, CLONAL ASSAY	+	0	4.5000	RIVEDAL & SANNER 1980
T	TCS	CELL TRANSFORMATION,SHE, CLONAL ASSAY	+	0	9.0000	PIENTA *ET AL.* 1977
T	TCS	CELL TRANSFORMATION,SHE, CLONAL ASSAY	+	0	1.0000	DIPAOLO & CASTO 1979
T	TCS	CELL TRANSFORMATION,SHE, CLONAL ASSAY	+	0	1.9000	ZHANG & BARRETT 1988
T	TEV	CELL TRANSFORMATION,OTHER VIRAL SYSTEMS	+	0	4.0000	WILSON & KHOOBYARIAN 1982
D	DIH	STRAND BREAKS/X-LINKS, HUMAN CELLS *IN VITRO*	-	0	56.0000	FORNACE 1982
S	SIL	SCE, HUMAN LYMPHOCYTES *IN VITRO*	+	0	1.4000	WULF 1980
S	SIL	SCE, HUMAN LYMPHOCYTES *IN VITRO*	+	0	0.6000	LARRAMENDY *ET AL.* 1981
S	SIL	SCE, HUMAN LYMPHOCYTES *IN VITRO*	+	0	0.1000	DENG & QU 1981
S	SIL	SCE, HUMAN LYMPHOCYTES *IN VITRO*	+	0	0.6000	ANDERSEN 1983
C	CIL	CHROM ABERR, HUMAN LYMPHOCYTES *IN VITRO*	+	0	1.0000	LARRAMENDY *ET AL.* 1981
T	TIH	CELL TRANSFORMATION, HUMAN CELLS *IN VITRO*	+	0	4.0000	LECHNER *ET AL.* 1984
T	TIH	CELL TRANSFORMATION, HUMAN CELLS *IN VITRO*	+	0	0.6000	BIEDERMANN & LANDOLPH 1987
C	CBA	CHROM ABERR, ANIMAL BONE MARROW *IN VIVO*	-	0	1.3000	MATHUR *ET AL.* 1978
C	CCC	CHROM ABERR, SPERMATOCYTES	-	0	1.3000	MATHUR *ET AL.* 1978
I	ICR	INHIBIT CELL COMMUNICATION, ANIMAL CELLS	+	0	60.0000	MIKI *ET AL.* 1987

[1]Doses are given as concentrations of the element, not the concentration of the compound.

END PT.	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
NICKEL NITRATE						
D	ERD	E. COLI REC, DIFFERENTIAL TOXICITY	-	-	605.0000	DE FLORA *ET AL.* 1984a
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA5	*S. TYPHIMURIUM* TA1535, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA7	*S. TYPHIMURIUM* TA1537, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA8	*S. TYPHIMURIUM* TA1538, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SAS	*S. TYPHIMURIUM* (OTHER), REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	DMM	*D. MELANOGASTER*, SOMATIC MUTAT/RECOMB	-	0	8.2500	RASMUSON 1985
G	DMX	*D. MELANOGASTER*, SEX-LINKED RECESSIVES	-	0	8.2500	RASMUSON 1985
G	DMX	*D. MELANOGASTER*, SEX-LINKED RECESSIVES	-	0	407.0000	VOGEL 1976
M	MVM	MICRONUCLEUS TEST, MICE *IN VIVO*	-	0	18.0000	DEKNUDT & LEONARD 1982
C	DLM	DOMINANT LETHAL TEST, NICE	-	0	37.0000	DEKNUDT & LEONARD 1982
C	DLM	DOMINANT LETHAL TEST, MICE	-	0	18.0000	JAQUET & MAYENCE 1982

[1]Doses are given as concentrations of the element, not the concentration of the compound.

NICKEL ACETATE						
D	PRB	PROPHAGE, INDUCT/SOS/STRAND BREAKS/X-LINKS	(+)	0	9.4000	ROSSMAN *ET AL.* 1984
D	ERD	*E. COLI* REC, DIFFERENTIAL TOXICITY	-	-	417.0000	DE FLORA *ET AL.* 1984a
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA5	*S. TYPHIMURIUM* TA1535, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA7	*S. TYPHIMURIUM* TA1537, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA8	*S. TYPHIMURIUM* TA1538, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
G	SAS	*S. TYPHIMURIUM* (OTHER), REVERSE MUTATION	-	-	0.0000	DE FLORA *ET AL.* 1984a
C	CIT	CHROM ABERR, TRANSFORMED CELLS *IN VITRO*	+	0	38.0000	UMEDA & NISHIMURA 1979
C	CIT	CHROM ABERR, TRANSFORMED CELLS *IN VITRO*	+	0	35.0000	NISHIMURA & UMEDA 1979
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	33.0000	HANSEN & STERN 1983
T	THH	CELL TRANSFORMATION, HUMAN CELLS *IN VITRO*	+	0	0.6000	BIEDERMANN & LANDOLPH 1987

[1]Doses are given as concentrations of the element, not the concentration of the compound.

END PT.	TEST CODE	TEST SYSTEM	RESULTS NM	M	DOSE[1] (LED OR HID)	REFERENCE
NICKEL (OTHER COMPOUNDS)						
G	SAO	*S. TYPHIMURIUM* TA100, REVERSE MUTATION	-	-	50-0000	HAWORTH *ET AL.*, 1983 [2]
G	SA5	*S. TYPHIMURIUM* TA1535, REVERSE MUTATION	-	-	50-0000	HAWORTH *ET AL.*, 1983 [2]
G	SA7	*S. TYPHIMURIUM* TA1537, REVERSE MUTATION	-	-	50-0000	HAWORTH *ET AL.*, 1983 [2]
G	SA9	*S. TYPHIMURIUM* TA98, REVERSE MUTATION	-	-	167:0000	HAWORTH *ET AL.*, 1983 [2]
C	CIT	CHROM ABERR, TRANSFORMED CELLS *IN VITRO*	+	0	12.0000	NISHIMURA & UMEDA 1979 [4]
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	2.6000	COSTA & MOLLENHAUER 1980c [5]
D	DVA	STRAND.BREAKS/X-LINKS, ANIMALS *IN VIVO*	+	0	5.0000	CICCARELLI & WETTERHAHN 1982 [5]
D	DVA	STRAND BREAKS/X-LINKS, ANIMALS *IN VIVO*	+	0	7.5000	CICCARELLI *ET AL.* 1981 [5]

[1] Doses are given as concentrations of the element, not the concentration of the compound.
[2] Nickelocene
[3] Nickel potassium cyanide
[4] Nickel subselenide (crystalline)
[5] Nickel carbonate

NICKEL OCCUPATIONAL EXPOSURE						
S	SLH	SCE, HUMAN LYMPHOCYTES *IN VIVO*	-	0	0.1400	WAKSVIK *ET AL.* 1984 [1]
S	SLH	SCE, HUMAN LYMPHOCYTES *IN VIVO*	-	0	0.0680	WAKSVIK & BOYSEN 1982 [2]
S	SLH	SCE, HUMAN LYMPHOCYTES *IN VIVO*	-	0	0.0280	WAKSVIK & BOYSEN 1982 [3]
S	SLH	SCE, HUMAN LYMPHOCYTES *IN VIVO*	(+)	0	0.0140	DENG *ET AL.* 1983 [4]
S	SLH	SCE, HUMAN LYMPHOCYTES *IN VIVO*	-	0	0.0000	DENG *ET AL.* 1987 [5]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES *IN VIVO*	+	0	0.1400	WAKSVIK *ET AL.* 1984 [1]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES *IN VIVO*	+	0	0.0680	WAKSVIK & BOYSEN 1982 [2]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES *IN VIVO*	+	0	0.0280	WAKSVIK & BOYSEN, 1982 [3]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES *IN VIVO*	+	0	0.0140	DENG *ET AL.* 1983 [4]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES *IN VIVO*	-	0	0.0000	DENG *ET AL.* 1987 [5]
M	MVH	MICRONUCLEUS TEST, HUMAN CELLS *IN VIVO*	-	0	0.00002	KHLUNEN *ET AL.* 1997 [6]

[1] Nio and Ni 3 S 2 /NiC1 2F NiSO 4 (crushing, roasting, smelting and/or electrolysis)
[2] NiO and Ni 3 S 2 (crushing, roasting, smelting)
[3] NiCl 2 and NiSO 4 (electrolysis)
[4] Ni and chromium (electroplating)
[5] Ni(CO) 4 (production of nickel carbonyl)
[6] Ni in air of respirator (refining)

Source: IARC 1990

TEST SYSTEM CODE WORDS

Endpoint	*Code*	*Definition*
C	ACC	*Allium cepa*, chromosomal aberrations
A	AIA	Aneuploidy, animal cells *in vitro*
A	AIH	Aneuploidy, human cells *in vitro*
G	ANIF	*Aspergillus nidulans*, forward mutation
R	ANG	*Aspergillus nidulans*, genetic crossing-over
A	ANN	*Aspergillus nidulans*, aneuploidy
G	ANR	*Aspergillus nidulans*, reverse mutation
G	ASM	*Arabidopsis* species, mutation
A	AVA	Aneuploidy, animal cells *in vivo*
A	AVH	Aneuploidy, human cells *in vivo*
F	BFA	Body fluids from animals, microbial mutagenicity
F	BFH	Body fluids from humans, microbial mutagenicity
D	BHD	Binding (covalent) to DNA, human cells *in vivo*
D	BHP	Binding (covalent) to RNA or protein, human cells *in vivo*
D	BID	Binding (covalent) to DNA *in vitro*
D	BIP	Binding (covalent) to RNA or protein *in vitro*
G	BPF	Bacteriophage, forward mutation
G	BPR	Bacteriophage, reverse mutation
D	BRD	Other DNA repair-deficient bacteria, differential toxicity
D	BSD	*Bacillus subtilis* rec strains, differential toxicity
G	BSM	*Bacillus subtilis*, multigene test
D	BVD	Binding (covalent) to DNA, animal cells *in vivo*
D	BVP	Binding (covalent) to RNA or protein, animal cells *in vivo*
C	CBA	Chromosomal aberrations, animal bone-marrow cells *in vivo*
C	CBH	Chromosomal aberrations, human bone-marrow cells *in vivo*
C	CCC	Chromosomal aberrations, spermatocytes treated *in vivo*, spermatocytes observed
C	CGC	Chromosomal aberrations, spermatogonia treated *in vivo*, spermatocytes observed
C	CGG	Chromosomal aberrations, spermatogonia treated *in vivo*, spermatogonia observed
C	CHF	Chromosomal aberrations, human fibroblasts *in vitro*
C	CHL	Chromosomal aberrations, human lymphocytes *in vitro*
C	CHT	Chromosomal aberrations, transformed human cells *in vitro*
C	CIA	Chromosomal aberrations, other animal cells *in vitro*
C	CIC	Chromosomal aberrations, Chinese hamster cells *in vitro*
C	CIH	Chromosomal aberrations, other human cells *in vitro*
C	CIM	Chromosomal aberrations, mouse cells *in vitro*
G	G90	Gene mutation, Chinese hamster lung V79 cells, ouabain resistance
G	GCL	Gene mutation, Chinese hamster lung cells exclusive of V79 *in vitro*
G	GCO	Gene mutation, Chinese hamster ovary cells *in vitro*
G	G9H	Gene mutation, Chinese hamster lung V79 cells, *hprt* locus
G	GIA	Gene mutation, other animal cells *in vitro*
G	GIH	Gene mutation, human cells *in vitro*
G	GML	Gene mutation, mouse lymphoma cells exclusive of L5178Y *in vitro*
G	G5T	Gene mutation, mouse lymphoma L5178Y cells *in vitro*, TK locus
G	GVA	Gene mutation, animal cells *in vivo*
H	HMA	Host-mediated assay, animal cells in animal hosts
H	HMH	Host-mediated assay, human cells in animal hosts
H	HMM	Host-mediated assay, microbial cells in animal hosts

Endpoint	*Code*	*Definition*
C	CIR	Chromosomal aberrations, rat cells *in vitro*
C	CIS	Chromosomal aberrations, Syrian hamster cells *in vitro*
C	CIT	Chromosomal aberrations, transformed animal cells *in vitro*
C	CLA	Chromosomal aberrations, animal leukocytes *in vivo*
C	CLH	Chromosomal aberrations, human lymphocytes *in vivo*
C	COE	Chromosomal aberrations, oocytes or embryos treated *in vivo*
C	CVA	Chromosomal aberrations, other animal cells *in vivo*
C	CVH	Chromosomal aberrations, other human cells *in vivo*
D	DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*
D	DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*
C	DLM	Dominant lethal test, mice
C	DLR	Dominant lethal test, rats
C	DMC	*Drosophila melanogaster*, chromosomal aberrations
R	DMG	*Drosophila melanogaster*, genetic crossing-over or recombination
C	DMH	*Drosophila melanogaster*, heritable translocation test
C	DML	*Drosophila melanogaster*, dominant lethal test
G	DMM	*Drosophila melanogaster*, somatic mutation (and recombination)
A	DMN	*Drosophila melanogaster*, aneuploidy
G	DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations
D	DVA	DNA strand breaks, cross-links or related damage, animal cells *in vivo*
D	DVH	DNA strand breaks, cross-links or related damage, human cells *in vivo*
G	EC2	*Escherichia coli* WP2, reverse mutation
D	ECB	*Escherichia coli* (or E coli DNA), strand breaks, cross-links; DNA repair
D	ECD	*Escherichia coli* pol A/W131 10-P3478 differential toxicity (spot test)
G	ECF	*Escherichia coli* exclusive of strain K 12, forward mutation
G	ECK	*Escherichia coli* K12, forward or reverse mutation
D	ECL	*Escherichia coli* pol A/W31 10-P3478, diff. tox. (liquid suspension test)
G	ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation
G	ECW	*Escherichia coli* WP2 uvrA, reverse mutation
D	ERD	*Escherichia coli* rec strains, differential toxicity
G	G51	Gene mutation, mouse lymphoma L5178Y cells *in vitro*, all other loci
D	RVA	DNA repair exclusive of unscheduled DNA synthesis, animal cells *in vivo*
G	SAO	*Salmonella typhimurium* TA100, reverse mutation
G	SA2	*Salmonella typhimurium* TA102, reverse mutation
G	SA3	*Salmonella typhimurium* TA 1530, reverse mutation
G	SA4	*Salmonella typhimurium* TA104, reverse mutation
G	SA5	*Salmonella typhimurium* TA 1535, reverse mutation
G	SA7	*Salmonella typhimurium* TA1537, reverse mutation
G	SA8	*Salmonella typhimurium* TA1538, reverse mutation
G	SA9	*Salmonella typhimurium* TA98, reverse mutation
D	SAD	*Salmonella typhimurium*, DNA repair-deficient strains, diff. tox.
G	SAF	*Salmonella typhimurium*, forward mutation
G	SAS	*Salmonella typhimurium* (other miscellaneous strains), reverse mutation

Endpoint	Code	Definition
C	HSC	*Hordeum* species, chromosomal aberrations
G	HSM	*Hordeum* species, mutation
I	ICH	Inhibition of intercellular communication, human cells *in vitro*
I	ICR	Inhibition of intercellular communication, animal cells *in vitro*
G	KPF	*Klebsiella pneumonia*, forward mutation
G	MAF	*Micrococcus aureus*, forward mutation
C	MHT	Mouse heritable translocation test
M	MIA	Micronucleus test, animal cells *in vitro*
M	MIH	Micronucleus test, human cells *in vitro*
G	MST	Mouse spot test
M	MVA	Micronucleus test, other animals *in vivo*
M	MVC	Micronucleus test, hamsters *in vivo*
M	MVH	Micronucleus test, human cells *in vivo*
M	MVM	Micronucleus test, mice *in vivo*
M	MVR	Micronucleus test, rats *in vivo*
G	NCF	*Neurospora crassa*, forward mutation
A	NCN	*Neurospora crassa*, aneuploidy
G	NCR	*Neurospora crassa*, reverse mutation
C	PLC	Plants (other), chromosomal aberrations
M	PLI	Plants (other), micronuclei
G	PLM	Plants (other), mutation
S	PLS	Plants (other), sister chromatid exchanges
D	PLU	Plants, unscheduled DNA synthesis
D	PRB	Prophage induction, SOS repair test or DNA strand breaks, cross-links or related damage
C	PSC	*Paramecium* species, chromosomal aberrations
G	PSM	*Paramecium* species, mutation
D	RIA	DNA repair exclusive of unscheduled DNA synthesis, animal cells *in vitro*
D	RIH	DNA repair exclusive of unscheduled DNA synthesis, human cells *in vitro*
S	SVA	Sister chromatid exchange, animal cells *in vivo*
S	SVH	Sister chromatid exchange, other human cells *in vivo*
D	SZD	*Schizosaccharomyces pombe*, DNA repair-deficient strains, differential toxicity
G	SZF	*Schizosaccharomyces pombe*, forward mutation
R	SZG	*Schizosaccharomyces pombe*, gene conversion
G	SZR	*Schizosaccharomyces pombe*, reverse mutation
T	TBM	Cell transformation, BALB/c 3T3 mouse cells
T	TCL	Cell transformation, other established cell lines
T	TCM	Cell transformation, C3H 10T1/2 mouse cells
T	TCS	Cell transformation, Syrian hamster embryo cells, clonal assay
T	TEV	Cell transformation, other viral enhancement systems
T	TFS	Cell transformation, Syrian hamster embryo cells, focus assay
T	THI	Cell transformation, human cells *in vitro*
T	TPM	Cell transformation, mouse prostate cells
T	T7R	Cell transformation, SA7/rat cells
T	TRR	Cell transformation, *RLV*/ Fischer rat embryo cells
T	T7S	Cell transformation, SA7/ Syrian hamster embryo cells
C	TSC	*Tradescantia* species, chromosomal aberrations

Endpoint	Code	Definition
G	SCIF	*Saccharomyces cerevisiae*, forward mutation
R	SCG	*Saccharomyces cerevisiae*, gene conversion
R	SCH	*Saccharomyces cerevisiae*, homozygosis by mitotic recomb. or gene conv.
A	SCN	*Saccharomyces cerevisiae*, aneuploidy
G	SCR	*Saccharomyces cerevisiae*, reverse mutation
G	SGR	*Streptomyces griseoflavus*, reverse mutation
S	SHF	Sister chromatid exchange, human fibroblasts *in vitro*
S	SHL	Sister chromatid exchange, human lymphocytes *in vitro*
S	SHT	Sister chromatid exchange, transformed human cells *in vitro*
S	SIA	Sister chromatid exchange, other animal cells *in vitro*
S	SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*
S	SIH	Sister chromatid exchange, other human cells *in vitro*
S	SIM	Sister chromatid exchange, mouse cells *in vitro*
S	SIR	Sister chromatid exchange, rat cells *in vitro*
S	SIS	Sister chromatid exchange, Syrian hamster cells *in vitro*
S	SIT	Sister chromatid exchange, transformed animal cells *in vitro*
S	SLH	Sister chromatid exchange, human lymphocytes *in vivo*
G	SLO	Mouse specific locus test, other stages
G	SLP	Mouse specific locus test, post spermatogonia
P	SPF	Sperm morphology, F1 mice
P	SPH	Sperm morphology, humans *in vivo*
P	SPM	Sperm morphology, mice
P	SPR	Sperm morphology, rats
D	SSB	*Saccharomyces* species, DNA strand breaks, cross-links, related damage
D	SSD	*Saccharomyces* species, DNA repair-deficient strains, differential toxicity
G	STF	*Streptomyces coelicolor*, forward mutation
G	STR	*Streptomyces coelicolor*, reverse mutation
M	TSI	*Tradescantia* species, micronuclei
G	TSM	*Tradescantia* species, mutation
T	TVI	Cell transformation, treated *in vivo*, scored *in vitro*
D	UBH	Unscheduled DNA synthesis, human bone marrow *in vivo*
D	UHF	Unscheduled DNA synthesis, human fibroblasts *in vitro*
D	UHL	Unscheduled DNA synthesis, human lymphocytes *in vitro*
D	UHT	Unscheduled DNA synthesis, transformed human cells *in vitro*
D	UIA	Unscheduled DNA synthesis, other animal cells *in vitro*
D	UIH	Unscheduled DNA synthesis, other human cells *in vitro*
D	UPR	Unscheduled DNA synthesis, rat hepatocytes *in vivo*
D	URP	Unscheduled DNA synthesis, rat primary hepatocytes
D	UVA	Unscheduled DNA synthesis, other animal cells in viv4o
D	UVC	Unscheduled DNA synthesis, hamster cells *in vivo*
D	UVH	Unscheduled DNA synthesis, other human cells *in vivo*
D	UVM	Unscheduled DNA synthesis, mouse cells *in vivo*
D	UVR	Unscheduled DNA synthesis, other rat cells *in vivo*
C	VFC	*Vicia faba*, chromosomal aberrations
S	VFS	*Vicia faba*, sister chromatid exchange

Source: IARC (1987)

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.

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Surgical Implants and Other Foreign Bodies

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1. EXPOSURE DATA

1A. Metallic Medical and Dental Materials

1A.1 Chemical and physical data

1A.1.1 *Metallurgy*

All metallic materials used for the fabrication of medical and dental devices are mixed in the molten state and poured into a mould for solidification. Some devices may be fabricated from parts moulded or cast in nearly their final shape; others are subjected to a series of thermomechanical processes to produce the final product from the initial ingot. Differences in the resulting microstructures can have significant effects on wear and corrosion rates. In order to understand what alloys were and are used, and how they may behave *in vivo*, it is therefore necessary to be aware of the physical metallurgy of the alloys used in implant surgery.

(*a*) *Solidification and casting*

As molten metal cools in a mould, solidification usually begins on the surface of the mould. If the mould is very hot, there are only a few locations where the solid begins to form (nucleate) and grow. If the mould is cold, there are many nucleation sites. At each site, atoms are laid down on the solid in an orderly crystalline manner. For most metallic alloy systems, the solid phase grows as an advancing front with side branches. This pattern resembles the leaf of a fern, and is referred to as dendritic growth. Solidification continues until growth areas meet and form a boundary. Each of these growth sites is called a crystal or grain, and each boundary is a crystal or grain boundary. On a microscopic scale, distinct regions can be identified as the dendrites, the interdendritic region and the grain boundary (Brick *et al.*, 1977). For dental castings, alloying elements are added to produce fine-grained non-dendritic structures.

The positional relationship between atoms is described by what is called a primitive cell or Bravais lattice. For example, atoms may arrange themselves with atoms at eight corners of a cube, with one in the middle; this is called the body-centred cubic lattice or structure. The most common crystal structures for surgical alloys are body-centred cubic, face-centred cubic and hexagonal close-packed. The principal base metals used for implants—iron, cobalt and titanium—undergo allotropic transformation during cooling, resulting in a change in crystal structure. Thus, for example, iron undergoes the phase transformation from liquid to a body-centred cubic solid structure, followed by additional transformations to face-centred cubic and then back to body-centred cubic during cooling (Jackman, 1981).

