NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for NICKEL COMPOUNDS

FINAL
MARCH 1999

Prepared for

the December 2-3, 1998,
Meeting of the Report on Carcinogens Subcommittee
of the NTP Board of Scientific Counselors

Prepared by

Integrated Laboratory Systems
Post Office Box 13501
Research Triangle Park, North Carolina 27709
NIEHS Contract No. N01-ES-25346

TABLE OF CONTENTS

NTP Report on Carcinogens Listing for Nickel Compounds

Carcinogenicity

Nickel compounds are *known to be human carcinogens* based on findings of increased risk of cancers in exposed workers and evidence of malignant tumor formation by multiple routes of exposure at various sites in multiple species of experimental animals. The combined results of epidemiological studies, carcinogenesis studies in rodents, and mechanistic data support the concept that nickel compounds act by the generation of nickel ions at critical sites in target cells of carcinogenesis and allow consideration and evaluation of these compounds as a single group. In 1990, an IARC evaluation of nickel and nickel compounds concluded that "nickel compounds are carcinogenic to humans" (IARC, 1990) based on sufficient evidence for the carcinogenicity of human exposure to nickel compounds as would be found in the nickel refining industry, and very strong evidence of carcinogenicity of a variety of nickel compounds in rodents.

In several cohort studies of workers exposed to various nickel compounds, the risk for death from lung cancer and nasal cancer are elevated (IARC, 1990). Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel refining industries are carcinogenic to humans. IARC (1990) made the overall evaluation of nickel compounds as a group based on indications from animal and mechanistic studies that the generation of ionic nickel in the target site is the event responsible for carcinogenic transformation. Additional study has shown that exposure to soluble nickel compounds alone or in combination with other forms of nickel in nickel refinery workers results in a significant excess risk of lung and nasal cancers and that smoking and nickel had a multiplicative effect (Andersen et al., 1996). Nickel exposure in welders is associated with carcinoma of the trachea, bronchus, and lung in some cases (Simonato, 1991), although these results are complicated by co-exposure to carcinogenic chromium.

Inhalation or intratracheal instillation of nickel subsulfide or nickel oxide has led to a dose-related formation of benign and malignant lung tumors, including carcinomas, in rats and in some studies with mice (IARC, 1990; NTP, 1996a,b). Inhalation of nickel compounds will also result in tumor formation in organs besides the lung, in particular malignant and benign pheochromocytoma in rats (NTP, 1996a,b). Injection of various nickel compounds has been repeatedly reported to produce dose-dependent increases in tumors at a variety of sites in several species of experimental animals. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral, intrarenal, intratesticular and intraocular injections of nickel compounds have all been reported to lead to the formation of malignant tumors at the site of injection. These tumors are usually sarcomas, but other types also develop. Injection of nickel will produce distant tumors in the liver in some strains of mice (IARC, 1990). Soluble nickel acetate is an effective, complete transplacental carcinogen in rats, and brief exposure during pregnancy to this soluble nickel salt will produce malignant pituitary tumors in the offspring. Additionally, transplacental exposure followed by barbital exposure (a known tumor promoter) in the offspring produces renal cortical and pelvic tumors (Diwan et al., 1992). Soluble nickel salts given by injection and followed by barbital resulted in the formation of renal cortical

adenocarcinomas that frequently metastasized to the lung, liver and spleen in adult rats (Kasprzak et al., 1990).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Many studies have shown in cultured animal and human cells that a variety of nickel compounds, including many soluble forms of nickel, damage genetic material. DNA strand breaks, mutations, chromosomal damage, cell transformations and disrupted DNA repair have been observed in *in vitro* studies. Nickel can bind electrovalently to cellular components including DNA. The redox activity of the nickel ion may produce reactive oxygen species that attack DNA and 8-hydroxy-2'-deoxyguanosine can be produced *in vitro* and *in vivo* in target tissues of nickel carcinogenesis (IARC, 1990; Kasprzak et al., 1990). Nickel can induce chromosomal aberrations in exposed human populations. No data are available that indicate the mechanisms thought to account for nickel carcinogenesis in experimental animals would not also operate in humans. The carcinogenic potency of various nickel compounds will vary widely based on solubility properties and speciation. The recent studies indicating that soluble nickel salts can be complete carcinogens (Diwan et al., 1992) and/or initiators of carcinogenesis (Kasprzak et al., 1990) in sites distant from the site of application confirm that ionic nickel is the carcinogenic species.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

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 A Human Carcinogen;

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.