Metallic alloys are mixtures of several elements in a solid solution, sometimes with intermetallic compound precipitates. For elements of similar atomic charge, diameter and crystal structure, there is no limit to the solubility of one element in another and they therefore solidify as a single phase. For example, copper and nickel are fully soluble in each other. The melting temperature of nickel is higher than that of copper, so that the solid that forms first (the dendrite) will be richer in nickel and that which solidifies later will be richer in copper. Thus, implants in the 'as cast' condition may have a distinct dendritic structure, with differences in chemical composition on a macroscopic scale. Cast devices may be subjected to a subsequent heat treatment known as homogenization or solution annealing to allow atomic diffusion to produce a more uniform chemical composition.

Small differences in the atomic diameter of the two (or more) elements in a single-phase alloy or a two-phase alloy provide strengthening. The presence of large atoms in a lattice of smaller atoms produces a localized strain in the lattice so that they are under localized compression. Similarly, a few small atoms in a lattice of larger atoms will be under localized tension. These localized strains increase the strength of the metal by a mechanism known as solid solution strengthening.

Elements with markedly different properties or crystal structures have limited solubility. For example, carbon atoms are much smaller than iron atoms. In small quantities, carbon is soluble in iron, but at higher concentrations, it precipitates out as a second phase, such as graphite, or forms a carbide. A number of alloy systems use the precipitation of second phases as a strengthening mechanism known as precipitation hardening. In some alloys such as the cobalt alloys, carbides are advantageous with regard to wear and strength. In contrast, they have a detrimental effect on the corrosion resistance of stainless steel.

Carbon also influences the crystal structure of iron. At room temperature, iron has a body-centred cubic crystal structure and is known as α ferrite. When heated, it undergoes a phase transformation to a face-centred cubic structure and is known as γ-austenite. With further heating, it reverts to a body-centred cubic form (δ ferrite) before it melts. Since the spaces, or interstices, between atoms are larger in the face-centred cubic than in the body-centred cubic structure, the carbon atoms fit better in the face-centred cubic structure and thus have a higher solubility in this structure. This has several implications. At low concentrations, carbon increases the thermodynamic stability of the face-centred cubic structure. In other words, the presence of carbon lowers the temperature at which the body-centred cubic α ferrite converts to the face-centred cubic γ austenite and increases the temperature at which the latter converts back to body-centred cubic δ ferrite. Carbon also provides interstitial solid solution strengthening of iron (Brick *et al.*, 1977; Jackman, 1981).

(*b*) *Mechanical forming of wrought alloys*

Mechanical forming methods, combined with appropriate heat treatments, can be utilized to produce fine-grained alloys with homogeneous microstructures. Composi-

tional differences associated with dendrites are decreased and formation of small, relatively strain-free grains results in enhancement of corrosion resistance. Hot and cold forging techniques can produce components with uniform composition and a wide range of strain-induced strengths (Jackman, 1981).

Point or line defects can occur in lattice structures of crystalline solids. When viewed as a two-dimensional grid, there is an occasional line of atoms that ends at what is called a dislocation. Above the dislocation, the atoms are in compression, while below it they are in tension. By pushing against the side of the dislocation line with a shear force, the position of the dislocation can move one line or plane at a time. Because of the mobility of dislocations, metals can be deformed plastically. When a metal solidifies, there are few dislocations. If the metal is then mechanically worked, as in pounding with a hammer or bending (like bending a paper clip), dislocations move around, and their number greatly increases. This is the mechanism of plastic deformation of metals. Increasing the number of dislocations, each with its localized stress field, makes it more difficult to implement more plastic deformation: the dislocations obstruct one another. Thus, a metal becomes stronger and harder by the mechanism of cold working (or work hardening). However, due to the high energy state of cold-worked metals, cold working tends to increase the corrosion rate of a metal (Brick *et al.*, 1977; Foley & Brown, 1979; Jackman, 1981).

1A.1.2 *Chemical composition of metals and alloys*

(*a*) *Specifications for surgical alloys*

Voluntary national and international consensus standard specifications for surgical alloys have been developed and widely adhered to since the early days of metallic implants. The International Organization for Standardization (ISO) and the American Society for Testing and Materials (ASTM) have played a central role in the development and promulgation of standards worldwide. While the actual compositions of alloys in specifications have changed somewhat over the years, these voluntary standards have generally guided the manufacturer's design of metallic implants.

(*b*) *Stainless steels*

Steel is an alloy of iron, carbon and other elements. In addition to mechanical strength, corrosion resistance is the most valuable feature of stainless steel, and the precipitation of carbon to form a two-phase alloy is undesirable, since the contact between two phases can lead to galvanic corrosion. One way to avoid precipitation of carbon is to keep the concentration of carbon low (typically in the 0.03–0.08% range). It is also important that the iron is in the face-centred cubic form, since the solubility of carbon is higher in this form (Williams & Roaf, 1973; Brick *et al.*, 1977; Foley & Brown, 1979).

A minimum of 12% chromium is added to make steel 'stainless', by the formation of a stable and passive oxide film. Since chromium has a body-centred cubic structure, the addition of chromium stabilizes the body-centred cubic form of iron. Carbon has a

great affinity for chromium, forming chromium carbides with a typical composition of $Cr_{23}C_6$. This leads to carbon precipitation in the region surrounding the carbide, where the chromium concentration is depleted as it is taken up into the carbide, and thus the corrosion resistance of the steel surrounding the carbide is reduced. If the chromium content is depleted to below 12%, there is insufficient chromium for effective repassivation, and the stainless steel becomes susceptible to corrosion (see Section 5A.1). To be on the safe side, surgical stainless steel contains 17–19% chromium and the carbon content of surgical alloys is kept below 0.03–0.08%, depending upon the application (Bechtol *et al.*, 1959; Williams & Roaf, 1973; Brick *et al.*, 1977).

Nickel has a face-centred cubic structure and is added to stabilize the face-centred cubic austenitic form of iron so as to keep the carbon in solution. Stainless steel cutlery typically has an '18–8' composition (18% chromium and 8% nickel). Stainless steel implants typically contain 17–19% chromium, 13–15% nickel and 2–3% molybdenum, the latter being added to improve corrosion resistance, while carbon content is below 0.03%. The result is a homogeneous, single-phase, corrosion-resistant stainless steel alloy. While stainless steel has good corrosion resistance, the options for strengthening mechanisms have been limited to cold working (Brick *et al.*, 1977).

The problem of carbide formation is especially important with welded stainless steel parts. If steel is heated to temperatures above 870°C, the carbon is soluble in the face-centred cubic lattice, while below 425°C, the mobility of the chromium is too low for the formation of carbide. However, if the peak temperature in the metal near a weld is in the 'sensitizing range' of 425–870°C, the chromium can diffuse within the solid and carbides can form. This can result in what is known as weld decay, or corrosion of the sensitized metal on each side of the weld. If the metal is heat-treated after welding, the carbides can be redissolved, and the metal is then quickly quenched to avoid reformation (Fontana & Greene, 1978; Foley & Brown, 1979).

Medical devices have generally been made with austenitic stainless steels designated by the American Iron and Steel Institute (AISI) as the '300 series'. The nomenclature used varies somewhat from country to country and between standards organizations, but there is now a trend towards using a Unified Numbering System (UNS). Reference here will be made to the UNS numbers, and the ASTM and ISO standards.

Table 7 shows the chemical composition of five alloys in the 300 series. There is increased nickel content and added molybdenum in S31600, while S30300 has an increased phosphorus content and a much higher sulfur content. The latter is referred to as free-machining stainless steel and has much lower corrosion resistance than the other alloys. While these standards are for instrument-grade stainless steel, some 302 or 304 stainless steels are used for items requiring spring-like properties, such as aneurysm clips. These are similar in composition to those used in the early history of implant surgery, as discussed below.

Over the past couple of decades, the specifications have been tightened. The original ASTM specifications for stainless steel for surgical implants (F 55 and F 56) were published in 1966. They indicated maximum concentrations of phosphorus and

Table 7. Specifications for stainless steels, AISI 300 series (wt %)[a]

Type[b]	Cr	Ni	Mo	Mn	Si	C	N	P	S
301	16–18	6–8	–	< 2	< 1	< 0.15	–	0.045	< 0.03
302	17–19	8–10	–	< 2	< 1	< 0.15	< 0.1	0.045	< 0.03
303	17–19	8–10	< 0.07	< 2	< 1	< 0.12	–	0.06	0.15–0.35
304	17–19	8–11	–	< 2	< 1	< 0.07	< 0.1	0.045	< 0.03
316	16.5–18.5	10.5–13.5	2–2.5	< 2	< 1	< 0.07	< 0.1	0.045	< 0.03

[a] Balance of composition in each case is iron (Fe)

[b] ISO and ASTM specifications:
ASTM F 899 Standard specification for Stainless Steel Billet, Bar, and Wire for Surgical Instruments; ISO 7153-1 Surgical Instruments - metallic materials – Part 1. Stainless steel (304 = S30400; (Fe73Cr18Ni8); 316 = S31600)
From ASTM (1998); ISO (1998)

sulfur of 0.03% and both < 0.08% ("316" stainless steel) and < 0.03% ("316L" stainless steel) of carbon. Since then, the high-carbon composition identified as grade 1 has been deleted, F 55 and F 56 specifications have been withdrawn and moved in 1971 to the new specifications F 138 and F 139 which are both called "316C".

Table 8 lists the composition of stainless steels used in implant applications according to the current ASTM and ISO specifications. Many of these specifications correspond to the wrought low-carbon S31673. ASTM separates the mechanical properties in individual standards for rolled, drawn, forging and fixation wire products. The casting alloy F 745 has a similar composition to S31673. There are also two slightly different nitrogen-strengthened wrought stainless steels, F 1314 and the matching standards ISO 5832-9 and ASTM F 1586.

(*c*) *Cobalt–chromium alloys*

Cobalt is a transition metal which has a hexagonal close-packed structure at room temperature, and a face-centred cubic structure above 417°C. The allotropic transformation on cooling to below this relatively low temperature takes place slowly and may not be complete in many alloy systems. The addition of some nickel and carbon can stabilize the face-centred cubic structure at room temperature. Cobalt metal is much more corrosion-resistant than iron, and therefore it can be used in a multiphase alloy for enhanced mechanical properties (Brick *et al.*, 1977; Planinsek, 1979).

Chromium is the primary alloying element in a wide variety of cobalt superalloys, being added primarily to give corrosion resistance. Chromium, tantalum, tungsten, molybdenum and nickel all enter the face-centred cubic structure and contribute to strengthening by solid-solution effects. Molybdenum and tungsten are significantly larger than cobalt, and are thus the elements most used for strengthening (Brick *et al.*, 1977).

Table 8. Specifications for implant-grade stainless steels (wt %)[a]

Type[b]	Cr	Ni	Mo	Mn	Si	C	N	P	S	Cu	Nb	V
F 138	17–19	13–15	2.25–3	< 2	< 0.75	< 0.03	< 0.10	< 0.025	< 0.01	< 0.50	–	–
5832-1 D	17–19	13–15	2.25–3.5	< 2	< 1	< 0.03	< 0.10	< 0.025	< 0.01	< 0.50	–	–
5832-1 E	17–19	14–16	2.35–4.2	< 2	< 1	< 0.03	0.1–0.2	< 0.025	< 0.01	< 0.50	–	–
F 745	17–19	11–14	2–3	< 2	< 1	< 0.06	–	< 0.045	< 0.03	–	–	–
F 1314	20.5–23.5	11.5–13.5	2–3	4–6	< 0.75	< 0.03	0.2–0.4	< 0.025	< 0.01	< 0.50	0.1–0.3	0.1–0.3
5832-9	19.5–22	9–11	2–3	2–4.5	< 0.75	< 0.08	0.25–0.5	< 0.025	< 0.01	< 0.25	0.25–0.8	–

[a] Balance of composition in each case is iron (Fe)

[b] ISO and ASTM specifications:

ASTM F 138 Standard specification for 18 Chromium-14 Nickel-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (S31673) (Fe64Cr18Ni14Mo2.5). Other standards with the same composition include ASTM F 139, F 621 and F 1350, also known as "316C".

ISO 5832-1 (composition D and E): Implants for Surgery - Metallic materials - Wrought stainless steel (S31673)

ASTM F 745 Standard specification for 18 Chromium-12.5 Nickel-2.5 Molybdenum Stainless Steel for Cast and Solution-Annealed Surgical Implant Applications (J31670)

ASTM F 1314 Standard specification for Wrought Nitrogen Strengthened-22 Chromium-12.5 Nickel-5 Manganese-2.5 Molybdenum Stainless Steel Bar and Wire for Surgical Implants (S20910) (Fe57Cr22Ni13Mn5Mo2.5)

ISO 5832-9 Implants for Surgery - Metallic materials - Wrought High Nitrogen Stainless Steel (S31675) (Fe63Cr21Ni10Mn3Mo2.5). ASTM F 1586 corresponds to the same composition.

From ASTM (1998); ISO (1998)

Carbon is also an alloying element of major importance because of the formation and distribution of carbides. In the cast form, the alloy is made of solid-solution dendrites surrounded by interdendritic carbides, with intergranular carbides precipitated at the grain boundaries. The carbides may be in the form of M_7C_3, M_6C or $M_{23}C_6$, where M is chromium, molybdenum, cobalt and tungsten in various proportions, depending on heat treatment. Implants in the 'as cast' condition may have an extensive amount of very large intergranular carbides. Homogenization-anneal (1180°C) or solution-anneal (1240°C) heat treatments result in a more uniform structure and dramatic changes in carbide morphology, with their ultimate dissolution in the matrix leaving 'Kirkendall' holes. Porosity from casting or heat treatment may be reduced by hot isostatic pressing ('HIPping') of the casting (Bardos, 1979; Semlitsch & Willert, 1980).

Thermomechanical processes such as forging and powder metallurgical methods typically produce very fine microstructures, with a dispersion of fine carbides. Much research in the past decade has concentrated on refining these techniques, using carbides for control of grain growth during heat treatments and controlling the size and distribution of the carbide for optimum wear resistance (Semlitsch, 1992).

The cast cobalt–chromium–molybdenum (CoCrMo) alloy, first introduced in 1911 by Haynes as 'stellite' (the 'star' among the alloys, now referred to as Haynes-Stellite-21), had a nominal composition of 30% chromium and 5% molybdenum with some nickel and carbon. In 1926, an alloy of similar composition was patented under the name of Vitallium, and this has become one of the principal cobalt alloys used for implant applications. In the cast form, its specifications are designated F 75 and ISO 5832-4, as shown in Table 9. This is used for cast implants for osteosynthesis and arthroplasty. With minor changes in chromium and carbon content, forged and wrought versions of this alloy have been developed for high-stress applications, as in total hip replacements. The first-generation metal-on-metal total hips used in the 1960s were cast, whereas the second generation in use today are wrought (Schmidt *et al.*, 1996).

Before the development of techniques for thermomechanically processing CoCrMo as a wrought alloy, a second alloy known as Haynes-Stellite-25, also known as wrought Vitallium, was introduced in 1952. This is a wrought alloy of cobalt, chromium, nickel and tungsten, with specifications F 90 or 5832-5 (Table 9). It has seen use primarily in intermedullary rods, side plates for stabilizing nails for femoral neck fractures, and some prosthetic heart valve frames.

Multiphase alloys have been developed in the search for stronger and corrosion-resistant alloys. For example, MP35N is an alloy of cobalt, nickel, chromium and molybdenum. In the solution-annealed condition, it has a face-centred cubic form which is very soft. With mechanical working, it undergoes a phase transformation to a hexagonal close-packed form, which appears as microscopically thin platelets that greatly increase its strength. Additional strengthening results from precipitation of Co_3Mo with ageing (Younkin, 1974). Other trade names for this alloy include Protasul-10 and Biophase. Its strength is excellent for total hip stems, but it is often used in conjunction with a cast cobalt–chromium–molybdenum head for improved

Table 9. Specifications for cobalt–chromium alloys (wt %)[a]

Type[b]	Cr	Ni	Mo	Mn	Si	C	Fe	Ti	W	N	P	S	Other
Cast alloy													
F 75	27–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75	–	< 0.20	< 0.25	< 0.02	< 0.01	B < 0.01, Al < 0.3
5832-4	26.5–30	< 1.0	4.5–7	< 1.0	< 1.0	< 0.35	< 1.0						
Wrought alloy													
5832-12	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75			< 0.25			
F 1537	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75	–	–	< 1.0	–	–	
R31537	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.149	< 0.75			< 0.25			
R31539	26–30	< 1.0	5–7	< 1.0	< 1.0	< 0.35	< 0.75			< 0.25			Al < 1, La < 0.5
F 90	19–21	9–11	–	1–2	< 0.4	0.05–0.15	< 3	–	14–16	–	< 0.04	< 0.03	
F 562	19–21	33–37	9–10.5	< 0.15	< 0.15	< 0.025	< 1	< 1	–	–	< 0.015	< 0.01	B < 0.015
5832-6	19–21	33–37	9–10.5	< 0.15	< 0.15	< 0.025	< 1	< 1			< 0.015	< 0.01	
5832-8	18–22	15–25	3–4	< 1.0	< 0.5	< 0.05	4–6	0.5–3.5	3–4			< 0.01	
F 1058,1	19–21	14–16	6–8	1.5–2.5	< 1.2	< 0.15	bal	–	–	–	< 0.015	< 0.015	Be < 0.10, Co 39–41
F 1058,2	18.5–21.5	15–18	6.5–7.5	1.0–2.0	< 1.2	< 0.15	bal	–	–	–	< 0.015	< 0.015	Be < 0.001, Co 39–42
5832-7	18.5–21.5	14–18	6.5–8	1–2.5	< 1	< 0.15	bal				< 0.015	< 0.015	Be < 0.001, Co 39–42

Table 9 (contd)

bal, iron makes up the balance of the alloy content

[a] Balance of composition in each case is cobalt (Co), except for ASTM F 1058 and ISO 5832-7.

[b] ISO and ASTM specifications (including some common trade names):

ASTM F 75 Standard specification for Cast Cobalt-Chromium-Molybdenum Alloy for Surgical Implants (R30075) - ASTM F 1377 has the same composition. (R30075) (Co66Cr28Mo6). *Haynes-Stellite 21, Vitallium®, Zimalloy, Protasul™-1, Protasul™-2, Vinertia, Francabal, CCM®*

ISO 5832-4 Implants for Surgery - Metallic materials -Co-28Cr-6Mo Casting Alloy (R30075)

ASTM F 799 Standard specification for Cobalt-28 Chromium-6 Molybdenum Alloy Forgings for Surgical Implants

ISO 5832-12 Implants for Surgery - Metallic materials - Wrought Co-28Cr-6Mo Alloy (R31538)

ASTM F 1537 Standard specification for Wrought Cobalt-28 Chromium-6 Molybdenum Alloy for Surgical Implants (R31537-9). *FHS Vitallium®, GADS, Zimaloy Micrograin, Protasul™-20, CCM Plus™*

ASTM F 90 Standard specification for Wrought Cobalt-20 Chromium-15 Tungsten-10 Nickel Alloy for Surgical Implant Applications (Co55Cr20W15 Ni10). *Haynes-Stellite 25, Vitallium®*. ISO 5832-5 has a similar composition.

ASTM F 1091 Wrought Co-20Cr-15W-10Ni Alloy surgical fixation wire - ASTM F 90 has the same composition

ASTM F 562 Standard specification for Wrought Co-35Ni-20Cr-10Mo Alloy for Surgical Implant Applications (Co35Ni35Cr20Mo10) - ASTM F 688 and F 961 have the same composition.

ISO 5832-6 Implants for Surgery - Metallic materials - Wrought Co-35Ni-20Cr-10Mo Alloy. *Protasul™-10, MP35N, Biophase*

ISO 5832-8 Implants for Surgery - Metallic materials - Wrought Co-20Ni-20Cr-3Mo-3W-5Fe Alloy (R30563) - (Co49Cr20Ni20Fe5Mo3W3) - ASTM F563 has the same composition. *Syntacoben*

ASTM F 1058 Standard specification for Wrought Co-Cr-Ni-Mo-Fe Alloys for Surgical Implant Applications, grade 1: Co40Cr20Ni15Mo7Fe18 (R30003) and grade 2 (R30008). *Elgiloy* (grade 1)

ISO 5832-7 Implants for Surgery - Metallic materials - Forgeable and cold-formed Co-Cr-Ni-Mo-Fe Alloy (R30008). *Phymox*

From ASTM (1998); ISO (1998)

wear resistance. The heads are welded to the MP35N stems (Süry & Semlitsch, 1978; Richards Manufacturing Company, 1980; Semlitsch & Willert, 1980).

Two other cobalt alloys, Syntacoben and Elgiloy, have been developed as high-strength, corrosion-resistant materials for mechanical spring applications. Elgiloy is used as the stent material in some prosthetic heart valves and endovascular stents and as orthodontic wires.

(*d*) *Titanium and titanium alloys*

At room temperature, titanium has a hexagonal close-packed structure (the alpha form). At 882°C, it transforms to a body-centred cubic (beta) form. Alloys with an all-alpha structure develop good strength and toughness and have superior resistance to oxygen contamination at elevated temperatures, but have relatively poor forming characteristics. The all-beta structures display better formability and have good strength, but are more vulnerable to contamination from the atmosphere. Elements that stabilize the alpha structure are aluminium, carbon, boron, oxygen and nitrogen, while molybdenum, vanadium, manganese, chromium and iron stabilize the beta structure. Zirconium has properties very similar to titanium and thus enters a solid solution without any effect on phase (Brick *et al.*, 1977; Knittel, 1983).

There are four grades of commercially pure (unalloyed) titanium (sometimes called CPTi), which contain small amounts of iron, nitrogen and oxygen. As the amounts of these other elements increase from grade 1 to 4, strength increases. The compositions of grades 1 and 4 are shown in Table 10.

The other common form of titanium for implant applications is known as Ti 6,4 (containing 6% aluminium and 4% vanadium), which has a two-phase structure with a dispersion of the beta form in the alpha phase. Heat treatment can have a significant effect on the phase morphology, from a very fine dispersion of beta particles to a very coarse plate-like structure. Another alloy, Ti 6,7 (containing 6% aluminium and 7% niobium), was developed due to concern regarding the toxicity of vanadium (Knittel, 1983; Semlitsch, 1992).

Recently there has been growing interest in the development of all-beta titanium alloys. The advantage of these alloys is reduced stiffness or elastic modulus, so that the material is mechanically more similar to bone (Brown & Lemons, 1996).

Titanium is very active electrochemically, lying between zinc and aluminium in the electromotive series. As a result, it reacts rapidly with oxygen (either gaseous or in an aerated solution) to form a very stable passive oxide film. With such a passive film, titanium is very resistant to electrochemical corrosion. However, it suffers from abrasive wear, and titanium total joint replacements have occasionally experienced catastrophic or 'run-away' wear (Knittel, 1983; Agins *et al.*, 1988).

(*e*) *Tantalum*

Tantalum is a corrosion-resistant metal with a high atomic weight (180.95), density (16.69) and melting-point (3000°C), but relatively poor mechanical strength.

It is difficult to cast and form into devices, although electron beam refining and powder metallurgical methods can be used; ASTM and ISO standards exist for two forms designated R05200 and R05400 (Table 11). Due to its density, tantalum is used medically as a radiographic marker in polymeric and carbon devices. Fabricated tantalum is malleable and has been used for many years for repair of cranial defects (Black, 1994).

1A.1.3 *Chemical composition of dental casting alloys*

Three groups of precious-metal alloys are used specifically in dental castings: gold-based, palladium-based and silver-based alloys. Two main groups of non-precious metal (base metal) alloys are used: cobalt- and nickel-based. Commercially pure titanium, as described previously, is also used as a dental casting material. Within these groups, the alloys can be described by the weight percentages of their constituents in decreasing order, e.g., Au70Ag13.5Cu8.8 for an alloy with 70% gold, 13.5% silver and 8.8% copper. The classification of an alloy is determined by the components with the highest percentage. For example, Ag40Pd23In17 is a typical silver alloy, which may be referred to as a silver–palladium alloy or as a silver–palladium–indium alloy.

Standards for dental casting alloys are:

ISO 1562: Dental casting gold alloys

ISO 6871-1: Dental base metal casting alloys. Part 1: Cobalt-based alloys

ISO 6871-2: Dental base metal casting alloys. Part 2: Nickel-based alloys

ISO 8891: Dental casting alloys with noble metal content of at least 25% but less than 75%

ISO 9693: Dental ceramic fused to metal restorative materials

(*a*) *Gold-based alloys*

The classical dental gold alloy is a ternary alloy of gold, silver and copper, containing not less than 75% gold. Palladium and platinum are added to modify the melting point and increase the mechanical strength. Zinc is added to ease the castability, and small amounts of ruthenium, or other platinum group metals such as iridium or rubidium, in the range of 0.005 to 1% are believed to enhance the development of nucleation centres and thus produce a fine-grained structure throughout the alloy (Lanam & Zysk, 1982; Lloyd & Showak, 1984; Anusavice, 1996).

The alloys used for metal–ceramic reconstructions additionally need at least approximately 1% of non-precious metallic elements such as indium, tin or gallium to produce a slight oxide film on the surface of the dental substructure to achieve a metal–ceramic bond strength that surpasses the cohesive strength of the ceramic itself. If the gold content is decreased and replaced by palladium for economic reasons, the content of low-melting elements such as tin, indium and especially gallium has to be increased in order to lower the melting point of the alloy (Table 12) (Anusavice, 1996).

Table 10. Specifications for titanium and titanium alloys (wt %)[a]

Type[b]	Al	V	Nb	Mo	Zr	Fe	N	C	H	O	Other
Commercially pure titanium											
F 67-1	–	–	–	–	–	< 0.20	< 0.03	< 0.10	< 0.015	< 0.18	–
F 67-4	–	–	–	–	–	< 0.50	< 0.05	< 0.10	< 0.015	< 0.40	–
5832-2,1						< 0.10	< 0.012	< 0.03	< 0.0125	< 0.10	
5832-2,4						< 0.50	< 0.05	< 0.10	< 0.0125	< 0.40	
Titanium alloys											
F 136	5.5–6.50	3.5–4.5	–	–	–	< 0.25	< 0.05	< 0.08	< 0.012	< 0.13	–
F 1108	5.5–6.75	3.5–4.5	–	–	–	< 0.30	< 0.05	< 0.10	< 0.015	< 0.20	–
F 1472	5.5–6.75	3.5–4.5	–	–	–	< 0.30	< 0.05	< 0.08	< 0.015	< 0.20	Y < 0.005
5832-3	5.5–6.75	3.5–4.5	–		–	< 0.30	< 0.05	< 0.08	< 0.015	< 0.20	–
F 1295	5.5–6.5	–	6.5–7.5		–	< 0.25	< 0.05	< 0.08	< 0.009	< 0.20	Ta < 0.50
5832-11	5.5–6.5	–	6.5–7.5		–	< 0.25	< 0.05	< 0.08	< 0.009	< 0.20	Ta < 0.50
F 1713	–	–	12.5–14	–	12.5–14	< 0.25	< 0.05	< 0.08	< 0.012	< 0.15	
F 1813	–	–	–	10–13	5–7	1.5–2.5	< 0.05	< 0.05	< 0.02	0.08–0.28	

Table 10 (contd)

[a] Balance of composition in each case is titanium (Ti)

[b] ISO and ASTM specifications (including some common trade names):

ASTM F 67 Standard specification for Unalloyed Titanium for Surgical Implant Applications (R50250, 400, 550, 700). ASTM F1341 has the same composition. *Protasul™-Ti*

ISO 5832-2 Implants for Surgery - Metallic materials - Unalloyed Titanium (R50250, 400, 550, 700)

ASTM F 136 Standard specification for Wrought Titanium 6Al-4V Extra Low Interstitial Alloy for Surgical Implant Applications (R56401) (Ti90Al6V4).

ASTM F 620 has the same composition.

ASTM F 1108 Standard specification for Titanium 6Al-4V Alloy castings for Surgical Implants (R56406)

ASTM F 1472 Standard specification for Wrought Titanium 6Al-4V Alloy for Surgical Implant Applications (R56400)

ISO 5832-3 Implants for Surgery - Metallic materials - Titanium 6Al-4V Wrought Alloy (R56406)

ASTM F 1580 Standard specification for Titanium and Titanium-6% Aluminium-4% Vanadium Alloys Powders for Coatings of Surgical Implants (R50700 & R56406). *Tivanium, Protasul™-64WF*

ASTM F 1295 Standard specification for Wrought Titanium 6Al-7Nb Alloy for Implant Applications (R56700) (Ti87Al6Nb7)

ISO 5832-11 Implants for Surgery - Metallic materials - Wrought Titanium 6Al-7Nb alloy (R56700). *Protasul™-100*

ASTM F 1713 Standard specification for Wrought Titanium 13Nb-13Zr Alloy for Surgical Implants (R58130) (Ti74Nb13Zr13)

ASTM F 1813 Standard specification for Wrought Titanium 12 Molybdenum-6 Zirconium-2 Iron Alloy for Surgical Implants (R58120) (Ti78Mo12Zr6Fe2)

From ASTM (1998); ISO (1998)

Table 11. Specifications for tantalum for implant application (wt %)[a]

Type[b]	C	O	N	H	Nb	Fe	Ti	W	Mo	Si	Ni
R05200	< 0.010	< 0.015	< 0.010	< 0.0015	< 0.100	< 0.010	< 0.010	< 0.050	< 0.020	< 0.005	< 0.010
R05400	< 0.010	< 0.030	< 0.010	< 0.0015	< 0.100	< 0.010	< 0.010	< 0.050	< 0.020	< 0.005	< 0.010

[a] Balance of composition is tantalum (Ta)
[b] ASTM and ISO specifications:
ASTM F 560 Standard specification for Unalloyed Tantalum for Surgical Implant Applications (R05200, R05400). ISO 13782 corresponds to the same composition.
From ASTM (1998); ISO (1998)

Table 12. Composition of commonly used precious-metal dental cast alloys and metal-ceramic alloys (wt %)

Alloy type	Au	Pt + Pd	Ag	Cu	Other non-precious metals (e.g., Zn, Sn, In, Ga)
Gold-based alloys					
High gold cast alloys	71–96	0–5	3–14	0–10	1–12
High gold metal-ceramic alloys	70–92	6–20	0–11	0–6	0.2–6
Low gold cast alloys	50–69	4–10	8–25	0–12	3–14
Low gold metal-ceramic alloys	50–69	20–36	0–18	0–14	3–13
Palladium-based alloys					
Palladium-based alloys (PdAgSn)	0–16	50–78	7–40	–	8–14
Palladium-based alloys (PdCuCa)	0–6	76–80	0–7	4–15	18–22
Palladium-based alloys (PdSnGaIn)	0–2	80–85	0–6	0–6	12–18
Silver-based alloys					
Silver-based alloys (AgPd)	0–25	15–27	40–70	0–18	3–24

(*b*) *Palladium-based alloys*

Palladium alloys contain 50–85% palladium (Table 12). The melting point of pure palladium (1552°C) is much too high for dental casting machines. High proportions of silver or copper, as well as other elements such as gallium, indium and tin have to be added in order to lower the melting point to 1200–1400°C. These non-precious metals also serve to form essential oxygen bridges at the surface for bonding to the veneering ceramic after appropriate heat treatment. In most cases, copper-free alloys are more corrosion–resistant (Lanam & Zysk, 1982; Anusavice, 1996).

(*c*) *Silver-based alloys*

Silver-based alloys with a grey colour have a silver content between 50 and 70% and contain copper, palladium and sometimes gold (Table 12). A gold-coloured silver alloy type consists of approximately 40% silver, 23% palladium, 17% indium and some gold, copper and zinc. It is a heterogeneous alloy, with an orange-coloured palladium–indium phase and a silver-coloured phase. The mixture of these phases has a golden colour which explains the popularity of this alloy, despite its low resistance to corrosion and tarnishing (Anusavice, 1996).

(*d*) *Cobalt- and nickel-based alloys*

These alloys (Table 13) are mainly used for removable partial dentures because of their high mechanical strength and stiffness. Nickel–chromium (NiCr) alloys are sometimes preferred over cobalt–chromium (CoCr) alloys by dental technicians because of their much easier casting properties and brilliant appearance, especially if 2% beryllium is added. The precious metal alloys have an inherent resistance to corrosion

Table 13. Composition of commonly used base metal dental casting alloys (wt %)

Alloy type	Co	Ni	Cr	Mo	Mn	W	Si	Fe	C	Other elements
Cobalt-based alloys	52–67	[a]	24–32	4–6	0–1	0–10	0–1.5	0–1	0–0.5	Ce 0.2; La 0.1; N 0.3
Nickel-based alloys	0.3–0.5	59–81	11–27	4–11	–	–	0–1.5	0–1.2	0.1	Be 0–2; Ce 0–0.2; Al 0.3

[a] The total cobalt + nickel + chromium content must be at least 85%, and cobalt must be ≥ 50%. 'Nickel-free' cobalt-based alloys must contain < 0.1% nickel.

because of their low reactivity to oxygen. In contrast, cobalt and nickel alloys contain metallic elements having a high affinity to oxygen, but the oxide film at the surface can protect against further corrosion. With a chromium content of around of 24% and a molybdenum content between 2 and 5%, the corrosion resistance can be similar to that of the precious-metal alloys (Planinsek, 1979; Tien & Howson, 1981; Anusavice, 1996). The drawback of the NiCr alloy with a high beryllium content is its very high corrosion rate compared with other CoCr or NiCr alloys (Geis-Gerstorfer & Pässler, 1993).

(*e*) *Copper-based alloys*

A copper alloy with typical composition Cu79.3Al7.8Ni4.3Fe4Zn3Mn1.6 and having gold-coloured appearance (trade name NPG = Non Precious Gold) but very low corrosion resistance is used mainly in the United States, South America and Eastern Europe because of its very low cost (Anusavice, 1996).

1A.1.4 *Dental amalgam*

To produce dental amalgam, mercury is mixed with an alloyed metallic powder consisting predominantly of silver and tin. Mercury comprises 40–50% of the amalgam, and the remainder is the alloy. The conventional alloy powder contains at least 65% silver, 29% tin and less than 6% copper. Other elements, such as zinc or gold are allowed in concentrations less than the silver or tin content. During the 1970s, high-copper alloys containing between 6 and 30% copper were developed. These alloys produce amalgams that are superior in many respects to the traditional low-copper amalgams. The amalgam is mixed by the dentist or the assistant to obtain a plastically formable mixture to be inserted in the tooth (IARC, 1993a; Anusavice, 1996).

1A.1.5 *Orthodontic metallic materials*

For orthodontic treatments, wrought base metal alloys are used for wires, brackets and bands. The types of alloy preferred in orthodontics can be divided into six groups according to their composition (Table 14) (Anusavice, 1996).

1A.1.6 *Analytical methods*

(*a*) *Measurement of composition of metallic alloys*

All ASTM metallic implant material specifications cite ASTM specifications for chemical analysis. These specifications describe a series of wet chemistry and photometric methods for determination of the alloy composition.

Specifically, the titanium alloy standards cite E 120 (Standard Test Methods for Chemical Analysis of Titanium and Titanium Alloys), the stainless steel and cobalt alloy standards cite E 353 (Standard Test Methods for Chemical Analysis of Stainless, Heat-Resisting, Maraging and Other Similar Chromium-Nickel-Iron Alloys) and E 354 (Standard Test Methods for Chemical Analysis of High-Temperature Electrical, Magnetic and Other Similar Iron, Nickel, and Cobalt Alloys).

Table 14. Composition of commonly used orthodontic materials

Alloy type	Typical composition	Applications
Stainless steel (type 301/302/304)	Fe74Cr17Ni7 (hard and spring hard)	Wires, brackets, bands
Manganese steel	Fe60.8Cr18Mn18Mo2	Wires, brackets
Cobalt–chromium–nickel alloys (Elgiloy®)	Co40Cr20Ni16 (soft and hard)	Wires
Nickel–titanium alloys	Ni52Ti45Co3 or Ni51Ti49	Wires
β-Titanium alloys	Ti78Mo11Zr6.5Zn4.5	Wires
Titanium (commercially pure)	Ti	Brackets

ISO material standards for stainless steel (5832-1 and 5832-9) cite a series of ISO standards for chemical analysis, and ASTM E 112 for determining average grain size. The other ISO TC-150 metal specifications do not cite chemical analysis test methods.

(*b*) *Measurement of metals in biological tissue and fluids*

ASTM F 561 (Practice for Retrieval and Analysis of Implanted Medical Devices, and Associated Tissues) contains detailed methods for chemical analysis of tissues by flame atomic absorption spectroscopy (flame AAS), graphite furnace atomic absorption spectroscopy (GFAAS), inductively coupled plasma optical emission spectroscopy (ICP-OES) or mass spectroscopy. Detection limits for metal analysis by flame AAS, GFAAS and ICP-OES are given in Table 15. Detection limits for elements in tissues depend upon, among other factors, the amount of specimen dilution during sample preparation.

1A.2 Production

Some metallic devices are formed by casting into the nearly final shape. Portions of the cast parts may be subjected to subsequent machining or polishing treatments. Some devices are used with the metal in the 'as cast' condition. In the case of certain devices or certain manufacturers, castings may be subjected to subsequent heat treatments.

Metallic devices can also be made by subjecting the original cast ingot to a series of mechanical rolling or drawing steps. After each process involving extensive cold working, the alloy is heated to anneal it or relieve stress. This results in the formation of new crystals with few dislocations. Suitable control of the temperature and time gives a soft, fine-grained metal that can be subsequently cold worked. Alternatively, the forming may be done with hot metal so that recrystallization occurs spontaneously after the rolling or drawing. Parts can also be formed mechanically by forging a piece from a nearly final form. Again, this can be done under hot or cold conditions (Jackman, 1981).

Metallic components can also be made using the techniques of powder metallurgy. A fine powder is usually made by melting the alloy and atomizing it. The powder is

Table 15. Comparison of detection limits[a] for selected analytical methods

Metal	Inductively coupled plasma optical emission spectroscopy	Flame atomic absorption spectroscopy	Graphite furnace atomic absorption spectroscopy
Aluminium	2	30	0.01
Beryllium	0.07	1	0.02
Chromium	2	3	0.01
Cobalt	1	4	0.02
Copper	0.9	1	0.02
Gallium	10	60	0.5
Indium	20	40	1
Molybdenum	3	20	0.02
Nickel	3	90	0.1
Palladium	4	10	0.3
Silver	0.8	2	0.005
Titanium	0.4	70	0.5
Vanadium	0.7	50	0.2
Zinc	0.6	0.5	0.001

[a] All values are shown as µg/L
From Gill (1993)

then compacted to a nearly final shape and subjected to controlled high temperature and pressure in sintering and HIPping processes (Bardos, 1979; Jackman, 1981).

The treatment of surfaces during manufacture can have a major effect on both wear and corrosion resistance. A wide variety of methods are used. Cast devices generally have a matte surface from the ceramic of the investment casting, or may be grit-blasted to remove residual cast material. Stainless steel implants are very often polished mechanically and then electropolished (Schneberger, 1981). Surfaces may also be treated by ion implantation, plasma or ion nitriding, or coated with hard ceramic-like materials for enhanced wear resistance. Bearing surfaces receive a very high degree of mechanical polishing, either by hand or by computer-controlled machines (Alban, 1981; Krutenat, 1981).

Since the early 1980s, a number of surface modifications have been used in total joint replacements to provide biological fixation by in-growth of bone into a porous or textured surface. Porosity can be created by sintering a layer of beads on the surface, diffusion-bonding a fibre metal mesh or micromachining to create a textured surface. Coatings are also applied by a variety of thermal spray techniques (Crowninshield, 1988).

In most cases, there is a final process of passivation (see Section 5A.1) in nitric acid. The term passivation may be a misnomer, since the surgical alloys are all self-

2. STUDIES OF CANCER IN HUMANS

2A. Metallic medical and dental materials

2A.1 Case reports

The pathology of the cases illustrated in the reports summarized in this section was reviewed by the Working Group and the diagnoses were deemed reliable.

Compilations of the published case reports describing malignant tumours at the site of the metallic implants are presented in Tables 19 (14 cases) (static orthopaedic metallic implants) and 20 (two cases) (joint prostheses).

A total of 16 case reports of local sarcoma or lymphoma at the site of metallic implants have been found in the medical literature. The time lapse between implantation and tumour diagnosis for these cases varied from a few months to 30 years. The ranges were 1.2–30 years for static orthopaedic implants (14 cases) but the majority were less than 10 years (seven cases) and 3.5 and five years for joint endoprostheses (two cases). Almost all case reports relating to tumours at the site of static implants involved the femur. The implanted materials (where reported) were stainless steel or cobalt–chromium alloys. The number of cases appears to be small in comparison with large numbers of implanted metallic devices. Reporting of individual cases is not systematic, so the actual number of occurrences is likely to be greater.

2A.2 Analytical studies

In a case–control study of soft-tissue sarcoma by Morgan & Elcock (1995) described in the chapter on 'composite implants' (see Section 2C.2.1b), a subgroup analysis of metal implants was performed, that yielded an odds ratio of 0.8 (95% confidence interval (CI), 0.3–1.5).

A case–control study in Australia (Ryan *et al.*, 1992) studied the relationship between dental amalgam containing mercury (see IARC, 1993a), diagnostic dental X-rays (IARC, 2000) and subsequent development of brain tumours. The study included 170 cases of brain tumours (110 gliomas, 60 meningiomas) and 417 general population controls. There was a decreased odds ratio of 0.5 (95% CI, 0.3–0.9) for glioma and an odds ratio of 1.0 (95% CI, 0.4–2.5) for meningioma associated with amalgam fillings for at least one year.

Table 19. Malignant tumours at the site of static non-articulating orthopaedic metallic implants

Reference	Implant	Metal	Age at implantation/ sex	Preoperative diagnosis	Site	Histopathology	Years between implantation and diagnosis	Remarks
McDougall (1956)	Plate and screws	Plate: stainless steel, 74% Fe 18% Cr, 8% Ni screws: 88% Fe, 12% Cr	12/M	Fracture	Humerus, diaphysis	Ewing's sarcoma	30	Extensive corrosion of plate and screws (difference in potential between plate and screws of 80 mV)
Bürkle de la Camp (1958)	Medullary nail	NR	22/M	Complicated fracture	Femur, great trochanter	Alveolar sarcoma	3	
Delgado (1958)	[Egger's plate (Hughes *et al.*, 1987) and screws]	NR	37/M	Fracture	Tibia, diaphysis	Unclassified sarcoma [probably osteosarcoma (McDonald, 1981)]	3	
Dube & Fisher (1972)	Sherman (stainless steel) plate and screws	(Plate and 8 screws: stainless steel 316: 18% Cr, 10% Ni, 3% Mo 2 screws: stainless steel 304: 20% Cr, 9% Ni	58/M	Non-union of a fracture (bilateral fracture)	Tibia, diaphysis of both legs	Haemangio-endothelioma	26	Fixed with bone graft, 2 loose screws, corrosion of 2 plate screw holes (the other tibia was also fixed with bone graft, and two screws)
Monkman *et al.* (1974)	Nail plate	NR	57/M	Fracture	Proximal femur	Chondrosarcoma (grade 3)	2	

Table 19 (contd)

Reference	Implant	Metal	Age at implantation/ sex	Preoperative diagnosis	Site	Histopathology	Years between implantation and diagnosis	Remarks
Tayton (1980)	Sherman plate and six screws	CoCr (Vitallium)[a]	4/F	Congenital hip dislocation	Proximal femoral diaphysis	Ewing's sarcoma	7.5	Bilateral osteotomies and plate fixation. Removal of plates and screws one year later
McDonald (1981)	Plate and screws	CoCr (Vitallium)[a]	31/M	Fracture	Tibia, diaphysis	Histiocytic type lymphoma	17	Tumour infiltrating the bone
Dodion *et al.* (1983)	1 Strycker screw + 1 Knowles screw, 1 McLaughlin plate and 5 Phillips screws	CoCr (Vitallium)[a]	49/M	Fracture of the femoral neck	Femur (neck)	Immunoblastic lymphoma	1.2	Deep infection
Lee *et al.* (1984)	Plate and screws	NR	30/M	Open femur fracture	Femur, diaphysis	Malignant fibrous histiocytoma	14	Removal of plate and screws and bone grafting for suspected osteomyelitis 4 months before diagnosis
Hughes *et al.* (1987)	One Sherman screw	CoCr[b]	14/M	Slipped proximal femoral epiphysis	Femur, neck	Malignant fibrous histiocytoma	29	Single screw
Ward *et al.* (1990)	Smith-Petersen nail	Stainless steel (Ni, Co, Cr, Mo, Fe)	56/F	Fracture of the femoral neck	Femur, neck	Osteosarcoma	9	

Table 19 (contd)

Reference	Implant	Metal	Age at implantation/sex	Preoperative diagnosis	Site	Histopathology	Years between implantation and diagnosis	Remarks
Khurana *et al.* (1991)	Hansen Street intramedullary nail	Stainless steel (17–19% Cr, 12–14% Ni, 2-3% Mo, 2% Mn; Fe)	25/M	Gunshot fracture	Proximal femoral diaphysis	Malignant fibrous histiocytoma	14	
Scully *et al.* (1991)	Staples	Stainless steel 316 (18% Cr, 10% Ni)	8/M	Morquio's syndrome, genu valgum	Distal femoral diaphysis	Osteosarcoma	10	Bilateral femoral osteotomies
Kumar (1996)	Two staples	NR	7/M	Post-poliomyelitic deformity	Distal femoral diaphysis (knee)	Osteosarcoma	9	

[a] Vitallium, 58.4% min. Co; 27–30% Cr; 5–7% Mo; 2.5% max. Ni; 1% max. Mn; 0.75% max. Fe

[b] CoCr = cobalt–chromium alloy, composition not stated

NR, not reported

Table 20. Malignant tumours at the site of joint endoprosthesis (metal only)

Reference	Prosthesis	Metal	Age at implantation/ sex	Preoperative diagnosis/site	Histopathology	Years between implantation and diagnosis	Remarks
Castleman & McNeely (1965)	Moore prosthesis	NR	49/M	Old fracture of the femoral neck (hip)	Giant cell sarcoma (malignant)	3.5	Nail and plate for 8 months before the prosthesis ('fatty' tumour excised from the knee 14 years before implantation)
Penman & Ring (1984)	Ring	Stem-head alloy: CoCr Cup: CoCr Fixation: Uncemented	75/F	Osteoarthritis THA	Osteosarcoma	5	

THA, total hip arthroplasty
NR, not reported

4A.2.4 *Intraosseous administration*

Rabbit: Two groups of 15–20 rabbits [strain, sex and age unspecified] received an implantation in the femoral cavity of metallic chromium dust or metallic cobalt dust [purity and particle size unspecified]. Physical examination by palpation and X-ray examination three years after implantation revealed no implantation-site tumour in 11 survivors of the chromium-treated group or six survivors of the cobalt-treated group (Vollmann, 1938). In a follow-up study of survivors [number unspecified] at intervals up to six years after implantation, sarcomas were observed at the implantation site in three chromium-treated rabbits and two cobalt-treated rabbits (Schinz & Uehlinger, 1942). [The Working Group noted the limited reporting.]