1.0 IDENTIFICATION AND CHEMICAL-PHYSICAL PROPERTIES OF NICKEL AND SELECTED NICKEL COMPOUNDS

Thousands of nickel compounds have been reported in the chemical literature and indexed by Chemical Abstracts Service according to their online Registry File. Scores are reported in the U.S. EPA's Toxic Substances Control Act (TSCA) Inventory. Besides elemental nickel and nickel compounds, workers may come in contact with numerous nickel alloys in fabricating and joining metal products. Selection of compounds to be included in this section, Table 1-1, was based on their potential for occupational exposure outside the research laboratory.

NIOSH (1976, 1990) listed many nickel compounds, alloys, and forms of elemental nickel that are potentially encountered in U.S. workplaces surveyed in the early 1970s and early 1980s. The NIOSH list is presented as Table 2-4. Those compounds in Table 2-4 for which a Chemical Abstracts Service Registry Number (CASRN) could be identified are included in Table 1-1 with the identifying NIOSH number.

The American Chemical Society's *Chemcyclopedia 98* (Rodnan, 1997) provided a list of nickel compounds currently sold in bulk quantities in the United States. These widely used nickel compounds are noted in Table 1-1.

Many nickel salts are available and used primarily as hydrates or aqueous solutions (Antonsen, 1996; Budavari, 1996) whereas the NIOSH list usually indicates an anhydrous form. Thus, both anhydrous and hydrated forms are generally included in Table 1-1 even though properties were often readily available for just the hydrated form.

Water solubilities of the compounds are noted when available. Note that even the extremely insoluble nickel hydroxide hydrate has measurable solubility. It is expected that ionic nickel may arise from any nickel compound at physiological pH.

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, E°C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s
Nickel	7440-02-0	X5918	Ni	58.6934	Lustrous silver-white solid	1453	2732	8.908 (at 20 EC)	Insoluble	Slowly attacked by dilute hydrochloric, sulfuric, and nitric acids. Rendered passive by treatment with concentrated nitric acid.	Finely divided metal reacts with oxygen in air; may be pyrophoric. Decomposes steam at red heat. Not attacked by fused alkali hydroxides. Not expected to solubilize at physiological pH.	Budavari (199 (*The Merck In*
Nickel acetate	373-02-4	81906	$C_4H_8NiO_4$, $Ni(O_2CCH_3)_2$	176.78	Green prismatic crystals	Decomposes	16.6	1.798		Insoluble in ethanol	Decomposition on heating gives NiO.	Budavari (199 Weast (1980) (*CRC Handbc of Chemistry Physics*)
Nickel acetate tetrahydrate	6018-89-9		$C_4H_8NiO_4$; $Ni(O_2CCH_3)_2 \cdot 4H_2O$; $(CH_3CO_2)_2Ni \cdot 4H_2O$	248.84	Green crystalline mass or powder	Decomposes	16	1.744	0.57 M (soluble in 6 parts water)	Soluble in dilute ethanol	Upon heating, loses water of crystallization and then decomposes to NiO.	Budavari (199 Weast (1980); Rodnan (199 (Chemcyclope 98); Antonsen (1996) (*Kirk-Othmer Encyclopedia Chemical Technology, ed.*)
Nickel acetylacetonate; Bisacetylacetonatonickel(II); Bis(2,4-pentanedionato)nickel(II); 2,4-Pentanedione nickel complex	3264-82-2	X5635	$C_{10}H_{14}NiO_4$; $Ni(CH_3COCHCOCH_3)_2$; $Ni(C_5H_7O_2)_2$; $Ni(acac)_2$; $Ni(AA)_2$	256.91	Emerald green orthorhombic crystals.	229-230	220-235 at 11 mm Hg	1.455	Soluble	Soluble in benzene, chloroform, and ethanol. Insoluble in diethyl ether and ligroin.	Exists as a trimer in the solid phase and as a monomer in the vapor phase. Sold in technical and anhydrous grades.	Budavari (199 Rodnan (199
Nickel, ammine[[2,3-butanedione oxime thiosemicarbazonate](2-)]-	16648-35-4	X9871	$C_5H_{11}N_5NiOS$	247.93								