4A.3 Metallic nickel

4A.3.1 *Inhalation exposure*

Mouse: A group of 20 female C57BL mice, two months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel; particle diameter, ≤ 4 μm) for 6 h per day on four or five days per week for up to 21 months. All mice had died by the end of the experiment. No lung tumour was observed. No control group was available (Hueper, 1958).

Rat: Groups of 50 male and 50 female Wistar rats and 60 female Bethesda black rats, 2–3 months of age, were exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel; particle diameter, ≤ 4 μm) for 6 h per day on four or five days per week for 21 months, when the experiment was terminated. Histological examination of the lungs of 50 rats showed numerous multicentric, adenomatoid alveolar lesions and bronchial proliferations that were considered by the author as benign neoplasms. No control group was included in the study (Hueper, 1958).

A group of 60 male and 60 female Bethesda black rats [age unspecified] was exposed by inhalation to metallic nickel powder (98.95% nickel; particle diameter, 1–3 μm) [concentration unspecified] in combination with 20–35 ppm (50–90 mg/m^3) sulfur dioxide as a mucosal irritant; powdered chalk (1:1) was added to the nickel to prevent clumping. Exposure was for 5–6 h per day. Forty-six of 120 rats lived longer than 18 months. No lung tumour was observed, but many rats developed squamous metaplasia and peribronchial adenomatoses (Hueper & Payne, 1962).

Guinea-pig: A group of 32 male and 10 female guinea-pigs (Strain 13), approximately three months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% nickel; particle diameter, ≤ 4 μm) for 6 h per day on four or five days per week for up to 21 months. Mortality was high; only 23 animals survived to 12 months and all animals had died by 21 months. Almost all animals developed adenomatoid alveolar lesions and terminal bronchiolar proliferations. No such lesion was observed in nine controls. One treated guinea-pig had an anaplastic intra-alveolar carcinoma, and another had an apparent adenocarcinoma metastasis in an adrenal node, although the primary tumour was not identified (Hueper, 1958).

4A.3.2 *Intratracheal administration*

Rat: Two groups of 39 and 32 female Wistar rats, 11 weeks of age, received either 20 or 10 weekly intratracheal instillations, respectively, of 0.3 or 0.9 mg metallic nickel powder [purity unspecified] in 0.3 mL saline (total doses, 6 mg and 9 mg, respectively) and were observed for almost 2.5 years. Lung tumour incidence in the two groups was 10/39 (nine carcinomas, one adenoma) and 8/32 (seven carcinomas, one mixed), respectively; no lung tumour developed in 40 saline-treated controls maintained for up to 124 weeks. Pathological classification of the tumours in the two groups combined revealed one adenoma, four adenocarcinomas, 12 squamous-cell carcinomas and one mixed tumour. Average time to observation of the tumours was 120 weeks, the first tumour being observed after 98 weeks (Pott *et al.*, 1987).

Hamster: A group of 27 male and 31 female Syrian golden hamsters (strain Cpb-ShGa51), 10–12 weeks of age, received 12 intratracheal instillations of 0.8 mg metallic nickel powder (99.9% nickel; mass median aerodynamic diameter, 9 μm) in 0.15 mL saline at two-week intervals (total dose, 9.6 mg). Median lifetime was 111 weeks for males and 100 weeks for females. One lung tumour, an adenocarcinoma, was observed in females that received nickel powder. No lung tumour was observed in males or in vehicle-treated controls (Muhle *et al.*, 1992).

4A.3.3 *Intrapleural administration*

Rat: A group of 25 female Osborne-Mendel rats, six months of age, received five injections of a 12.5% suspension of metallic nickel powder in 0.05 mL lanolin into the right pleural cavity [6.25 mg nickel powder] once a month for five months. A group of 70 rats received injections of lanolin only. The experiment was terminated after 16 months. Four of the 12 nickel-treated rats that were examined developed round-cell and spindle-cell sarcomas at the site of injection; no control animal developed a local tumour (Hueper, 1952).

A group of five male and five female Fischer 344 rats, 14 weeks of age, received injections of 5 mg metallic nickel powder suspended in 0.2 mL saline into the pleura once a month for five months (total dose, 25 mg nickel). Two nickel-treated rats developed mesotheliomas within slightly over 100 days; no tumour occurred in 20 controls (Furst *et al.*, 1973). [The Working Group noted the small number of animals and the limited reporting of the experiment.]

4A.3.4 *Subcutaneous administration*

Rat: A group of five male and five female Wistar rats, 4–6 weeks of age, received subcutaneous implantation of four pellets (approximately 2 mm in diameter) of metallic nickel. [No control group of sham-operated rats was available.] The animals were observed for 27 months. Sarcomas (fibrosarcoma or rhabdomyosarcoma) developed within 7–23 months around the implants in 5/10 rats that received metallic nickel pellets (Mitchell *et al.*, 1960).

4A.3.5 *Intramuscular administration*

Rat: Groups of 25 male and 25 female Fischer 344 rats [age unspecified] received five monthly intramuscular injections of 5 mg metallic nickel powder in 0.2 mL trioctanoin. Fibrosarcomas occurred in 38/50 nickel-treated animals but in none of a group of 25 male and 25 female controls given trioctanoin alone (Furst & Schlauder, 1971).

Groups of 20 or 16 male Fischer 344 rats, 2–3 months old, received a single intramuscular injection of 14 mg metallic nickel powder (99.5% nickel) in 0.3–0.5 mL penicillin G procaine vehicle into the right thigh. The metal was ground to median particle diameter of < 2 μm. Of the 20 rats receiving nickel powder, 13 developed tumours (mainly rhabdomyosarcomas) at the site of injection, with an average latency of 34 weeks. No local tumour developed in 44 controls given penicillin G procaine or in 40 controls given an injection of glycerol (Sunderman, 1984).

Two groups of 10 male Fischer 344 rats, three months of age, received a single intramuscular injection of 3.6 or 14.4 mg per rat of metallic nickel powder in 0.5 mL penicillin G procaine suspension. Surviving rats were killed 24 months after the injection. Sarcomas at the injection site were found in 0/10 and 2/9 nickel-treated rats, respectively, compared with 0/20 vehicle controls (Sunderman & Maenza, 1976). [The Working Group noted the small number of animals.]

Groups of 20 WAG rats [sex and age unspecified] received a single intramuscular injection of 20 mg metallic nickel powder in an oil vehicle [type unspecified]. A group of 56 control rats received 0.3 mL of the vehicle alone. Local sarcomas developed in 17/20 nickel-treated and 0/56 control rats injected with oil (Berry *et al.*, 1984). [The Working Group noted the inadequate reporting.]

A group of 40 male WAG rats, 10–15 weeks of age, received a single intramuscular injection of 20 mg metallic nickel in paraffin oil; 10 of these rats also received intramuscular injections of 50 000 U interferon per rat twice a week beginning in the 10th week after nickel treatment. Rhabdomyosarcomas occurred in 14/30 and 5/10 rats in the two groups, respectively. No local tumour occurred in 60 control rats that received the vehicle (Judde *et al.*, 1987).

Hamster: Furst and Schlauder (1971) studied the local tumour response to metallic nickel powder in Syrian hamsters compared with that in Fischer 344 rats (see above). Groups of 25 male and 25 female hamsters, 3–4 weeks of age, received five monthly intramuscular injections of 5 mg nickel powder in 0.2 mL trioctanoin. Two fibrosarcomas at the injection site occurred in males. No local tumours occurred in 25 male and 25 female controls injected with trioctanoin alone.

4A.3.6 *Intraperitoneal administration*

Rat: In a study reported in an abstract, a group of male and female Fischer rats [number and age unspecified] (weighing 80–100 g) received 16 intraperitoneal injections of 5 mg metallic nickel powder in 0.3 mL corn oil twice per month for eight months. A control group received injections of corn oil only. In the nickel-treated

group, 30–50% of rats were reported to develop intraperitoneal tumours (Furst & Cassetta, 1973).

A group of 50 female Wistar rats, 12 weeks of age, received 10 weekly intraperitoneal injections of 7.5 mg metallic nickel powder [purity and particle size unspecified] (total dose, 75 mg nickel). Abdominal tumours (sarcoma, mesothelioma or carcinoma) developed in 46/48 (96%) nickel-treated rats, with an average tumour latency of approximately eight months. Concurrent controls were not reported, but in non-concurrent groups of saline controls, abdominal tumours were found in 0–6% of animals (Pott *et al.*, 1987).

4A.3.7 *Intraosseous administration*

Rat: In groups of 20 WAG rats [sex and age unspecified], subperiosteal injection of 20 mg metallic nickel powder resulted in local tumours in 11/20 rats; intramedullary injection of 20 mg metallic nickel powder resulted in local tumours in 9/20 rats (Berry *et al.*, 1984). [The Working Group noted the absence of controls and the inadequate reporting of tumour induction.]

4A.3.8 *Intrarenal administration*

Rat: A group of male Fischer 344 rats, approximately two months of age, received an intrarenal injection of 7 mg metallic nickel powder in 0.1 mL saline solution into each pole of the right kidney (total dose, 14 mg nickel per rat). The study was terminated after two years; the median survival time was 100 weeks compared with 91 weeks in a group of saline-treated controls. Renal tumours occurred in 0/18 rats compared with 0/46 saline-treated controls (Sunderman *et al.*, 1984).

4A.3.9 *Intravenous administration*

Mouse: A group of 25 male C57BL mice, six weeks of age, received two intravenous injections of 0.05 mL of a 0.005% suspension of metallic nickel powder in 2.5% gelatin into the tail vein (2.5 μg nickel). Nineteen animals survived more than 52 weeks, and six survived over 60 weeks. No tumour was observed. No control group was used (Hueper, 1955b). [The Working Group noted the short period of observation.]

Rat: A group of 25 Wistar rats [sex unspecified], 24 weeks of age, received intravenous injections of 0.5 mL/kg bw (0.1–0.18 mL) of a 0.5% suspension of nickel powder in saline into the saphenous vein once a week for six weeks. Seven rats developed sarcomas in the groin region along the injection route [probably from seepage at the time of treatment]. No control group was used (Hueper, 1955b).

4A.4 Metallic titanium

4A.4.1 *Intramuscular administration*

Rat: Groups of 15 male and 15 female Sprague-Dawley rats, 20–30 days old, received intramuscular implants of polished rods (1.6 mm in diameter, 8 mm in length) of metallic titanium (> 99% titanium) and were observed for up to two years [survival

unspecified]. Two groups of 15 male and 15 female untreated or sham-operated control animals were available. No benign or malignant tumour developed at the implantation site or in the sham-operated control group. The incidences of malignant tumours at distant sites did not differ significantly between control and treated rats (Gaechter *et al.*, 1977).

4A.4.2 *Intraosseous administration*

Rat: Four groups of 11–15 male and 11–15 female Sprague-Dawley rats, 30–43 days of age, received implants in the femoral bone of metallic titanium as small rods (1.8 mm in diameter, 4 mm in length), as powders (fine, diameter < 28 μm; coarse, diameter 28–44 μm) or as compacted wire (4 × 2.8 mm). A total of 77 rats in three groups of 12–13 male and 13 female untreated or sham-operated controls were available. Average survival in all groups exceeded 21 months; the animals were observed for up to 30 months. No sarcoma at the implantation site was observed in rats that received titanium implants or in two groups of 25 and 26 untreated rats or in a group of 26 sham-treated control rats. Two implant site-associated lymphomas were observed in the groups receiving titanium powder, but none in sham-operated controls (Memoli *et al.*, 1986).

4A.5 Metallic foils

4A.5.1 *Subcutaneous administration*

Rat: Three groups of Wistar rats [initial number, sex and age unspecified] were given subcutaneous implants of gold, silver or platinum foils as discs (17 mm diameter [thickness unspecified]) and observed for 23 months. The total number of sarcomas at the implantation site was 68/77 (88.3%) for gold foil, 65/84 (77.4%) for silver foil and 39/73 (53.4%) for platinum foil (Nothdurft, 1956). [The Working Group noted that no sham-operated controls were available.]

Five groups of 25 male Wistar rats [age unspecified] were given subcutaneous implants of silver, tin, tantalum, Vitallium or stainless steel foils as discs or squares (1.5 cm; two discs or squares per rat) and observed for > 596 days. Local sarcomas were found in 14/25 (56%) rats with silver foil, 5/21 (24%) rats with steel foil, 2/23 (8.7%) rats with tantalum foil, 0/25 (0%) rats with tin foil and 5/23 (21.7%) rats with Vitallium foil (Oppenheimer *et al.*, 1956). [The Working Group noted that no sham-operated controls were available and that the composition of the stainless steel was not specified.]

4A.5.2 *Intraperitoneal administration*

Mouse: A group of 43 female Marsh mice, three months of age, received intraperitoneal implants of open-end tin foil cylinders (2 × 4 mm; 151 mm^2 surface area). A control group of 39 female mice was sham-operated. The animals were observed for 18 months. Local sarcomas were found in 8/31 test animals versus 1/23 controls. [The low effective numbers of test and control rats reflect the occurrence of pneumonia.] (Bischoff & Bryson, 1977).

Rat: Groups of 31 male and 29 female Evans rats, five to six weeks of age, received intraperitoneal implants of open-end tin foil cylinders (25 × 8 mm; 628 mm^2 surface area). Four control groups of 29–31 male and female mice were sham-operated. The animals were observed for 18–24 months. Local sarcomas were found in the four groups of effective animals as follows: experiment 1, males, 10/16; females 8/13 and experiment 2, males 7/8; females 9/12. In controls the corresponding incidences were 0/16, 0/21, 0/8 and 0/14. Histiocytic lymphomas appeared sporadically in all groups of test and control animals (Bischoff & Bryson, 1977).

4A.6 Metal alloys

The results of experimental carcinogenicity studies on metal alloys are tabulated in Table 40. Alloy composition is specified by the chemical symbol of each metal followed by its percentage. Silica, carbon and other elements are not always given.

4A.6.1 *Intratracheal administration*

Hamster: Groups of 50 male and 50 female Syrian golden hamsters, three months of age, received a single intratracheal instillation of 10, 20 or 40 mg metallic nickel powder (particle diameter, 3–8 μm) or powders of nickel-containing alloys (particle diameter, 0.5–2.5 μm; alloy I: Fe39Ni27Cr16; alloy II: Ni67Cr13Fe7) or four intratracheal instillations of 20 mg of each of the substances every six months (total dose, 80 mg). In the groups receiving single instillations of alloy II, the incidences of malignant intrathoracic tumours were reported to be 1, 8 and 12%, respectively, suggesting a dose–response relationship. In the group receiving repeated instillations of alloy II, 10% of animals developed an intrathoracic malignant neoplasm (fibrosarcoma, mesothelioma or rhabdomyosarcoma). Metallic nickel induced comparable numbers and types of intrathoracic neoplasms, but no tumour was observed in animals treated with alloy I or in control animals (Ivankovic *et al.*, 1987, 1988).

A group of 27 male and 31 female Syrian golden hamsters (strain Cpb-ShGa51), 10–12 weeks of age, received 12 intratracheal instillations of 0.8 mg metallic nickel powder (99.9% nickel; mass median aerodynamic diameter, 9 μm) in 0.15 mL saline at two-week intervals (total dose, 9.6 mg). Three additional groups (28–31 animals of each sex per group) were treated with 12 intratracheal instillations of 3 or 9 mg nickel stainless-steel dust (Fe59Cr14Ni7C4Al2Mn1; mass median aerodynamic diameter, 3–5 μm) or 9 mg chromium stainless-steel dust (Fe68Cr13C3Al2; mass median aerodynamic diameter, 3–5 μm). The observation period was 26 months for females and 30 months for males. The median lifespan was 90–111 weeks in the various groups. One lung tumour was observed: an adenocarcinoma in the group that received nickel powder. No lung tumour was observed in vehicle-treated controls or in the groups treated with the stainless-steel powders (Muhle *et al.*, 1992).

Table 40. Studies of cancer in animals given implants of metallic alloy medical and dental materials

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Nickel-containing alloys except stainless steels							
Ni67Cr13Fe7	Intratracheal/powder 0.5–2.5 µm/	Hamster				Ivankovic *et al.* (1987, 1988)	
	10 mg			1/100	1		Single instillation
	20 mg			8/100	8		
	40 mg			12/102	12		Repeated instillation
	20 mg × 4			10/100	10		
Ni27Fe39Cr16	Intratracheal/powder 0.5–2.5 µm/	Hamster				Ivankovic *et al.* (1987, 1988)	
	10 mg			0/100	0		Single instillation
	20 mg			0/100	0		
	40 mg			0/100	0		Repeated instillation
	20 mg × 4			0/100	0		
Ni60Ga40	Subcutaneous/pellets (~ 2 mm diameter)/ 4 pellets	Rat	27 months	9/10	90	Mitchell *et al.* (1960)	
Ni35Co35Cr20Mo10 (MP35N alloy)	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/30	0	Gaechter *et al.* (1977)	
Ni35–36Co33Cr20–22Mo9 (MP35N alloy)	Intraosseous/rod (4 × 1.6 mm diameter) powder (< 28 µm)/43 g	Rat	30 months	0/26	0	Memoli *et al.* (1986)	
				3/26	12		
Ni38Fe62	Intramuscular/particles (< 2 µm)/14 mg as Ni	Rat	2 years	0/16	0	Sunderman (1984)	In penicillin G procaine vehicle

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Nickel-containing alloys except stainless steels (contd)							
Ni50Al50	Intraperitoneal/powder (< 10 µm)/50 mg (as Ni)	Rat	30 months	8/35	23	Pott *et al.* (1989, 1992)	52% Ni after milling
	3 × 50 mg (as Ni)			13/35	37		
Ni32Fe55Cr21Mn1	50 mg (as Ni)			2/33	6.1		29% Ni after milling
	2 × 50 mg (as Ni)			1/36	2.8		
Ni74Cr16Fe7	50 mg (as Ni)			12/35	34		66% Ni after milling
	3 × 50 mg (as Ni)			22/33	66.7		
Ni38Fe62	Intrarenal/powder/ 14 mg (as Ni)	Rat	2 years	1/14	7	Sunderman *et al.* (1984)	
Ni67Cu30Fe2Mn1	Ear tag	Rat	2 years	14/168	8.3	Waalkes *et al.* (1987)	Observed in a carcinogenicity study on cadmium compounds
				2/193	1.0		
Cobalt-based alloys							
Vitallium (CoCrMo)	Subcutaneous/pellet (~ 2 mm diameter)/ 4 pellets	Rat	27 months	0/10	0	Mitchell *et al.* (1960)	
Co67Cr26Mo7Mn1	Intramuscular/particles (0.1~1 µm)/2 mg	Rat	29 months	3/16	18.8	Heath *et al.* (1971); Swanson *et al.* (1973)	Obtained by frictional movement of prostheses in Ringer's solution
				4/14	25.0		
				15/50	30.0		

				Local tumour outcome			
Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	No.	%	Reference	Comments
						et al. (1973)	Ringer's solution

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome No.	Local tumour outcome %	Reference	Comments
Cobalt-based alloys (contd)							
Co68Cr28Mo4	Intramuscular/powder (100–250 µm)/28 mg	Rat	2 years	0/51	0	Meachim *et al.* (1982)	
	powder (0.5~50 µm)/ 28 mg			0/61	0		
Co53Cr19W15Ni10 (wrought Vitallium)	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/30	0	Gaechter *et al.* (1977)	
Co63Cr29Mo6Ni2 (cast Vitallium)	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/30	0	Gaechter *et al.* (1977)	
Co68Cr28Mo4	Intramuscular/powder (0.5~50 µm)/28 mg	Guinea-pig	Lifetime	0/46	0	Meachim *et al.* (1982)	
Co41Cr18Zr16Si11	Intraosseous/powder (< 28 µm)/42 mg	Rat	30 months	1/18	5.6	Memoli *et al.* (1986)	
Co51Cr20W14Ni10 Fe2Mn2	Wire			3/32	9.4		
Co70Cr25Mo5	Rod (4 × 1.6 mm diameter)			0/25	0		
Co47Cr20W14Ni12	Rod (4 × 1.6 mm diameter)			0/26	0		

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Cobalt-based alloys (contd)							
Co67Cr27Mo6 (F 75 alloy)	Smooth, solid extra-osseous half-cylinder (5 mm diameter × 13 mm) on lateral femur	Rat	24 months	14/101	14.0	Bouchard *et al.* (1996)	Not sintered
	Sintered porous extraosseous half-cylinder (5 mm diameter × 13 mm) on lateral femur	Rat		3/102	3.0		Sintered
	Injection of a suspension of microspheres (50–80 µm diameter) in the dorsal subcutis	Rat		15/103	15.0		
Co59Cr29Mo6Mn1Si1 (F 75-82)	Intra-articular/wear debris (1.5–50 µm)/20 mg	Rat	24 months	0/12	0	Lewis *et al.* (1995)	In saline vehicle
Titanium-based alloys							
Ti75V8Cr6Mo4Zr4Al3 (RMI alloy)	Intramuscular/rod (8 × 1.6 mm diameter)/1 rod	Rat	2 years	0/30	0	Gaechter *et al.* (1977)	
Ti89Al6V4	As above	Rat	2 years	0/30	0		
Ti89Al6V4 (F 136 alloy)	Intraosseous/half-cylinder (33 mm × 5 mm diameter)	Rat	24 months	23/102	22.5	Bouchard *et al.* (1996)	Not sintered
Ti89Al6V4 (F 136 alloy)	Intra-articular/wear debris (20–650 µm)/20 mg	Rat	24 months	0/8	0	Lewis *et al.* (1995)	In 50% glycerol vehicle

Table 40 (contd)

Implant material/composition (wt %)	Route/size/amount	Species	Duration of observation	Local tumour outcome		Reference	Comments
				No.	%		
Stainless steels							
Fe59Cr14Ni7C4Al2Mn1	Intratracheal/dust (3–5 μm)/12 × 3 mg	Hamster	26–30 months	0/63	0	Muhle *et al.* (1992)	
	(3–5 μm)/12 × 9 mg	Hamster		0/62			
Fe68Cr13C3Al2	(3–5 μm)/12 × 9 mg	Hamster		0/56	0	Muhle *et al.* (1992)	
Stainless steel[a]	Intramuscular/discs 18-, 12- and 4-mm diameter; 1.5 mm thick	Guinea-pig Rat	> 30 months	0/47 6/59	0 10	Stinson (1964)	
Fe65Cr17Ni14Mo2	Intramuscular/rod (8 × 1.6 mm diameter)/ 1 rod	Rat	2 years	0/40	0	Gaechter *et al.* (1977)	
Fe65Cr17Ni14 (316L solid)	Intraosseous/rod (4 × 1.6 mm diameter)	Rat	30 months	0/26	0	Memoli *et al.* (1986)	
Fe68Cr16Ni13 (316L powder)	Powder (< 2 μm)/40 mg			0/52	0		
Fe70 Cr15 Ni12	Intrabronchial/wire (28 gauge, approx. 10 mm long)	Rat (35)	24 months	0/32	0	Autian *et al.* (1976)	

[a] Metal composition unspecified

4A.6.2 *Intrabronchial administration*

Rat: A group of 35 male Bethesda black rats, approximately three months old, received implants via tracheotomy into the left inferior bronchus of a coiled wire fabricated of surgical-grade stainless steel suture material (Fe70Cr15Ni12, 28 gauge, approximately 1 cm long). Thirty-two of the rats survived for two years; none developed a lung tumour at the implant site. In contrast, three squamous-cell carcinomas were observed after 17–21 months in another group of rats that received intrabronchial implants of a polyether chlorinated polyurethane sheet (1 × 1 × 10 mm) (Autian *et al.*, 1976).