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel ammonium sulfate; Ammonium nickel sulfate; ammonium disulfatonickelate(II); Sulfuric acid, ammonium nickel(2+) salt (2:2:1); Diammonium nickel disulfate	15699-18-0	81907; X4948	$H_8N_2NiO_8S_2$; $Ni(NH_{42})(SO_4)_2$	286.90								Budavari (1996); Rodnan (1997
Nickel ammonium sulfate hexahydrate	7785-20-8		$H_20N_2NiO_{14}S_2$; $Ni(NH_4)_2(SO_4)_2 \bullet 6H_2O$	394.99	Blue-green crystals			1.923	0.24 M (soluble in 10.4 parts water)	Practically insoluble in ethanol.	A 0.1 M aqueous solution has a pH of 4.6.	Budavari (1996)
Nickel antimony titanate yellow; C.I. Pigment Yellow 53	8007-18-9	M1782	Unspecified	N/A							The NIOSH survey databases list "nickel antimony titanates" with number M1782 (see Table 2-1).	
Nickel bromide; Nickel dibromide	13462-88-9	83009	$NiBr_2$	218.5	Yellow-brown deliquescent crystals	963		5.098 (27 °C)	0.52 M (112.8 g/100 mL)	Soluble in ammonium hydroxide, diethyl ether, and ethanol.	Sublimes in the absence of air.	Budavari (1996); Weast (1980); Rodnan (1997 (no CASRN given)
Nickel bromide trihydrate	7791-20-0		$Br_2H_6NiO_3$; $NiBr_2 \bullet 3H_2O$	272.5	Yellow-green deliquescent needles				2 M (soluble in 1 part water)	Soluble in ammonium hydroxide, diethyl ether, and ethanol.	Begins to lose water of hydration at about 200 °C with complete loss at 300 °C.	Budavari (1996); Weast (1980)
Nickel carbonate; Carbonic acid, nickel salt	16337-84-1		Ni_xCO_3	N/A								Rodnan (1997
Nickel carbonate; Carbonic acid, nickel(2^+) salt (1:1); Nickelous carbonate	3333-67-3	81905	$NiCO_3$	118.72	Light green rhombic crystals	Decompn.			0.78 M (0.0093 g/100 mL)	Soluble in acids.		Weast (1980); Rodnan (1997

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel carbonate; Carbonic acid, nickel(2+) salt (2:1); Nickelous bicarbonate	17237-93-3		$C_2H_2NiO_6$; $Ni(HCO_3)_2$	180.73								Rodnan (1997
Nickel carbonate hydroxide; Basic nickel carbonate	12607-70-4	E0714	$CH_4Ni_3O_7$; $NiCO_3 \cdot 2Ni(OH)_2$; $Ni_3(CO_3)(OH)_4$	304.12								Budavari (1996)
Nickel carbonate hydroxide tetrahydrate; Nickel, (carbonato(2-))tetrahydroxytri-	39340-27-8		$NiCO_3 \cdot 2Ni(OH)_2 \cdot 4H_2O$	376.18	Emerald green cubic crystals, green powder			2.6	Insoluble	Soluble in ammonia, ammonium hydroxide, hot dilute acids with effervescence (decomposes).	The CASRN of the mineral zaratite, which has the same molecular formula, is 1319-49-9.	Budavari (1996); Weast (1980)
Nickel carbonyl; Nickel tetracarbonyl	13463-39-3		C_4NiO_4; $Ni(CO)_4$	170.74	Colorless volatile liquid	-19.3	43	1.318 (17 °C)	1.2 mM (about 5000 parts air-free water)	Soluble in acetone, benzene, carbon tetrachloride, chloroform, and ethanol.	Flammable in air. Explodes at 60 °C.	Budavari (1996); Weast (1980)
Nickel chloride	37211-05-5	50440	Unspecified	N/A								Rodnan (1997
Nickel chloride; Nickel dichloride	7718-54-9	X7161	Cl_2Ni; $NiCl_2$	129.60	Yellow deliquescent scales	1000	Sublimes at 273 °C.	3.55	~0.5 M (64.2 g/100 mL water)	Slightly soluble in ammonium hydroxide and ethanol; insoluble in ammonia.	Readily absorbs ammonia. An aqueous solution is acidic with a pH of about 4.	Budavari (1996); Weast (1980); Rodnan (1997
Nickel chloride hexahydrate	7791-20-0	X4330	$Cl_2H_{12}NiO_6$; $NiCl_2 \cdot 6H_2O$	237.69	Green deliquescent crystals or monoclinic crystalline powder				10.7 M (254 g/100 mL)	Soluble in ethanol.		Budavari (1996); Weast (1980)
Nickel chloride tetrahydrate; Nickel chloride ($NiCl_2$), tetrahydrate	34304-82-0		$Cl_2H_8NiO_4$; $NiCl_2 \cdot 4H_2O$	237.69								Rodnan (1997