4A.6.3 *Subcutaneous administration*

Rat: Six groups of five male and five female Wistar rats, 4–6 weeks of age, received subcutaneous implants of four pellets (~2 mm diameter) of: (*a*) Vitallium alloy, (*b*) metallic nickel, (*c*) metallic copper, (*d*) Ni60Ga40 alloy, (*e*) metallic silver or (*f*) AgHg dental amalgam. [The percentage compositions of the metal constituents of the Vitallium alloy and the dental amalgam were unclear. No control group of sham-operated rats was available.] The animals were observed for 27 months. Sarcomas (fibrosarcoma or rhabdomyosarcoma) developed around the implants in 5/10 rats that received metallic nickel pellets and in 9/10 rats that received Ni60Ga40 alloy pellets. No local tumour occurred in the other groups of treated rats (Mitchell *et al.*, 1960).

4A.6.4 *Intramuscular administration*

Rat: A group of 59 female rats of the Chester-Beatty strain, three months old, received intramuscular implants of stainless steel discs (18-, 12- and 4-mm diameter, 1.5 mm thick). Each rat received one large (18-mm) disc into the left buttock and one small (4-mm) and one medium (12-mm) disc into the right buttock. Three animals were killed at 6, 12, 18, 24 and 30 months; the remainder were observed for their lifespan. Six rats developed a total of seven sarcomas in juxtaposition to the large discs or medium-sized discs. The minimum latent period was 332 days (Stinson, 1964). [The Working Group noted that no sham-operated controls were available.]

In a series of three experiments, a total of 80 female hooded rats, 7–9 weeks of age, received an intramuscular injection of 28 mg of wear particles (Co67Cr26Mo7Mn1; particle diameter, mostly 0.1–1 μm; obtained following repeated frictional movement in Ringer's solution of artificial hip or knee prostheses) in 0.4 mL horse serum and were observed for up to 29 months [survival not specified]. No control group was reported. Sarcomas developed at the injection site in 3/16, 4/14 and 15/50 rats in three series, respectively. Of the 22 tumours, 10 were rhabdomyosarcomas, 11 were fibrosarcomas and one was an unclassified sarcoma with giant cells. Distant metastases were found in 11/22 tumour-bearing rats (Heath *et al.*, 1971; Swanson *et al.*, 1973).

Groups of female Wistar and hooded Lister rats, weighing 190–310 and 175–220 g, respectively, received intramuscular implants of 28 mg of coarse (100–250 μm diameter; 51 Wistar rats) or medium (0.5–50 μm diameter, 85% 0.5–5 μm; 61 Wistar and 53

hooded rats) particles as dry powder (obtained by grinding Co68Cr28Mo4 alloy) and were observed for life. A sham-operated control group of 50 female Wistar rats was used. Survival at two years was 11/51 Wistar rats receiving the coarse particles, 7/61 Wistar rats receiving the fine particles. 0/53 hooded rats receiving the fine particles and 5/50 Wistar controls. No tumour was noted at the implantation site in rats treated with either type of alloy particles or in sham-operated control animals (Meachim *et al.*, 1982).

[The Working Group noted in comparing these two studies that the particle size was smaller in the studies by Heath *et al.* and Swanson *et al.* than either of the dry powders tested by Meachim *et al.*, and that the studies differed in the method of production of the test powders (the former being more relevant to the in-vivo situation), and that in the Heath *et al.* and Swanson *et al.* studies, horse serum was used as vehicle.]

Seven groups of 15 or 20 male and 15 or 20 female Sprague-Dawley rats, aged 20–30 days, received intramuscular implants of polished rods (1.6 mm in diameter, 8 mm in length) of one of seven alloys: (*a*) Fe65Cr17Ni14Mo2 alloy (stainless steel 316L); (*b*) Co53Cr19W15Ni10 alloy (wrought Vitallium); (*c*) Co63Cr29Mo6Ni2 alloy (cast Vitallium); (*d*) Ni35Co35Cr20Mo10 alloy (MP35N alloy); (*e*) metallic titanium (> 99% titanium), (*f*) Ti75V8Cr6Mo4Zr4Al3 alloy (RMI alloy) and (*g*) Ti89Al6V4 alloy. The animals were observed for up to two years [survival unspecified]. Two groups of 15 male and 15 female untreated or sham-operated control animals were available. No benign or malignant tumour developed at the implant site in any of the groups receiving metal implants or in the sham-operated control group. The incidence of malignant tumours at distant sites did not differ significantly between any of the treated and two control groups (Gaechter *et al.*, 1977).

Groups of 20 or 16 male Fischer 344 rats, two to three months old, received a single intramuscular injection of 14 mg metallic nickel powder (99.5% nickel) or 14 mg (as nickel) of Fe62Ni38 alloy in 0.3–0.5 mL penicillin G procaine vehicle into the right thigh. Each compound was ground to a median particle diameter of < 2 μm. Of the 20 rats receiving nickel powder, 13 developed tumours (mainly rhabdomyosarcomas) at the site of injection, with an average latency of 34 weeks. No local tumour developed in the 16 rats given the Fe62Ni38 alloy, in 44 controls given penicillin G procaine or in 40 controls given an injection of glycerol (Sunderman, 1984).

Guinea-pig: A group of 47 female guinea-pigs of the Hartley strain, 4–6 months old, received intramuscular implants of stainless steel discs (18-, 12- and 4-mm diameter, 1.5 mm thick). Each guinea-pig received one large (18-mm) disc into the left gluteal muscle, and one small (4-mm) and one medium (12-mm) disc into the right. Three animals were killed at 6, 12, 18, 24 and 30 months; the remainder were observed for their lifespan. No local tumours developed (Stinson, 1964).

A group of 46 female Dunkin-Hartley guinea-pigs (weighing 550–930 g) received intramuscular implants of 28 mg of a dry powder (particle diameter, 0.5–50 μm, 85% 0.5–5 μm) obtained by grinding Co68Cr28Mo4 alloy. The guinea-pigs were observed for life and 12/46 animals were alive at three years. No control group was available.

No tumour was observed at the implantation site in any guinea-pig; nodular fibroblastic hyperplasia was noted in eight animals (Meachim *et al.*, 1982).

4A.6.5 *Intraperitoneal administration*

Rat: Groups of female Wistar rats, 18 weeks of age, received single or repeated intraperitoneal injections of one of three nickel-containing alloys (milled to particle size < 10 μm) in 1 mL saline solution once or twice per week. The alloys were (*a*) Ni50Al50 alloy (nickel content 52% after milling), (*b*) Fe55Ni32Cr21Mn1 alloy (nickel content 29% after milling) and (*c*) Ni74Cr16Fe7 alloy (nickel content 66% after milling). All animals were killed 30 months after the first injection. The incidences of local sarcomas and mesotheliomas in the peritoneal cavity are shown in Table 41. A dose–response trend was apparent for metallic nickel and the tumour responses to the nickel alloys increased with the proportion of nickel present and the dose (Pott *et al.*, 1989, 1992).

Table 41. Tumour responses of rats to intraperitoneal injection of nickel and nickel alloys

Compound	Total dose (mg as nickel)	Schedule	Mesotheliomas	Sarcomas	Local tumours
Metallic nickel	6	Single injection	2	3	4/34*
	12	2 × 6 mg	3	2	5/34*
	25	25 × 1 mg	9	6	25/35*
Alloy (66% nickel after milling)	50	Single injection	0	12	12/35*
	150	3 × 50 mg	5	19	22/33*
Alloy (52% nickel after milling)	50	Single injection	1	7	8/35*
	150	3 × 50 mg	3	11	13/35*
Alloy (29% nickel after milling)	50	Single injection	1	1	2/33
	100	2 × 50 mg	0	1	1/36
Saline controls		3 × 1 mL	0	1	1/33
		50 × 1 mL	0	0	0/34

From Pott *et al.* (1989, 1992)
* $p < 0.05$

4A.6.6 *Intrarenal administration*

Rat: Groups of male Fischer 344 rats, approximately two months of age, received an intrarenal injection of 7 mg metallic nickel powder or 7 mg (as nickel) Fe62Ni38 alloy in 0.1 or 0.2 mL saline solution into each pole of the right kidney (total dose, 14 mg nickel per rat). The study was terminated after two years; the median survival time was 100 weeks in the two treated groups compared with 91 weeks in a group of saline-treated controls. Renal tumours occurred in 0/18 (nickel-treated) and 1/14

(alloy-treated) rats, compared with 0/46 saline-treated controls. The tumour, a nephroblastoma, was observed at 25 weeks (Sunderman *et al.*, 1984).

4A.6.7 *Intraosseous administration*

Rat: Groups of 10–17 male and 8–15 female Sprague-Dawley rats (total number, 409), 30–43 days of age, received implants in the femoral bone of various metallic materials as small rods (1.6 mm diameter, 4 mm length), powders (fine, diameter < 28 μm; coarse, diameter 28–44 μm) or porous compacted wire. A total of 77 rats in groups of 12–13 male and 13 female untreated or sham-operated controls was available. Average survival in all groups exceeded 21 months; the animals were observed for up to 30 months. Sarcomas at the implantation site were observed in 1/18 rats given Co41Cr18Zr16Si11 powder, 3/32 rats given Co51Cr20W14Ni10Fe2Mn2 compacted wire and 3/26 rats given Ni35Co33Cr22Mo9Ti1 powder (MP35N alloy). No sarcoma at the implant site was observed in rats that received other metallic implants or in two groups of 25 and 26 untreated rats or in a group of 26 sham-treated control rats. A total of 12 implant site-associated lymphomas was observed sporadically in the test groups, but none in sham-operated controls (Memoli *et al.*, 1986).

Four groups of 52 male and 52 female Sprague-Dawley rats, four weeks of age, were given implants of metal half-cylinders (5 mm in diameter, 13 mm in length) fixed on the left, lateral femur by an intraosseous cylindrical peg (1.5 mm diameter, 3 mm length) (groups 1, 2 and 3) or subcutaneous injections of metal microspheres (50–80 μm diameter, group 4). Group 1 received half-cylinders of Ti89Al6V4 alloy (F 136 alloy); group 2 received half-cylinders of Co67Cr27Mo6 alloy (F 75 alloy); group 3 received half-cylinders of sintered-porous Co67Cr27Mo6 alloy (F 75 alloy); and group 4 received microspheres of Co66Cr28Mo6 (F 75 alloy). No sham-operated or vehicle-injected control groups were available. The experiment was terminated 24 months after implantation [survival data not specified]. Implant-associated tumours were observed in 23/102, 14/101, 3/102 and 15/103 rats of Groups 1, 2, 3 and 4, respectively. The total of 55 implant-associated tumours included 52 malignant tumours (mostly sarcomas) and three benign tumours (lipomas, all in Group 4). Within Groups 1–3, 34/40 of the tumours were associated with loose implants, 3/40 with undetermined implant fixation status and 3/40 with implants fixed to the bone, supporting an association between implant looseness and implant-associated neoplasms ($p < 0.001$) (Bouchard *et al.*, 1996).

4A.6.8 *Intra-articular administration*

Rat: Two groups of 12 and eight male Fischer 344 rats, 2–4 months old, received an intra-articular injection into the suprapatellar pouch of 20 mg wear-debris powders of either Co59Cr29Mo6Mn1Si1 alloy (F 75-82 alloy; particle dimensions, 1.5–50 μm; suspended in 0.1 mL saline vehicle) or Ti89Al6V4 alloy (F 136-84 alloy; particle dimensions, 20–650 μm; suspended in 0.1 mL 50% glycerol vehicle). Two control groups were available: a negative control group of 11 rats received a similar intra-articular injection of metallic manganese powder (Mn 94%, O 6%; median particle diameter, 1.5 μm;

suspended in 0.1 mL saline vehicle); a positive control group of 12 rats received a similar intra-articular injection of nickel subsulfide powder (median particle diameter, 1.5 μm; suspended in 0.1 mL saline vehicle). The animals were followed up to 24 months after injection. Median survival exceeded 18 months in the test groups and the negative control group, and was 10 months in the positive control group. Tumours (mostly malignant fibrous histiocytomas) developed at the injection site in 10/12 rats in the positive control group. No injection site tumour was observed in either test group or in the negative control group (Lewis *et al.*, 1995).

4A.6.9 *Implantation of ear tags*

Rat: In two studies on the carcinogenicity of cadmium salts, groups of male Wistar rats, six weeks of age, received identification ear-tags made of a Ni67Cu30Fe2Mn1 alloy. In one study, a total of 14/168 rats surviving to two years developed a tumour (mostly osteosarcoma) at the site of ear-tag implantation. In the second study, 2/193 surviving rats developed a tumour (one osteosarcoma, one giant-cell tumour) at the site of ear-tag implantation within two years. The authors implicated nickel in the alloy as the probable causative agent and suggested that local microbial infection might be a contributory factor (Waalkes *et al.*, 1987).

4B. Non-metallic Medical and Dental Materials

4B.1 Polydimethylsiloxanes (silicones)

4B.1.1 *Subcutaneous administration*

Mouse: Three groups of 50 male and female C57BL/6JN mice [age unspecified] received subcutaneous implants of a silicone rubber cube (prepared by heat-curing of linear gum (polysilicone gum) with silica powder and a catalyst (benzoyl peroxide)) (10 mm thickness, 200 mg), a polysilicone gum ball (200 mg) or silica powder (200 mg) into the nape of the neck. All animals were observed for a maximal period of 24 months. No tumour was found at the site of implantation with any sample (Hueper, 1961).

Rat: A group of Wistar rats [sex and age unspecified] was given subcutaneous implants of plain films of Silastic (15 × 15 mm × 0.25 mm). Of the 35 rats that survived at the minimal latent period, 14 animals developed malignant tumours at the implantation site within a latent period of 300–609 days (Oppenheimer *et al.*, 1955).

Five groups of 25–30 male and female Wistar rats, weighing 60 g, received subcutaneous implants of Silastic 250, 450, 675, 2000 or 9711 (4 × 5 × 0.16 mm) and were observed for two years. At 300 days, 112 rats were still alive. Two malignant fibrosarcomas developed at the site of implantation of Silastic 250 and Silastic 2000 at 583 and 562 days, respectively (Russell *et al.*, 1959). [The Working Group noted the small size of the film.]

Three groups of 30 female Bethesda black rats, three months of age, received subcutaneous implants of a Silastic cube (300 mg), a polysilicone gum ball (300 mg) or

5. OTHER DATA RELEVANT TO AN EVALUATION OF CARCINOGENICITY AND ITS MECHANISMS

5A. Metallic Medical and Dental Materials

5A.1 Degradation of metallic implants in biological systems

Implanted metallic materials are subject to corrosion, which can result from direct interaction with the surrounding tissue or body fluids or be the consequence of mechanical damage. The resistance of metallic biomaterials to corrosion depends on the presence of a passive, protective film of oxide covering the surface. Titanium, which appears as an active metal in the electromotive series, forms a resistant oxide, which prevents further corrosion. Stainless steel and cobalt alloys form chromium oxide films. The composition of the oxide film has an important influence on biocompatibility. Metallic biomaterials in an aqueous environment represent a system in which active and passive surfaces exist simultaneously in contact with electrolyte (Kelly, 1982). At the surface of the metal oxide film, there is a continuous process of dissolution and reprecipitation, so that the composition of the film can change even though it seems macroscopically stable. Calcium, phosphorus and sulfur have been found to be incorporated into the surface film of titanium bolts surgically implanted into human jaw bone (McQueen *et al.*, 1982). Similarly, calcium and phosphorus have been detected in the oxide film of 316L stainless steel pins and wires that had been implanted during hand surgery and maxillofacial surgery (Sundgren *et al.*, 1985).

5A.1.1 *Mechanisms of degradation*

The principal mechanisms by which surgical alloys corrode are galvanic, crevice and fretting corrosion. These types of degradation involve the release of ions. Galvanic corrosion can occur when two metallic implants of different composition or two regions of the same implant with different electrochemical properties are in contact. For example, during the development of techniques for internal fixation of fractures, plates of one material were occasionally fixed with screws of another material. In modular total hip prostheses, femoral components may have a head made of a cobalt–chromium–molybdenum (CoCrMo) alloy and a stem made of titanium–aluminium–vanadium alloy (Ti 6,4). However, as more corrosion-resistant materials have become used in such mixed metal combinations, the issue of mixed metal galvanic corrosion has become less problematic.

Crevice corrosion can occur in a confined space that is exposed to a chloride solution. Such a space can exist in a gasket-type connection between a metal and a non-metal or between two pieces of metal bolted or clamped together. Crevice corrosion involves an electrochemical reaction which may take six months to two years to develop. Crevice corrosion has been observed in implants in which metals are in contact, such as in some total hip replacement devices, screws and plates used in fracture fixation and some orthodontic appliances (Fontana & Greene, 1978).

Fretting corrosion is a phenomenon of microscopic shear motion between two surfaces. The range of motion is typically less than 100 μm. Fretting corrosion involves continuous disruption of the oxide film and the associated oxidation of exposed metal. In devices that undergo crevice corrosion, fretting corrosion may accelerate the degradation.

Wear is a form of degradation which involves the release of particulate debris. Surface damage due to wear can occur by several mechanisms. On a microscopic scale, contact between two surfaces is not across an entire area, but rather occurs at high points or local asperities. Adhesive wear occurs when asperities of two surfaces adhere to each other, as with local spot welding due to high contact stress. With sliding between the surfaces, portions of one surface are torn off. Abrasive wear involves a harder material ploughing through the surface of a softer one. With ductile materials like metals and some plastics, such ploughing results in a deep furrow with a raised ridge on either side. These ridges may subsequently cause wear of the opposite surface. Three-body wear occurs when free particles in a bearing space abrade the surfaces. They may cause abrasive wear of both, or may become embedded in the softer surface and cause abrasive wear of the counterface. Under suitable conditions, the protective oxide film can be restored following damage (repassivation).

5A.1.2 *In-vitro corrosion of dental alloys*

The expression 'corrosion-resistant' in connection with precious-metal or well passivated base-metal alloys would suggest that there is no corrosion at all. In fact this is not true, as is clear from the fact that patients often claim a metallic taste and mouth burning following metallic restoration in the mouth. The recommended in-vitro test for such corrosion involves immersion of specimens in a solution of 0.1 M lactic acid and 0.1 M sodium chloride (pH 2.2) at 37°C for seven days. The low pH is thought to mimic oral crevice conditions. The total amount of metal(s) released is determined by atomic absorption spectrophotometry (AAS) or mass spectrometry. The corrosion is expressed as μg metal released per cm^2 surface area per day. Typical values are given in Table 55. Because corrosion is exceptionally rapid in the first few days, these measurements are made after a four-day period of conditioning the specimens in a similar test solution. With precious-metal alloys, the ion-specific corrosion rate does not correlate with the amount of alloying elements; the base metals are released at a proportionately higher rate compared with the alloy composition. Beryllium as an alloying element considerably increases the corrosion rate of other metals such as nickel (Kappert *et al.*, 1998; see Table 55).

Table 55. Ion release from preconditioned specimens of various cast alloy types

Alloy type	Composition	Released ions	Amount of release (μg/cm² per day)
High gold	Au 77–87; Pt 9–19; Zn 1–2; In 0.7–1.6	In	1.97–2.88
Low gold	Au 51–57; Pd 31–38; In 8; Ga 1.5	In	0.48–3.84
		Ga	0.76–3.57
Palladium–copper	Pd 73–78; Cu 8.5–11.5; Ga 7–9; Sn 3–16	Pd	3.65–11.11
		Cu	6.03–9.98
		Ga	10.8–21.0
Palladium–silver	Pd 75–77; Ag 6–8; Ga 2–6.5; Au 5–6	Pd	0.1
		Ag	< 0.1
		Ga	1.22–2.36
Cobalt-based alloy	Co 63–65; Cr 27–29 Mo 5–7; Mn < 1	Co	0.3
Nickel-based alloy without Be	Ni 65; Cr 22.5; Mo 9.5	Ni	0.07
Nickel-based alloy with 1.5% Be	Ni 76; Cr 13; Mo 3; Be 1.5	Ni	101
		Cr	5.6
		Mo	2.3
		Be	10.3
CPTi (grade 2, cast)	Ti 99	Ti	0.36
NPG	Cu 79.3; Al 17.8; Ni 4.3; Fe 4; Zn 3; Mn 1.6	Cu	1226
		Al	117
		Ni	67
		Fe	45
		Zn	40
		Mn	32

From Kappert *et al.* (1998)
CPTi, commercially pure Ti; NPG, non-precious gold

A similar analysis of various types of alloy used in orthodontics has shown that nickel and chromium were released when these alloys were stored in physiological saline. Soldered stainless steel bows were very susceptible to corrosion. The release of nickel seemed to be related to both the composition of the alloys and the method of manufacture of the appliances, but was not proportional to the nickel content (Grimsdottir *et al.*, 1992).

5A.2 Absorption, distribution and excretion

Implants in soft tissue or bone give rise to exposure in that tissue, and the biological effects depend on the interactions of the tissue with the surface of the implant. Such

effects may remain localized to the site of the implant itself, but metal ions or particulate debris released as a result of corrosion or wear may cause effects at distant sites. Oral exposures prevail in the case of dental fillings, while materials released from these may be ingested and give rise to exposure via the gastrointestinal tract.

Published studies of biological effects of implants in surrounding tissue have various limitations; many were based on cases of failed implants, which may have led to additional corrosion and/or wear, hence to stronger effects than would normally be the case. Furthermore, the composition and properties of the implants are often poorly described. In addition, it is not always clear whether the effects observed are due to the implant itself or to material released from it. In terms of their possible carcinogenic hazard, metal ions released systemically can be regarded as metal salts, several of which have been the subject of previous IARC Monographs (IARC, 1990a,b, 1991, 1993a,b). When metal ions are released systemically, accumulation may occur in specific organs. Thus nickel accumulates in the liver, spleen and kidney of mice after administration of high doses of the metal ion (Pereira *et al.*, 1998), vanadium accumulates in the liver, spleen and bone, but titanium is reported to accumulate less (Merritt & Brown, 1995). A complex mixture of ionic species may be formed during corrosion, and a wide range of sizes, shapes and numbers of particles may be produced by wear, but many reports provide very little information on these aspects.

5A.2.1 *Humans*

Doorn *et al.* (1998) described the analysis of metallic particles in tissue from 13 patients with cobalt–chromium–molybdenum metal-on-metal total hip implants for periods ranging from seven months to 25 years. Samples were obtained at either revision or autopsy from different sites around the implant and particles were found in eight patients. There was marked inter- and intra-individual variability in both the number (range, 1–580) and size (range, 6–834 nm, most < 50 nm) of particles. The authors had previously determined volumetric wear in three of these patients (McKellop *et al.*, 1996). They estimated that wear produced 6.7×10^{12}, 4.9×10^{13} and 2.5×10^{14} particles per year in three metal-on-metal prostheses and contrasted these figures with their estimate for polyethylene wear debris of 5×10^{11} particles per year in a metal-on-polyethylene hip implant.

Willert *et al.* (1996) determined metal concentrations in tissue samples from 19 patients with cobalt–chromium metal-on-metal total hip implants for periods of one to 282 months (average, 86). Samples were obtained at revision from various sites around the implant, mainly the joint capsule, and metal particles were found in 15 patients. As far as they were visible in the light microscope, these were irregularly shaped, ranged from 0.5 to 5 μm in size and were most often found in the vicinity of blood vessels. Poly(methyl methacrylate) bone cement particles were found at greater concentrations than metal particles. Both the worn surface and the wear particles undergo repassivation to cobalt(II) hydroxide, chromium(III) oxide, chromium(III) hydroxide and nickel(II) hydroxide. While these cobalt and nickel compounds have

solubilities greater than 10^{-4} M at physiological pH, the chromium compounds are essentially insoluble under the same conditions, so that chromium accumulates in local tissues while the other products are eliminated by urinary and faecal excretion. Merritt and Brown (1996) reported that the estimated dissolution of cobalt–chromium alloy is 0.15–0.30 μg/cm² per day, which corresponds to around 11 mg per year for a total hip replacement. This can be increased by corrosion.

Jacobs *et al.* (1996) determined cobalt and chromium concentrations in serum and chromium concentrations in urine from eight patients with long-term (> 20 years) cobalt–chromium metal-on-metal total hip replacements, six patients with short-term (< 2 years) cobalt–chromium metal-on-metal surface replacement arthroplasties and three controls. Single samples were obtained at average implantation times of 295 (range 266–324) months from the total hip replacements and 12.4 (range 2–19) months from the surface replacements. No details of diet were recorded, nor was this variable controlled. The controls had chromium concentrations in serum and urine of 0.14 ng/mL (2.7 nmol/L) and 0.035 ng/mL (0.66 nmol/L), respectively, and cobalt concentrations in serum were below the detection limit (0.3 ng/mL, 5.2 nmol/L). The mean total 24-h urinary chromium excretion in the controls was 0.071 μg per day (1.37 nmol per day). The mean serum chromium and cobalt concentrations in the total hip replacement patients were nine- and threefold higher respectively, whilst urinary chromium concentrations were 35-fold higher than in the controls. The mean total 24 h urinary chromium excretion was 30-fold higher than in the controls. The mean serum chromium and cobalt concentrations in the subjects with surface replacements were three- and four-fold higher, respectively than in the hip replacement patients, whilst urinary chromium concentrations were four-fold higher. The mean total 24-h urinary chromium excretion was 2.5-fold higher in the surface replacement group than in the hip replacement subjects.

In a study to investigate nickel and chromium concentrations in saliva of patients with different types of fixed dental appliances (containing 8–12% nickel and 17–22% chromium), fresh saliva samples were obtained from each of 47 orthodontic patients before insertion of the appliance and 1–2 days, 1 week and 1 month after treatment. The method of sampling shows the momentary total concentration of soluble nickel and chromium. The saliva concentrations of both metals showed considerable variation, and no significant differences were found in samples taken before and after treatment. The authors note that minor amounts of nickel released from dental fixtures could be important in case of hypersensitivity to nickel or in evoking allergic reactions in the oral mucosa (Kerusuo *et al.*, 1997).

5A.2.2 *Experimental systems*

Harmand *et al.* (1994) described the dissolution in culture medium and cellular uptake in an osteoblast cell line of ISO 5832/3 titanium alloy, ISO 5832/1 316L stainless steel and ISO 5832/4 cobalt–chromium alloy (defined in Tables 8–10) over a nine-day period. The presence of the cells had varying effects (increase, decrease or none) on release of metal ions from these metals. Uptake of extracellular ions by the

cells was limited to chromium, vanadium, titanium, iron and cobalt, with the highest uptake been observed for chromium.

Gray and Stirling (1950) exposed serum and red blood cell cultures to radioactive chromium (^{51}Cr) with a valency of +3 ($^{51}CrCl_3$) and with a valency of +6 ($Na_2{}^{51}CrO_4$). Almost all of the trivalent chromium remained in the plasma, whereas hexavalent chromium crossed the red cell membrane and was primarily cell-associated. Similar results were obtained with fretting corrosion experiments in cell culture (Merritt *et al.*, 1991). These results imply that the valency of chromium affects its biological activity. It is clear that the biological fate of corrosion products needs to be understood before conclusions can be drawn regarding the relevance of chemical analytical data of tissues and fluids for effects of implant corrosion.

In a study to investigate the effect of anodization on the dissolution of titanium, Sprague-Dawley rats were given anodized or unanodized titanium implants intraperitoneally, in the left paracolic gutter. At days 7, 14 and 28, peritoneal lavages and blood samples were obtained. At day 28 the animals were killed and liver, kidneys, spleen, lung and brain were removed, as well as tissue surrounding the implant. Titanium was not detected in any distant organs or in the lavage fluid. In the capsular tissues surrounding the implants titanium concentrations were higher in animals with unanodized implants than in those with anodized implants, but the difference was not significant. Peritoneal leukocytes showed significantly higher titanium levels in animals from the unanodized implant group, compared with the controls, while titanium levels in leukocytes from animals with anodized implants were not significantly different from the controls. Despite the presence of titanium in leukocytes, only minimal biological responses and histopathological changes were detected. The presence of titanium in the tissue surrounding the implants is probably the result of corrosion. Surface treatment of titanium by anodization reduces passive dissolution (Jorgenson *et al.*, 1999).

To examine the biological transport of released metal ions, Merritt *et al.* (1984a) injected metal salts (nickel chloride, cobalt chloride, chromium chloride, potassium dichromate) intramuscularly into hamsters. Blood samples were taken at 2, 4, 6, 24, 48 and 96 h after injection. Nickel was found in the blood serum at 2, 4 and 6 h, but the levels dropped rapidly. Levels of nickel in red and white blood cells were low. Cobalt and trivalent chromium were similarly found in serum, but the levels did not drop as rapidly. In contrast, hexavalent chromium from potassium dichromate was found in the red blood cells, confirming the results of Gray and Stirling (1950). Corrosion products generated by fretting corrosion of 316 LVM stainless steel or MP35N plates and screws were suspended in serum and injected intramuscularly into hamsters; chromium was again found in the red blood cells. When serum that had interacted with the metal salts or corrosion products was separated into its components by isoelectric focusing on polyacrylamide gels, almost all of the metal, whatever the source, was detected in the albumin region of the gels, indicating strong albumin binding (Merritt *et al.*, 1984b).

Brown *et al.* (1988) carried out chemical analysis of urine from Syrian hamsters after intramuscular injection of nickel(ous) chloride, cobalt chloride and potassium dichromate, or after accelerated anodic corrosion both *in vitro* and *in vivo* of stainless steel implants. The amounts of metal injected were 90 μg of nickel, 94 μg of cobalt and 117 μg of chromium in one group of animals, and 5.18 μg of nickel, 5.40 μg of cobalt and 6.91 μg of chromium in the second group. Total daily urine samples were collected during three days. In both dose groups, virtually all of the injected nickel and most of the cobalt were excreted in the first 24 h, whereas less than 50% of the chromium dose was excreted. After accelerated anodic corrosion of stainless steel, nickel excretion was complete within 24 h, while chromium excretion was minimal. Similar studies were performed with rods of a nickel–cobalt–chromium–molybdenum alloy (F 75) with a porous coating. These rods were implanted subcutaneously in Syrian hamsters and subjected to accelerated anodic corrosion *in situ*. Even though the nickel content of F 75 alloy is less than 1%, it was rapidly excreted and detected in the urine, as was the molybdenum. Recovery in urine of cobalt was close to 80%, whereas that of chromium was in the range of 37–67% due to *in vivo* storage and significant binding of chromium to red cells (Brown *et al.*, 1993).

These studies also showed that the corrosion rates of these alloys in 10% serum were much lower those that in saline. The rates *in vivo* were similar to those in serum. Thus, for testing materials for corrosion, the use of proteins in the test solution provides a better simulation of the in-vivo environment (Brown *et al.*, 1988).

The implication of these results is that chemical analysis of body fluids and tissues must be interpreted in light of the mechanism of degradation. If an implant corrodes and releases metal ions, nickel and cobalt will be transported and excreted, while chromium may be cell-bound, either in local tissues or in organs such as the lung, kidney, liver and spleen. Thus tissue levels may be different from that of the alloy composition. Also, if there is significant wear and particulate debris in the tissues, chemical analysis of the tissue will indicate a composition different from that of the alloy.

5A.3 Tissue responses and other expressions of toxicity

5A.3.1 *Humans*

(*a*) *Inflammatory and immunological responses*

No relevant systematic studies of tissue responses in orthopaedic implant patients have been reported, although some reviews of case reports have tried to link the occurrence of tumours to carcinogenic mechanisms. In a review of nine cases of implantation site tumours following knee arthroplasty, and in a wider-ranging review of the use of metallic implants, it was suggested that carcinogenicity could result from the release of carcinogenic corrosion products (Jacobs & Oloff, 1985; Wapner, 1991).

A case series of 20 failed hip replacements (two Charnley (metal (TiAlV)-on-polyethylene) and 18 McKee-Farrar (metal-on-metal)) revealed mild to severe acute inflammatory response (characterized by the predominant occurrence of polymorpho-

nuclear leukocytes) in all 12 cases that failed due to infection. The remaining eight cases failed due to loosening. Chronic inflammation was seen in all but one of the 12 infected cases (predominantly lymphocytes and plasma cells). Acrylic debris from the cement was found in all cases extracellularly and in three also intracellularly; one patient from this group and one other patient showed polyethylene debris (Charosky *et al.*, 1973).

A case was reported of aseptic aggressive granulomatosis seven years after knee arthroplasty. Both titanium- and polyethylene-containing fragments were observed around the prosthesis, some titanium being found within macrophages or giant cells (Tigges *et al.*, 1994).

None of the pathological changes noted in clinical reports are suggestive of pre-cancerous states.

When a material is implanted, it is recognized as a foreign body and macrophages adhere to the surface of the material (Tang *et al.*, 1993; Mrksich & Whitesides, 1996). Large amounts of macrophages and polyethylene debris are observed in tissues around aseptically loosened hip arthroplasty (Dorr *et al.*, 1990; Wroblewski, 1997). Macrophages generate active oxygen species by themselves without being active in phagocytosis, but the production of active oxygen is much higher during this process (Johnston & Kitagawa, 1985; Edwards *et al.*, 1988). The primary oxygen radical (O_2^-) is converted by superoxide dismutase to hydrogen peroxide, which penetrates the metal surface to which the macrophage has adhered. In the case of a titanium implant, hydrogen peroxide reacts with the surface oxide film of titanium, which results in the formation of a stable $TiOOH(H_2O)_n$ complex. This TiOOH matrix traps the superoxide radical so that no or very small amounts of free hydroxyl radicals are formed. Apart from titanium, other biocompatible metals such as zirconium and aluminium also show low hydroxyl radical production (Tengvall *et al.*, 1989).

(*b*) *Oral contact lichenoid reactions*

Contact lichenoid reactions topographically related to dental restorations display various clinical characteristics, ranging from asymptomatic papular, reticular and plaque type lesions to symptomatic atrophic and reticular lesions (Holmstrup, 1991). Contact lesions present with similar clinical characteristics as oral lichen planus. These two types of lesion can be discriminated only by the degree to which the oral mucosa is involved (Bolewska *et al.*, 1990a,b). By definition, contact lesions are limited to areas of frequent contact with dental restorations, whereas oral lichen planus also involves other regions of the oral mucosa. In a study of the effect of replacement of dental amalgam with gold or metal–ceramic crowns on oral lichenoid reactions, Bratel *et al.* (1996) found that the lesions showed considerable improvement in 95% of the patients. This effect was parallelled by a disappearance of symptoms, in contrast to patients with persisting contact lesions (5%), who did not report any significant improvement. The healing response was not found to correlate with age, gender, smoking habits, subjective dryness of the mouth or current medication. The healing

effect in patients who received gold crowns was superior compared with that of patients receiving metal–ceramic crowns. Similar contact lesions have been seen in the topographical relationship to dental composite restorations (Lind, 1988) and palladium-based crowns (Downey, 1989).

The etiology of these lesions remains uncertain. An immunological mechanism is involved in some cases, whereas others seem to be related to irritative or cumulative insult-type reactions. Microbial factors such as viral or fungal infections may also contribute to the clinical appearance. It is unclear whether oral lichen planus is a multivariant group of etiologically diverse diseases or a disease entity characterized by a type IV hypersensitivity reaction to an antigen in the junction zone between epithelium and connective tissue. The premalignant potential of oral lichenoid lesions requires regular follow-up at three- to six-month intervals (for reviews, see Scully *et al.*, 1998; Holmstrup, 1999).

(*c*) *Allergic reactions*

In questionnaire surveys about side-effects associated with dental materials, the prevalence was estimated to be 1:300 in periodontics and 1:2600 in pedodontics. None of these reactions was related to dental casting alloys. In prosthodontics, the prevalence was calculated to be about 1:400, and about 27% were related to base-metal alloys for removable partial dentures (cobalt, chromium, nickel) and to precious-metal-based alloys for porcelain-fused-to-metal restorations. The complaints consisted of intra-oral reactions (such as redness, swelling and pain of the oral mucosa and lips), oral/gingival lichenoid reactions and a few instances of systemic allergic reactions. In orthodontics, the prevalence was 1:100, and most reactions (85%) were related to metal parts of the extra-oral anchorage devices (Hensten-Pettersen, 1992).

Even though the extensive use of base-metal alloys has been of major concern to the dental profession, relatively few case reports of allergic reactions substantiate this concern. Allergy to gold-based dental restorations has been more commonly reported. Palladium-based alloys have been associated with several cases of stomatitis and oral lichenoid reactions. Palladium allergy seems to occur mainly in patients who are highly sensitive to nickel. All casting alloys, except titanium, seem to have a potential for eliciting adverse reactions in individual hypersensitive patients. Induction of tolerance may be a possible benefit of the use of intra-orally placed alloys. In non-sensitized individuals, oral antigenic contacts to nickel and chromium may induce tolerance rather than sensitization (Hensten-Pettersen, 1992).

Both local and systemic reactions may sometimes occur following implantation of metallic devices (Rostoker *et al.*, 1986; Wilkinson, 1989; Guyuron & Lasa, 1992). Metal allergy has been suggested as a predisposing factor for infection of periprosthetic tissues (Hierholzer & Hierholzer, 1984). However, the majority of individuals—even the majority of sensitized individuals—seem to tolerate low levels of allergens in the tissues without adverse effect. Induction of immunological tolerance may be a potential benefit.

The mechanisms by which local cutaneous and systemic reactions are induced by nickel in orthopaedic implants remain obscure and the development of such reactions is unpredictable. Some reactions appear to be type I in nature. In others, there is good evidence of type IV hypersensitivity. In some patients, however, type I, III (Arthus) and IV reactions seem to coexist (Wilkinson, 1989). The reaction patterns elicited by other metals seem to be similar to those induced by nickel.

5A.3.2 *Experimental systems*

(*a*) *Animal studies*

The chemical carcinogenicity of metal compounds (such as that of chromium, nickel, cobalt and arsenic) is believed to be dependent largely on their oxidation state and solubility, with oxidative DNA damage or interference with DNA repair having been postulated as likely mechanisms (Hartwig *et al.*, 1996). Additional mechanisms of metal carcinogenesis include epigenetic changes, chromatin condensation or altered patterns of gene methylation (Costa, 1997; Salnikow *et al.*, 1997). However, very few experimental studies have provided information on tissue responses to metallic implants that is of relevance to carcinogenicity.

A series of five 18–24-month studies of tumour incidence following implantation of tin revealed unusual non-neoplastic pathology, but only in tumour-bearing groups. The studies were carried out in female Marsh mice and male and female Evans rats given intraperitoneal tin implants (open-end cylinders, 12 × 4 mm in mice, 25 × 8 mm in rats). In addition to tumours (an increase was seen in local sarcomas with metastases, but not in spontaneous lymphoid tumours in rats), atypical mesothelial hyperplasia, adenomatous hyperplasia and osseous metaplasia were noted. Chronic inflammatory responses were also common. These included focal histiocytic aggregation, multinucleate giant cells, granulomata, fibrohyalinized capsular tissue, necrosis, fibrocellular fat, lack of capsule, hyalinized sclerosis and cysts (Bischoff & Bryson, 1977).

Male WAB rats, 20 weeks of age, were given implants of either Walker 256 carcinoma cells (as 5-mg solid tumour fragments) or syngeneic neonatal thymus tissue. These tissues were placed in the centre of platinum–silicone elastomer loops, which had been implanted earlier. Control animals received tissues without implants. Colchicine was used to facilitate the assessment of cell proliferation. Rats with thymus grafts were killed after three weeks and those with tumour grafts after up to six days. Group sizes were not reported. Historical data indicated 100% tumour growth at six days in 1500 controls, whereas tumour growth was inhibited in 200/230 rats with implants. Marked reductions in cell density and mitotic rate were seen, in comparison with controls, at two, three, four and six days after tumour implantation, the cell density being lowest close to the implant. Unlike in controls, proliferation of tumour cells in the vicinity of implants was concentrated into foci of intense activity. In contrast, proliferation of thymus tissue was unaffected by the presence of the platinum–silicone implant. The authors ruled out restriction of the blood supply as a reason for the observed effects and suggested that the selective inhibition of tumour cell proliferation

may be a result of an alteration of the electrochemical environment by the implant (Hinsull *et al.*, 1979). [The Working Group found it difficult to interpret these data.]

(*b*) *Cytotoxicity of metal ions*

The cytotoxicity of metal ions has been investigated systematically in L-929 fibroblasts (Takeda *et al.*, 1989; Schedle *et al.*, 1995; Yamamoto *et al.*, 1998) and 3T3 fibroblasts (Wataha *et al.*, 1991; Yamamoto *et al.*, 1998). The rank orders of cytotoxicity that were found are: Cr > Co > V > Fe > Mn > Cu > Ni >> Mo (Takeda *et al.*, 1989); $Cd^{2+} > Ag^{-} > Zn^{2+} > Cu^{2+} > Ga^{3+} > Au^{3+} > Ni^{2+} > Pd^{2+} > In^{3+}$ (Wataha *et al.*, 1991), $Ag^{-} > Pt^{4+} > Co^{2+} > In^{3+} > Ga^{3+} > Au^{3+} > Cu^{2+} > Ni^{2+} > Zn^{2+} > Pd^{2+} > Mo^{5+} > Sn^{2+} > Cr^{2+}$ (Schedle *et al.*, 1995); $Cd^{2+} > In^{3+} > V^{3+} > Be^{2+} > Sb^{3+} > Ag^{-} > Hg^{2+} > Cr^{6+} > Co^{2+} > Bi^{3+} > Ir^{4+} > Cr^{3+} > Hg^{-} > Cu^{2+} > Rh^{3+} > Tl^{3+} > Sn^{2+} > Ga^{3+} > Pb^{2-} > Cu^{+} > Mn^{2+} > Tl^{+} > Ni^{2+} > Zn^{2+} > Y^{3+} > W^{6+} > Fe^{3+} > Pd^{2-} > Fe^{2+} > Ti^{4+} > Hf^{4+} > Ru^{3+} > Sr^{2+} > Sn^{4+} > Ba^{2+} > Cs^{-} > Nb^{5+} > Ta^{5+} > Zr^{4+} > Al^{3+} > Mo^{5+} > Rb^{-} > Li^{-}$ (data for 3T3 cells; Yamamoto *et al.*, 1998). The concentrations that reduced [^{3}H]thymidine incorporation to 50% of the control ranged between 0.4 and > 435 µmol/L (Wataha *et al.*, 1991) and between 0.017 mmol/L and > 1 mmol/L (Schedle *et al.*, 1995). Yamamoto *et al.* (1998) calculated the IC_{50} values (50% of cell growth inhibition), which ranged from 1.36×10^{-6} to 1.42×10^{-2} (mol L^{-1}). For both cell types studied, the ions of chromium, cadmium, vanadium, silver and cobalt were generally the more cytotoxic. Sun *et al.* (1997) tested the effects of Al^{3+}, Co^{2+}, Cr^{3+}, Ni^{2+}, Ti^{4+} and V^{3+} on osteoblast-like cell metabolism and differentiation. DNA synthesis, succinate dehydrogenase and alkaline phosphatase activities, culture calcification and osteocalcin and osteopontin gene expression were investigated in ROS 17/2.8 cells. It was shown that metal ions can alter osteoblast behaviour at subtoxic concentrations, but do not affect the expression of all genes similarly. Granchi *et al.* (1998) showed that large amounts of nickel and cobalt extracted from the metal powders induced necrosis *in vitro* in mononuclear cells from human peripheral blood and high concentrations of chromium or limited amounts of nickel and cobalt caused cell death by apoptosis. The cytotoxicity of metal ions extracted from commercial gold alloys, silver alloys and nickel–chromium alloys was tested on L929 mouse fibroblasts (Schmalz *et al.*, 1998a). The TC_{50} values were slightly lower in corresponding salt solutions than in extracts. Nickel and cobalt ions upregulated the expression of adhesion molecules as well as of the cytokines interleukin (IL)-6 and -8 in human endothelial cell cultures, as do proinflammatory mediators (Wagner *et al.*, 1998). Silver, mercury and, to a lesser extent, gold ions induced direct toxicity (histamine release, ultrastructural signs of necrosis) and platinum ions induced cell death through induction of apoptosis in the human mast cell line HMC-1 (Schedle *et al.*, 1998a). Extracts from titanium–nickel alloy (50:50) were not cytotoxic *in vitro*, not allergenic *in vivo* in guinea-pig, nor genotoxic *in vitro* in *Salmonella typhimurium* for gene mutation or in V79 cells for chromosomal aberrations (Wever *et al.*, 1997). Extracts from cobalt–chromium orthopaedic alloys caused inhibitory effects on cell viability, on alkaline phosphatase activity and, to a lower extent, on protein production in all rat, rabbit and human bone-marrow

cell cultures tested, the human cells being most sensitive to exposure to metal ions (Tomás *et al.*, 1997). Ions associated with the titanium–chromium–vanadium alloy Ti 6,4 inhibited the normal differentiation of rat bone-marrow stromal cells to mature osteoblasts *in vitro* (Thompson & Puleo, 1996).

(*c*) *Cytotoxicity of metallic materials*

Cobalt–chromium alloy was toxic to macrophages *in vitro*, as reflected by release of tumour necrosis factor (TNF) α, prostaglandin E2 and the enzyme lactate dehydrogenase (Horowitz *et al.*, 1998). Test specimens fabricated from copper, cobalt, zinc, indium, nickel and precious-metal cast alloys reduced cell viability by 10–80% (copper being the most active) in a three-dimensional cell-culture system consisting of human fibroblasts and keratinocytes (Schmalz *et al.*, 1998b). Nickel–titanium (Nitinol) did not induce cytotoxic effects in human osteoblasts and fibroblasts *in vitro* (Ryhänen *et al.*, 1997).

(*d*) *Effects of metal ions and metallic materials on cytokine levels and histamine release*

Effects of dental amalgam and heavy metal cations on cytokine production by peripheral blood mononuclear cells were investigated *in vitro* (Schedle *et al.*, 1998b). Fresh amalgam specimens and salt solutions containing Cu^{2+} and Hg^{2+} induced a decrease in interferon-γ and IL-10 levels, whereas fresh amalgam specimens and Hg^{2+} caused an increase in TNF-α levels. Amalgam specimens preincubated in cell-culture medium for six weeks did not cause any effects. Ag^{-}, Au^{3+} and Hg^{2+} induced rapid histamine release from human tissue mast cells *in vitro* (Schedle *et al.*, 1998a). Exposure of macrophages cocultured with osteoblasts to cobalt–chromium alloy led to significant release of TNF-α and prostaglandin E2, but no significant IL-6 or IL-1β production (Horowitz *et al.*, 1998).

5A.4 Genetic and related effects

5A.4.1 *Humans*

Case *et al.* (1996) studied chromosomal aberrations in blood and bone marrow in 71 patients (mean age 73 years) with hip (n = 69) or knee (n = 2) replacements who required revision surgery because of worn prostheses, and in 30 control patients (mean age 70.3 years) having primary arthroplasty. Bone marrow was taken at the site of the worn prostheses in the case of revision surgery or at the site of the newly inserted prostheses in the case of primary arthroplasty. Bone marrow from the ipsilateral iliac crest and peripheral blood samples were also taken from all patients for metaphase analysis. The frequency of chromosomal aberrations (mean ± SD) in marrow taken from the femur at primary arthroplasty (5.8 ± 4.3 aberrant cells per 100 cells) was not different from that found in the iliac crest marrow taken from revision cases (4.6 ± 3.3 aberrant cells per 100 cells). However, there was a significant increase in the frequency of chromosomal aberrations (mean ± SD; aberrant cells per 100 cells) in the cells taken from

the femoral marrow adjacent to a worn prosthesis (11.4 ± 10.2, $n = 16$, ≤ 10 years after primary arthroplasty; 12.7 ± 10.8, $n = 9$, > 10 years) compared with the frequency in the iliac crest marrow from the same patients (3.3 ± 2.7, $n = 11$, ≤ 10 years; 5.6 ± 2.0, $n = 10$, > 10 years) or with femoral marrow from patients at primary arthroplasty (see above). Nine out of 27 femoral marrow samples from revision cases had higher chromosomal aberration frequencies (17–40 aberrations/100 cells) than any of the control femoral bone marrow (1–15 aberrations/100 cells) or iliac crest marrow samples from revision cases (0–15 aberrations/100 cells). Chromosomal aberration frequencies were only slightly higher in patients requiring revision more than 10 years after primary arthroplasty. Two patients with a long duration of arthroplasty (18 and 20 years) showed clonal expansion of B or T cells which was associated in one case with a high level of chromosomal aberrations in the femur (26/100 cells) compared with ipsilateral iliac crest (6/100 cells). The authors cautioned that the results should be seen as preliminary due to the low patient numbers. They discounted concomitant disease and X-rays as predisposing factors, leaving wear debris as a potential causative agent.

5A.4.2 *Experimental systems*

Very few mutagenicity studies have been performed with metallic medical and dental materials. The evaluation of the mutagenic potential is normally based on either the results of tests with extracts or on knowledge of the mutagenic potential of the individual metallic components of the biomaterial.

(*a*) *Genotoxic activity of metals and metal compounds*

Data on the genotoxicity and mutagenicity of some of the metals used in implants have been compiled in previous IARC Monographs and are summarized here.

Chromium[VI] compounds of various solubilities in water were consistently active in numerous studies covering a wide range of tests for genetic and related effects (IARC, 1990a).

The chromium[III] compounds tested were generally not genotoxic in numerous studies and only weak effects were observed in some tests (IARC, 1990a).

Soluble nickel compounds were generally active in the human and animal cells in which they were tested *in vitro* (IARC, 1990b).

Cobalt[II] compounds induced DNA damage, mutations, sister chromatid exchanges and aneuploidy in mammalian cells. Some cobalt[III] complexes with heterocyclic ligands were also active in these assays (IARC, 1991).

Chromosomal aberrations and aneuploidy were observed in mammalian cells *in vitro* and in rodents *in vivo* after treatment with cadmium chloride. DNA strand breaks, mutations, chromosomal damage and cell transformation have been observed after exposure of mammalian cells to cadmium compounds *in vitro* (IARC, 1993b).

DNA damage, sister chromatid exchanges, chromosomal aberrations and aneuploidy (spindle disturbances) have been induced by mercury compounds in mammalian

cells *in vitro*. Weak positive genotoxic effects were observed with mercuric chloride in rodents *in vivo* (IARC, 1993a).

Beryllium salts are not mutagenic in most bacterial systems but they induced sister chromatid exchanges and possible chromosomal aberrations in mammalian cells *in vitro*. Beryllium chloride induced gene mutation and chromosomal aberrations in mammalian cells *in vitro* (IARC, 1993c).

(*b*) *Tests using extracts*

Extracts for testing are generally prepared by adding the biomaterial to water, saline or cell-culture medium for a few hours or days at 37°C. The corrosion that occurs under these conditions has generally not been compared with the corrosion that is observed *in vivo*. Also, an analysis of leachable material is often not made, so there is no assurance that any such substances have indeed been extracted from the biomaterial. Reference to the mutagenicity of individual metallic components can be misleading, because the ionic species tested may be different from those generated by leaching.

Tests on extracts are often performed for regulatory compliance, and results are not usually published in the open literature. [The Working Group noted that many genotoxicity tests carried out for such purposes are not adequate to identify all mutagenic hazards and they may not address all relevant mutagenic end-points or optimize exposure to the test system.]

Assad *et al.* (1998) studied single-strand DNA breakage in interphase and metaphase human lymphocytes *in vitro* using an in-situ end-labelling method with electron microscopy. Twenty-four-hour extracts of particles of a nickel–titanium alloy (diameter 250–500 μm) were prepared using complete RPMI medium at 37°C. The lymphocytes were exposed to the extracts for 72 h. The results were compared with those obtained with extracts of commercially pure titanium or 316 L stainless steel particles. No determination of the quantity of each metal extracted by the medium was performed. DNA strand breaks were significantly increased in metaphase chromatin with extracts of 316 L stainless steel. Extracts of the nickel–titanium alloy or of pure titanium did not show an effect. However, no information on the metallic species from stainless steel producing the effect was provided. No effect on chromatin in interphase nuclei was observed with any of the extracts.

Wever *et al.* (1997) tested a nickel–titanium alloy (50% nickel) and compared the results with those obtained with stainless steel containing 13–15% nickel. Both alloys were extracted in aqueous 0.9% sodium chloride for 72 h at 37°C. No determination of the metal content of the extracts was performed. Extracts were tested with and without metabolic activation for mutagenic activity in four strains of *Salmonella typhimurium* (TA1535, TA1537, TA98 and TA100) and for induction of chromosomal aberrations in Chinese hamster ovary (CHO) cells. The two alloys gave negative results in both tests.

The potential to induce neoplastic transformation in C3H T½ fibroblasts was tested for eight metals (cobalt, chromium, nickel, iron, molybdenum, aluminium, vanadium and titanium) and their alloys (stainless steel, chromium alloy, titanium–aluminium–

vanadium alloy). The cells were exposed to solutions of the metal salts or to metal or alloy particles (particle size ≤ 5 μm). Cell transformation was observed with soluble forms of cobalt, chromium, nickel and molybdenum, although in some cases only at cytotoxic concentrations. Vanadium, iron, aluminium and titanium salts did not induce cell transformation. The particulate metals and alloys failed to induce cell transformation, although large differences in toxicity were noted (Doran *et al.*, 1998).

5A.5 Mechanisms of carcinogenic action

Surgical alloys and metallic medical devices are insoluble in physiological media, but are subject to corrosion and wear. Corrosion can result in the release of soluble ions. Information with respect to the potential carcinogenic hazard of such ions is available in previous IARC Monographs. However, it is difficult to evaluate whether the metal salts play any significant role in the possible carcinogenic effects observed with implants, because there is a striking lack of data on the actual amounts of ions released into the surrounding tissue and on the nature of the ionic species involved. It is possible that irritation of the surrounding tissue by the implant itself, presumably occurring at the boundary between the metal surface and the tissue, can provoke responses that lead to disturbances of normal cellular function. In addition, inflammatory reactions observed at the site of implants may enhance oxidative processes, inducing cellular damage and regenerative cell proliferation. Particulate debris generated by wear may induce similar reactions in the surrounding tissue or at more distant sites. One single study has reported an enhanced frequency of chromosomal aberrations in cells adjacent to a loose or worn prosthesis (hip or knee replacement) in elderly patients (Case *et al.*, 1996).

5B. Non-metallic Medical and Dental Materials

Of the many components of non-metallic medical and dental materials, only a few are discussed here, which are those for which some data are available.

5B.1 Degradation, distribution, metabolism and excretion

5B.1.1 *Humans*

(a) Degradation of polyurethane foam

Following early studies on degradation of polyurethane foam in implants in humans, it was widely suggested that the foam either broke up or disappeared. However, Szycher and Siciliano (1991) considered that the apparent fragmentation was observed because of ingrowth of tissue into the foam structure and preparation of histological sections cut through the three-dimensional matrix of the foam. It is however clear that degradation of the foam *in vivo* can lead to loss of at least 30% over nine years.

The urine of a female patient was analysed following implantation of Même® polyurethane-covered breast implants. The implants were replaced at a revision operation

abnormal band migration patterns consistent with *p53* gene mutation. Reamplification and direct sequencing of an abnormal SSCP band revealed a double mutation in exon 6 of the gene (C→T, G→T). Further analysis revealed a hot-spot mutation in 50% of the tumours with *p53* mutations, comprising GCT→CCC (Ala→Pro), at codon 201 of exon 6. The authors concluded that these results suggest, for the first time, that indirect genotoxic mechanisms resulting in *p53* mutations are involved in foreign-body carcinogenesis (Pogribna *et al.*, 1997). [The Working Group noted that *p53* mutations may arise during the later stages of tumour development.]

5C. OTHER FOREIGN BODIES

5C.1 Degradation in biological systems

No data were available to the Working Group.

5C.2 Distribution and excretion

The potential for components of implanted bullets and shell fragments to be mobilized (solubilized or degraded by phagocytosis) and distributed to distant parts of the body is relevant to the systemic carcinogenicity of such foreign bodies. Of the possible metals in these objects, lead and depleted uranium are those of greatest concern.

5C.2.1 *Lead*

(*a*) *Humans*

That lead is distributed from the site of retained bullets to other areas of the body has been clearly demonstrated from the number of case reports of lead toxicity in individuals with retained bullets.

Machle (1940) reported in detail on two cases in which clinical diagnoses of lead poisoning were correlated with retained bullets. He further reviewed 40 other cases that had been described in the literature from 1867 to 1938 and was impressed with the paucity of cases compared with the frequency of gunshot wounds and of bullets that had been permitted to remain in the body. Bird and buck shot accounted for a fairly high proportion of the cases, even though it is likely that many more persons had implanted artillery shrapnel and rifle bullets from the First World War. The interval between lodgment of the bullets (including buckshot) and initial lead poisoning symptoms varied considerably (from 12 days to 48 years), although among the 13 cases in which the symptoms developed in less than one year, only two would be considered cases of lead poisoning at the present time. The location of lodgment seemed important, as more than half of the bullet-related lead poisoning cases consisted of bullets retained within bones or joints.

Since Machle's review, a number of individual case reports of bullet-related lead poisoning have been published. In 1982, Linden *et al.* (1982) presented three additional bullet-lead poisoning cases plus a review of 13 other cases. Additional sporadic

reports of bullet retention and resultant lead poisoning have been reported since that time.

In a more recent review and critical analysis of lead poisoning associated with retained bullets, Magos (1994) analysed the data presented by Machle (1940), Linden *et al.* (1982) and other published reports. On the basis of this extensive review, the author concluded that while it is likely that only a fraction of persons with implanted lead projectiles actually develop lead poisoning, it is even more likely that only a fraction of those with bullet-related lead poisoning were actually diagnosed with the condition. The number of mild lead poisoning cases is probably quite high but many were missed by the examining clinicians due to (1) non-specificity of signs and symptoms of lead poisoning, (2) general lack of awareness and familiarity as to the toxicity of lead and (3) inappropriate use of laboratory tests of lead indicators (blood, serum, urine analysis). Mobilization of lead from retained bullets and shot may be influenced by several factors, depending on mobilization from either the projectile itself or from the surrounding tissues and other secondary storage sites. The factors that can be considered most important are indicated in Table 62. On the basis of the cases reviewed, the risk of lead poisoning and the latent period could not be predicted, but it was noted that the number of known clinical cases was small in relation to the actual number of persons carrying lead-containing bullets (Magos, 1994).

(*b*) *Experimental systems*

Discs of lead (enriched with two natural isotopes) were implanted into the knee joints or leg (thigh) muscle of two mongrel dogs. The animals were monitored by mass spectrometry for release of lead in blood over a three-year period. ^{206}Pb served as a marker for the discs implanted into the synovium, while ^{208}Pb served as the marker for lead implanted in the muscle. The knee implant underwent vigorous attack by the synovial fluid and blood lead levels reached a maximum in four to six months, declining thereafter as the remaining fragments became encapsulated. In contrast, there was only minor mobilization of lead from the discs placed in the muscle during the first month and even less thereafter as the discs became encapsulated. Very little physical change was noted in the muscle implants, whereas the joint implants had disintegrated after six months into a number of particles with corroded outlines. The smaller particles subsequently became encapsulated within the joint (Manton & Thal, 1986).

5C.2.2 *Depleted uranium*

(*a*) *Humans*

The distribution of uranium was determined radiochemically in tissues obtained at autopsy of a man who had been employed in the uranium processing industry for 26 years. The deposition of uranium in human tissues followed the order: skeleton > liver > kidney, with concentration ratios of 63:2.8:1. This study indicates that the long-term storage compartment for uranium in the skeleton may be greater than previously estimated (Kathren *et al.*, 1989).

Table 62. Factors that may affect the mobilization of lead from retained bullets

Mobilization from the projectile (lead bullet)	
Surface area	Dissolution is faster from multiple pellets than from an equal mass of a single bullet and is faster from fragmented bullets than from non-fragmented ones.
Location	Bullets retained in soft tissues tend to become encapsulated by fibrous tissue which impedes release of lead.
Mechanical effects	Impact of bullet with bone creates abrasive effect on bullet lodged in a joint, which promotes disintegration of the bullet.
Acidity	Low pH of synovial and bursal fluids promotes dissolution, with high lead concentrations in the fluids and surrounding tissues.
Mobilization from surrounding tissues and other secondary storage sites	
Inflammation	Lead taken up by the surrounding tissues may cause synovitis and arthritis, which will promote dispersal of lead to other areas. Cell migration and increased blood flow may also play a role.
Impaired use of limbs	Inactivity due to painful arthritis can promote mobilization of lead from bones.
Hypermetabolic conditions	Alcoholic acidosis, hyperthyroidism and fever may promote lead mobilization and increase sensitivity to lead.

Modified from Magos (1994)

(*b*) *Experimental systems*

The distribution of implanted depleted uranium was studied with Sprague-Dawley rats using three dose levels (low, medium, high: 4, 10, 20 pellets). The implants consisted of 99.25% depleted uranium and 0.75% titanium with the uranium isotopes amounting to 99.75% ^{238}U and 0.2% ^{235}U and trace levels of ^{234}U. [The Working Group noted that the authors did not consider the radioactivity of the residual ^{235}U and ^{234}U isotope as a major concern.] The pellets were implanted into the gastrocnemius muscle of male Sprague-Dawley rats and tissue samples were analysed at day 1 and at 1, 6, 12 and 18 months. Within one day, uranium had appeared in the kidney and bone. By six months, the uranium level had reached a plateau in the kidney but continued to rise in bone throughout the 18-month period in the high-dose group. The urine concentration of uranium reached a maximum at 12 months and had declined by 18 months. A dose- and time-related increase in uranium levels was found in many tissues. The greatest concentrations were found in the kidney and bone, the primary reservoirs for uranium redistributed from intramuscularly embedded depleted uranium

fragments. Many tissues other than muscle had significant concentrations of uranium, including the brain, liver, spleen, lung, lymph nodes and testes (Pellmar *et al.*, 1999).

The effects of implantation of depleted uranium pellets were studied in Sprague-Dawley rats. Groups of animals received 20 depleted uranium pellets (high dose), 10 depleted uranium pellets and 10 tantalum (inert control) pellets (medium dose), or four depleted uranium and 16 tantalum pellets (low dose). The control group received 20 tantalum pellets. At 6, 12 and 18 months after implantation, the concentrations of uranium in urine were significantly increased in all dose groups, peak concentrations being observed at 12 months (Miller *et al.*, 1998a). In the same study, mutagenicity in urine was investigated (see Section 5C.4.2).

5C.3 Tissue responses and other expressions of toxicity

5C.3.1 *Lead*

The toxicity of systemically distributed lead is well known and has been reviewed by IARC (1980) and elsewhere. The toxic effects in humans involve several different organ systems with subtle clinical symptoms in most cases. In adults, the main organs affected are the neurological system, the haem-synthesizing system and the kidneys. With excess occupational exposure or accidental exposures to lead, the most evident effects have been peripheral neuropathy and chronic nephropathy. The most sensitive effects in adults may be hypertension and anaemia. Less commonly, lead-induced toxicity may affect the gastrointestinal and reproductive systems (sterility and neonatal deaths).

5C.3.2 *Depleted uranium*

In humans, the kidney and bone are the primary target organs of internal exposure to uranium, regardless of the route of exposure. Most of the absorbed uranium is cleared from the blood stream and excreted in the urine within 24 h. The uranium that is not excreted is reabsorbed by the proximal tubules of the kidney, where it causes its primary toxic effects (Kathren *et al.*, 1989; Pellmar *et al.*, 1999). Chronically exposed uranium mill workers showed mild dysfunction of the kidney and increased urinary excretion of beta-2-microglobulin (Thun *et al.*, 1985). In one case study, neurological effects were seen (Goasguen *et al.*, 1982). These data indicate that embedded fragments of depleted uranium may lead to neural damage, which may affect both cognitive and motor functions.

Preliminary results have been published of toxicity studies in rats with implanted depleted uranium. Depleted uranium pellets (1 × 2 mm) consisting of 99.25% depleted uranium and 0.75% titanium by weight were implanted at three dose levels (4, 10 and 20 pellets) into the gastrocnemius muscle of male Sprague-Dawley rats. Clinical and laboratory analyses are being performed to detect kidney, behavioural and neural toxicity. Six months after implantation, decreased weight gain, a dose-related increase in levels of depleted uranium in the kidneys, bone and urine, and a decrease in neuronal excitation in the hippocampus were reported. However, while uranium was found in the

brain, no behavioural toxicity was observed at six months after implantation. The authors indicated that the kidney toxicity was less than would be expected on the basis of the uranium levels in the kidneys (Pellmar *et al.*, 1998).

A preliminary report was given of an ongoing study to assess the potential carcinogenicity of long-term exposure of rats to implants of depleted uranium (DU), such as shrapnel in wounds. Groups of 50 male Wistar rats were given implants into the thigh muscle of 5.0 × 5.0 × 1.5-mm or 2.5 × 2.5 × 1.5-mm DU squares composed of 99.25% uranium and 0.75% titanium. Other groups were given implants of 2.0 × 1.0-mm diameter DU pellets, tantalum squares (negative controls) and thorotrast (thorium dioxide) injections (positive controls). After 15 months of the planned 24-month exposure period, a marked local tissue reaction (including fibrous capsule formation) had developed around the DU and tantalum implants, the capsules being much thicker around the uranium implants. There was also a decrease in weight of the group that received the largest mass of DU, although survival was not affected in any of the groups. Carcinogenic response is not yet known (Hahn *et al.*, 1999).

5C.4 Genetic and related effects

5C.4.1 *Lead*

The genetic and related effects of lead have been reviewed (IARC, 1987c).

5C.4.2 *Depleted uranium*

(*a*) *Humans*

No data were available to the Working Group.

(*b*) *Experimental systems*

Mutagenicity induced by depleted uranium implants has been demonstrated in experiments with male Sprague-Dawley rats. Urine and serum of these animals were evaluated for mutagenic potential using the Ames *Salmonella* mutation assay. The implants consisted of pellets implanted into the gastrocnemius muscle at three dose levels. Tantalum was used as a negative control. Urine and blood were collected at 0, 6, 12 and 18 months for the mutagenicity assay. While no mutagenicity was observed with the sera, a substantial dose- and time-dependent increase in mutagenicity was seen with urine samples. Positive results were obtained with *S. typhimurium* strain TA98 and the Ames II™ mixed strains (TA7001-7006). A significant elevation in mutagenic potential was observed in TA98 strain and Ames II™ tests with the Amberlite XAD-4 and XAD-8 column fractions of urine, which was dependent on both the length of time since implantation and the number of uranium pellets implanted. Urine from animals that had tantalum implants showed no increase in mutagenicity. A strongly positive correlation was observed between urinary mutagenicity and urinary uranium levels at 6, 12 or 18 months after pellet implantation (Miller *et al.*, 1998a).

A doubling of sister chromatid exchanges was found in human osteoblast-like cells treated with 10 μM of depleted uranium-uranyl chloride for 24 h. This was a

greater response than that found with the positive control, nickel sulfate (Miller *et al.*, 1998b).

In the same series of experiments, in-vivo transformation of human osteoblast-like cells with depleted uranium was demonstrated. Human osteosarcoma cells (HOS TE85, clone F-5) were treated with depleted uranium-uranyl chloride (10 μM) for 24 h, at which time the cells were rinsed, trypsinized and seeded onto tissue culture dishes. The dishes were incubated for five weeks and examined for the appearance of transformed foci. Morphologically, the uranium-exposed cells developed into diffused type II foci. A 10-fold increase in transformation frequency was observed in the treated compared to the non-treated cells. The transformation response was stronger with depleted uranium than with the positive controls (nickel sulfate or lead acetate). The transformed cells showed increased expression of the K-*ras* oncogene, and suppression of the phosphorylation of the Rb protein. Transformation was confirmed by injection of 1×10^6 or 5×10^6 of uranyl chloride-treated cells subcutaneously into four- to five-week-old female athymic mice. Tumours developed within four weeks. The histological appearance resembled a carcinoma characterized by an undifferentiated, sheet-like growth (Miller *et al.*, 1998b).

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6. SUMMARY OF DATA REPORTED AND EVALUATION

6.1 Exposure data

A wide range of metals and their alloys, polymers, ceramics and composites are used in surgically implanted medical devices and prostheses and dental materials. Most implanted devices are constructed of more than one kind of material (implants of complex composition). Since the early 1900s, metal alloys have been developed for these applications to provide improved physical and chemical properties, such as strength, durability and corrosion resistance. Major classes of metals used in medical devices and dental materials include stainless steels, cobalt–chromium alloys and titanium (as alloys and unalloyed). In addition, dental casting alloys are based on precious metals (gold, platinum, palladium or silver), nickel and copper and may in some cases contain smaller amounts of many other elements, added to improve the alloys' properties.

Orthopaedic applications of metal alloys include arthroplasty, osteosynthesis and in spinal and maxillofacial devices. Metallic alloys are also used for components of prosthetic heart valve replacements, and pacemaker casings and leads. Small metallic parts may be used in a wide range of other implants, including skin and wound staples, vascular endoprostheses, filters and occluders. Dental applications of metals and alloys include fillings, prosthetic devices (crowns, bridges, removable prostheses), dental implants and orthodontic appliances.

Polymers of many types are used in implanted medical devices and dental materials. Illustrative examples are silicones (breast prostheses, pacemaker leads), polyurethanes (pacemaker components), polymethacrylates (dental prostheses, bone cements), poly(ethylene terephthalate) (vascular grafts, heart valve sewing rings, sutures), polypropylene (sutures), polyethylene (prosthetic joint components), polytetrafluoroethylene (vascular prostheses), polyamides (sutures) and polylactides and poly(glycolic acids) (bioresorbables).

Ceramic materials based on metal oxides (alumina, zirconia) find use in joint replacements and dental prostheses. Other materials based on calcium phosphate are used as bone fillers and implant coatings. Pyrolytic carbon applications include heart valves and coatings for implants. Composites are used mainly in dental fillings.

Although precise numbers are not available, many millions of people worldwide have implanted devices, which may remain in place for years.

Foreign bodies, such as bullets and pellets from firearms and metallic fragments from explosions, may penetrate and remain in human tissues for long periods of time. Internal exposure to constituents, including lead (from bullets and pellets) and depleted uranium (from shell and missile fragments), may result.

6.2 Human carcinogenicity data

Sixteen case reports have described neoplasms originating from bone or soft connective tissue in the region of metal implants. An analytical study did not report an increased risk for soft-tissue sarcoma after metal implants. No association with dental amalgam was found in a case-control study in Australia.

The 30 case reports of breast cancer following silicone implants for cosmetic breast augmentation appear unlikely to correspond to an excess of breast cancer. All five cohort studies involving a total of more than 18 000 women treated with surgical prostheses made of silicone (or polyurethane-coated silicone) for cosmetic breast augmentation conducted in Canada, Denmark, Sweden and the United States consistently found no evidence of increased risk of breast cancer. The combined results of the four largest cohort studies show a 25% reduction in risk. Similar results were reported by a large case–control study including more than 2000 cases and 2000 controls in the United States. All cohort studies were based on subjects exposed to implanted silicone at an early age, usually between the ages of 30 and 40 years, so that the number of breast cancer cases observed in each study was relatively small. Except for the case–control study in the United States, only limited allowance was made for potential confounding factors, although no clear evidence has emerged as to the relevance of any such factor to a possible association between implanted silicone and breast cancer risk.

Three of the studies considered the issue of latency, with observation periods of up to 10 years or more, but even in the group of women with follow-up of 10 years or more, there was no suggestion of increased risk. The risk of cancer following surgical implantation of silicone prostheses for breast reconstruction after breast cancer was considered in a study in France. The results of this study suggest no excess risk of second primary breast or other cancer, distant metastases, local recurrence or death from breast cancer. The reduced risks for breast cancer found in the cohort and case–control studies are unlikely to be due to chance, and no bias that would explain these findings has been identified. Four cohort studies of women with surgical breast implants in Denmark, Sweden and the United States reported on cancers at sites other than the breast. None of these studies found an increased risk for all cancers combined. Two studies reported increased risk for lung cancer, but these results were based on a total of only nine observed cases. For no other cancer site was there consistent evidence of an increased risk, although the statistical power to detect an increased risk of rare neoplasms, including soft-tissue sarcomas, was small.

Out of the large number of patients with orthopaedic implants of complex composition (metal with bone cement with or without polyethylene), a total of 35 cases have been reported of malignant neoplasms arising from the bone or the soft tissue in the region of an implant. Fourteen cohort studies of patients following total knee or total hip replacement from six countries were performed to investigate cancer incidence in these populations. Two of the studies from Finland and two studies from Sweden were partially overlapping. One study included only patients with metal-on-metal implants, five studies included only patients with polyethylene-on-metal implants, while the

remaining studies included patients with mixed or unspecified types of implant. One study showed a small increase in overall cancer incidence, while the remaining studies showed overall decreases. Four of these studies suggested an excess risk for specific cancers, including Hodgkin's disease, non-Hodgkin lymphoma, leukaemia and kidney cancer. However, results of the other studies were not consistent with this observation. In one small cohort study from Denmark of patients with a finger or hand implant, an increased risk of lymphohaematopoietic cancer was observed. Additionally, two case–control studies, one including cases with soft-tissue sarcoma and the other including lymphoma and leukaemia, were carried out in the United States. The latter overlaps with one of the cohort studies. Neither of these studies showed an association with the presence of implants of complex composition. Most of the studies did not have information on possible confounding variables such as immunosuppressive therapy or rheumatoid arthritis for the lymphomas and analgesic drugs for kidney cancer. The follow-up in most of the studies may have been too short to evaluate cancer occurring many years after exposure; in some studies with longer follow-up, the numbers of long-term survivors were low.

Thirteen cases of breast cancer and one case of plasmacytoma have been reported in patients with cardiac pacemakers. Ten cases of different neoplasms have been reported at the site of non-metallic foreign bodies. Eight cases of sarcoma have been reported at the site of vascular grafts. No conclusions can be drawn from these case reports.

Twenty-three cases of sarcomas, twenty-three cases of carcinomas and seven cases of brain tumours have been reported at the site of metallic foreign bodies, mainly bullets and shrapnel fragments.

6.3 Veterinary studies

Despite the large number and variety of both metallic and non-metallic internal fixation devices used in dogs in recent decades, only about 60 cases of sarcomas, primarily of bone, have been reported. In addition, four cases of sarcomas at the site of other foreign bodies have been reported in dogs. One case–control study found no association between metallic implants used to stabilize fractures in dogs and the development of bone or soft-tissue tumours.

In contrast, at least 563 cases of vaccine-associated sarcomas in cats have been reported in just six years, with an estimated annual incidence of 1–13 per 10 000 vaccinated cats. Vaccine-associated sarcomas have been mostly associated with administration of recently introduced feline vaccines containing adjuvant. Tumours that develop at vaccination sites are morphologically different from those that develop at non-vaccination sites. A cohort study found that cats developed sarcomas in a shorter time at sites used for vaccination than at non-vaccination sites and that there was an increased risk for sarcoma development with increased numbers of vaccines at a given site.

6.4 Animal carcinogenicity data

Chromium metal powder was tested in rats by intramuscular and intrarenal administration, in mice and rats by intrapleural and intraperitoneal administration, in rats and rabbits by intraosseous implantation and in mice, rats and rabbits by intravenous injection. No increase in tumour incidence was observed in these studies, although most studies had limitations in design, duration or reporting.

Cobalt metal powder was tested in rats by intramuscular or intrathoracic injection, producing sarcomas at the injection site. Studies in rats by intrarenal injection and in rabbits by intraosseous injection had limitations in design, duration or reporting.

Nickel metal powder was tested by inhalation exposure in mice, rats and guinea-pigs, by intratracheal instillation in rats and Syrian hamsters, by intramuscular injection in rats and hamsters and by intrapleural, intraperitoneal, intraosseous and intrarenal injection in rats. It was also tested by intravenous injection in mice and rats. Nickel metal pellets were tested by subcutaneous administration in rats. The studies by inhalation exposure were inadequate for an evaluation of carcinogenicity. After intratracheal instillation of nickel, significant numbers of squamous-cell carcinomas and adenocarcinomas of the lung were observed in rats; one adenocarcinoma of the lung was observed in hamsters. Intrapleural injections induced sarcomas in rats. Subcutaneous administration of nickel metal pellets induced sarcomas in rats; intramuscular injection of nickel powder induced sarcomas in rats and hamsters; and intraperitoneal injections induced local carcinomas, mesotheliomas and sarcomas in rats. No significant increase in the incidence of local kidney tumours in rats was seen following intrarenal injection. Studies by the intraosseous and intravenous routes were inadequate for evaluation.

Titanium metal was tested in rats by intramuscular implantation of rods and by intraosseous administration of powder, rods or wire. No local tumours occurred.

Most *nickel-based alloys* that have been tested for carcinogenicity in animals are not actually used in clinical devices, and carcinogenicity data are not available for a number of alloys which are commonly used, including nickel–titanium.

Metal alloys containing a preponderance of *nickel* in combination with varying amounts of chromium, iron, gallium, copper, aluminium and manganese have been tested as powder or pellets by subcutaneous or intraperitoneal administration to rats and by intratracheal administration to hamsters. In these studies, local sarcomas were consistently found at the injection site in the treated animals and were absent in vehicle controls. One of the nickel-based alloys (which contained approximately 66–67% nickel, 13–16% chromium and 7% iron) was tested independently by two laboratories, using different species (hamsters and rats) and different routes of administration (intratracheal and intraperitoneal). In both studies, local tumours were seen in proportion to the dose of alloy. Local tumours were also observed in two bioassays in which rats received identification ear tags made of an alloy that contained 67% nickel, 30% copper, 2% iron and 1% manganese.

Most other nickel-containing alloys tested as powder and rods in rats by intramuscular, intraperitoneal, intrarenal and intraosseous administration gave negative or

equivocal results for induction of tumours at the injection site. One study in hamsters by intratracheal administration of an alloy powder containing approximately 27% nickel, 39% iron and 16% chromium also gave negative results.

One clinically relevant alloy, Ni35Co35Cr20Mo10 (MP35N alloy), gave negative results for carcinogenicity when tested in two studies by intramuscular implantation in rats as rods, but produced local sarcomas in one study following intramuscular administration to rats as a powder.

Titanium-based alloys were tested in rats by intramuscular administration of rods and by intraosseous administration of rods and intra-articular administration of wear-debris. No local tumours were observed at the injection site in these experiments, except in one study by intraosseous administration in which a titanium/aluminium/vanadium alloy implanted into the femur as hemi-cylinders produced a high incidence of local tumours, especially where there was loosening of the implant.

Cobalt-based alloys were tested in rats by intramuscular administration. Local tumours were induced by a powder (particle size, 0.1–1 μm) in horse serum but not by dry powders (particle size, 0.5–50 and 100–250 μm) or by polished rods. No local tumours were observed in guinea-pigs following intramuscular injection of cobalt as a dry powder (particle size, 0.5–50 μm). A low incidence of local tumours was observed in rats following intraosseous administration of two cobalt-based alloys given as powder or wire. Local tumours did not occur following intraosseous implantation of rods of two other cobalt-containing alloys. No local tumours occurred in rats following intra-articular administration of a cobalt alloy powder.

Stainless steels containing 13–17% chromium were tested by intratracheal administration of powder to hamsters, intrabronchial administration of wire to rats and by intramuscular administration of rods and discs to rats and intraosseous administration of rods and powder to rats. No local tumours were observed, except in rats receiving stainless steel discs.

Thin foils of silver, gold, platinum, tin, steel, Vitallium (CoCrMo alloy) and tantalum were tested by subcutaneous implantation in rats. All of these foils produced local sarcomas.

In one study in rats, subcutaneous implantation of discs of aluminium oxide ceramic produced local sarcomas. In a few studies in mice and rats, local sarcomas were observed following subcutaneous implantation of glass sheets.

Numerous polymeric materials have been tested for carcinogenicity in mice and rats, most frequently by subcutaneous, intramuscular or intraperitoneal injection. Many materials—cellophane, ε-caprolactone-L-lactide copolymer, polyamide (Nylon), poly(ethylene terephthalate), polyethylene, poly-L-lactide, poly(2-hydroxyethylmethacrylate), poly(methyl methacrylate), polypropylene, polystyrene, polytetrafluoroethylene, polyurethane, poly(vinyl alcohol), poly(vinyl chloride), polymethylsiloxane (silicone) film or polysilicone gum and vinyl chloride–vinyl acetate copolymers—produced sarcomas at the site of implantation with varying incidence. When several polymers were tested in rats according to the same experimental protocol, sarcoma

incidences ranged from 70% (polypropylene) to 7% (silicone). A low incidence of local tumours was seen with silicone in five separate experiments using rats.

A few experiments with various polymeric materials have been reported using a small number of other animal species, such as rabbits, guinea-pigs and hamsters, with generally negative findings.

Polymeric materials with a large surface area and a flat and smooth surface morphology generally induced a significantly increased incidence of sarcomas at the site of implantation. In most studies, perforated or foam materials or textiles induced lower incidences of sarcomas in comparison with flat films. Some studies suggest that surface roughening decreases local sarcoma incidence. The diameter and number of transmembrane channels (pores) per unit surface area are critical for this trend of decrease in sarcoma incidence. Segmenting or pulverizing polymeric materials significantly decreases local sarcoma incidences, often to nil.

For biodegradable polymers, the degradation rate is critical for local tumour induction in rodents. No local tumours were observed with poly(glycolic acid), which is quickly degraded within two months, whereas local sarcomas were induced by poly-L-lactide and ε-caprolactone-L-lactide copolymer which degraded more slowly (the polylactide degraded but was dimensionally unchanged at 24 months; ε-caprolactone-L-lactide copolymer fragmented after six months).

6.5 Other relevant data

The mutagenicity and carcinogenicity of a biomaterial are influenced by the exact composition of the biomaterial or extract(s); the composition and rates of release of leachable materials into the biological environment; degradation, which may lead to the formation of compounds with different mutagenic properties or leachability; the physical environment; and the surface properties. Much of the information available for assessment is inadequate in these respects, and methods are often not validated.

Wear and corrosion of metal implants result in the generation and release of a wide range of degradation products. The composition of the material surface or particles can vary as individual components are selectively removed or chemically modified. In the case of alloys, the release of one type of metal ion can be strongly influenced by the identity of other metals in the alloy. Most studies provide inadequate characterization data, but there is potential for the release of chemical species of known mutagenicity or carcinogenicity.

Experimental studies have shown that the potential for lead toxicity as a complication of lead projectile or bullet injury appears to be related to the surface area of the bullet (the greater the surface area, the greater the absorption), the location of the bullet (muscle or joint tissues), the presence of synovial fluid and length of time that the bullet resided in the body.

Available studies are inadequate to permit reliable and accurate estimates of long-term effects of depleted uranium in humans. Because of the low specific radioactivity of depleted uranium, the long-term toxicity is thought to be due to chemical rather than radiation effects.

Inflammatory (fibrotic) reactions have been observed with several non-metallic implant materials, including silicones and polyurethanes. Depending on the physical properties of the biomaterial, its presence can be associated with implantation-site sarcomas in rodents. There are insufficient data to conclude that a genotoxic mechanism operates in solid-state carcinogenesis. There are in-vitro data demonstrating the inhibitory effects of polyurethane, polyethylene and poly(ethylene terephthalate) on gap junctional intercellular communication.

Mutagenic properties of some biomaterial extracts have been demonstrated in some studies. The compounds shown or suspected to be responsible for this are components of the biomaterial, unreacted monomers or products of secondary reactions.

Data on the local and systemic availability of chemical species have been reported for only a limited number of biomaterials. In the case of poly(ester urethane) foam, biodegradation results in the generation of 2,4-diaminotoluene. This compound induces hepatocellular carcinomas when fed to mice and rats. There is no evidence that chemical carcinogenesis due to this compound plays a direct role in the mechanism of implant-site sarcoma development. There is no convincing evidence for the biodegradation of polydimethylsiloxanes (silicones).

Cytotoxicity of freshly cured dental composite materials and bonding agents has been demonstrated. Also, the components of resin composites all cause significant toxicity in direct contact with fibroblasts. However, the hazard for the dental pulp depends on the quantities which permeate the dentin and accumulate in the pulp.

A limited number of animal studies have shown pulpal responses to acid etching and bonding agents, which indicates a possible risk of pulpal reactions in patients. Composite materials may give rise to biological effects, but microleakage and bacterial infection complicate the evaluation of pulpal effects of composites.

Clinical reports on the adverse effects of composite filling materials indicate that pulpal and mucosal reactions rarely occur.

With few exceptions, the amounts of individual chemicals to which professionals and patients are exposed from adhesive agents and composite dental filling materials seem to be insufficient to cause clear, systemic toxic effects. Some constituents of adhesive agents and composite materials may have genotoxic potential. For most compounds of dental composites, there is little information on toxicity. With the exception of methyl methacrylate, no relevant data are available to compare local concentrations of released compounds with levels that produce toxic effects.

Formaldehyde has been shown to be released from some dental polymers *in vitro*, but the levels appear to be low.

6.6 Evaluation

There is *evidence suggesting lack of carcinogenicity* in humans of breast implants, made of silicone, for female breast carcinoma.

There is *inadequate evidence* in humans for the carcinogenicity of implanted prostheses made of silicone for neoplasms other than female breast carcinoma.

There is *inadequate evidence* in humans for the carcinogenicity of non-metallic implants other than those made of silicone.

There is *inadequate evidence* in humans for the carcinogenicity of metallic implants and metallic foreign bodies.

There is *inadequate evidence* in humans for the carcinogenicity of orthopaedic implants of complex composition and of cardiac pacemakers.

No epidemiological data relevant to the carcinogenicity of ceramic implants or dental alloys of precious metals were available.

There is *sufficient evidence* in experimental animals for the carcinogenicity of implants of metallic cobalt, metallic nickel and for nickel alloy powder containing approximately 66–67% nickel, 13–16% chromium and 7% iron.

There is *limited evidence* in experimental animals for the carcinogenicity of implants of alloys containing cobalt and alloys containing nickel, other than the specific aforementioned alloy.

There is *inadequate evidence* in experimental animals for the carcinogenicity of implants of chromium metal, stainless steel, titanium metal, titanium-based alloys and depleted uranium.

There is *sufficient evidence* in experimental animals for the carcinogenicity of polymeric and metallic materials in the form of thin films, foils or sheets when implanted into connective tissues of rodents.

There is *inadequate evidence* in experimental animals for the carcinogenicity of poly(glycolic acid) implants.

There is *inadequate evidence* in experimental animals for the carcinogenicity of polymeric materials in the form of powders when inserted into connective tissues of rodents.

There is *inadequate evidence* in dogs for the carcinogenicity of metallic implants and metallic and non-metallic foreign bodies.

There is *limited evidence* in cats for the carcinogenicity of certain feline vaccines containing adjuvants.

Overall evaluation

Organic polymeric materials as a group are *not classifiable as to their carcinogenicity to humans (Group 3).*

Polymeric implants prepared as thin smooth films (with the exception of poly(glycolic acid)) are *possibly carcinogenic to humans (Group 2B).*

Orthopaedic implants of complex composition and cardiac pacemakers are *not classifiable as to their carcinogenicity to humans (Group 3).*

Silicone breast implants are *not classifiable as to their carcinogenicity to humans (Group 3).*

Metallic implants prepared as thin smooth films are *possibly carcinogenic to humans (Group 2B).*

Implanted foreign bodies of metallic cobalt, metallic nickel and an alloy powder containing 66–67% nickel, 13–16% chromium and 7% iron are *possibly carcinogenic to humans (Group 2B).*

Implanted foreign bodies of metallic chromium or titanium and of cobalt-based, chromium-based and titanium-based alloys, stainless steel and depleted uranium are *not classifiable as to their carcinogenicity to humans (Group 3).*

Dental materials are *not classifiable as to their carcinogenicity to humans (Group 3).*

Ceramic implants are *not classifiable as to their carcinogenicity to humans (Group 3).*

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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.