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel chromate; Chromic acid (H_2CrO_4), nickel(2+) salt (1:1); Nickel chromate ($NiCrO_4$)	14721-18-7	X4331	$CrNiO_4$; $NiCrO_4$									
Nickel cyanide	557-19-7	82846	C_2N_2Ni; $Ni(CN)_2$	110.73	Yellow-brown solid				Insoluble	Soluble in potassium cyanide.	The usual commercial nickel cyanide contains about 20% to 25% water.	Budavari (1996); Weast (1980)
Nickel cyanide tetrahydrate	13477-95-7		$C_2H_8N_2NiO_4$; $Ni(CN)_2 \cdot 4H_2O$	182.82	Apple-green powder, crystalline plates				Insoluble	Freely soluble in alkali cyanides, in ammonia, and in ammonium carbonate. Slightly soluble in dilute acids.	Loses all water of hydration at 200 °C.	Budavari (1996); Weast (1980)
Nickel di-*N*-butyldithiocarbamate; Nickel dibutyldithiocarbamate; NBC; Nickel, bis(dibutyldithiocarbamato)-	13927-77-0		$C_{18}H_{36}N_2NiS_4$; $Ni[(C_4H_9)_2NCS_2]_2$	467.47	Dark olive-green powder	89-90		1.29	Insoluble	Slightly soluble in benzene and petroleum compounds. Insoluble in ethanol.	Sold in oil-coated powder and granulate forms.	Weast (1980); Rodnan (1997
Nickel dimethyldithiocarbamate; Nickel, bis(dimethylcarbamodithioato-*S,S'*)-, (SP-4-1)-; Bis(dimethyldithiocarbamato)nickel complex	15521-65-0	X4332	$C_6H_{12}N_2NiS_4$; $Ni[(CH_3)_2NCS_2]_2$	299.13								
Nickel dithiocarbamate; Nickel bis(dithiocarbamate); Nickel bis(carbamodithioato-*S,S'*)-, (SP-4-1)-	13985-94-9	83311	$C_2H_4N_2NiS_4$; $Ni(NH_2CS_2)_2$	243.02								
Nickel ferrocyanide; Dinickel hexacyanoferrate	14874-78-3	T1625	$Ni_2Fe(CN)_6$	329.34								
Nickel ferrocyanide [hydrate]	Not found		$Ni_2Fe(CN)_6 \cdot xH_2O$	N/A	Green-white crystals			1.892 (?) [sic]	Insoluble	Soluble in ammonium hydroxide and potassium cyanide; insoluble in hydrochloric acid.	Weast (1980) lists as "nickel ferrocyanide," but gives the hydrate formula.	Weast (1980)

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel ferrocyanide [hydrate]	Not found		$Ni_2Fe(CN)_6 \bullet xH_2O$	N/A	Green-white crystals			1.892 (?) [sic]	Insoluble	Soluble in ammonium hydroxide and potassium cyanide; insoluble in hydrochloric acid.	Weast (1980) lists as "nickel ferrocyanide," but gives the hydrate formula.	Weast (1980)
Nickel fluoride; Nickel difluoride; Nickelous fluoride	10028-18-9	50450	F_2Ni; NiF_2	96.69	Yellowish to green tetragonal crystals (rutile type)	1000		4.72	0.41 M (4 g/100 mL water); sl. soluble	Insoluble in ammonia, diethyl ether, and ethanol	Sublimes in an HF stream above 1000 °C. Decomposes in boiling aqueous solutions.	Weast (1980); Budavari (1996); Antonsen (1996)
Nickel formate; Nickel diformate; Formic acid, nickel(2+) salt	3349-06-2	M4033	$C_2H_2NiO_4$; $Ni(HCOO)_2$	148.73							Decomposes at 180 °C to 200 °C, giving elemental nickel, carbon oxides, hydrogen, methane, and water.	Budavari (1996)
Nickel formate dihydrate	15694-70-9		$C_2H_6NiO_6$; $Ni(HCOO)_2 \bullet 2H_2O$	184.78	Fine green monoclinic crystals	180 decompn.		2.154	Moderately soluble	Insoluble in ethanol and formic acid.	Careful heating at 130 °C to 140 °C gives anhydrous nickel formate.	Budavari (1996); Weast (1980); Antonsen (1996)
Nickel hydroxide; Nickel dihydroxide; Nickelous hydroxide; Nickel(II) hydroxide	12054-48-7	X7142	H_2NiO_2; $Ni(OH)_2$	92.71								Budavari (1996)
Nickel hydroxide monohydrate	1311-07-5		H_4NiO_3; $Ni(OH)_2 \bullet H_2O$	110.73	Apple-green powder (crystals or amorphous)	Decom-poses		4.15	1.4 mM (0.013 g/100 mL water)	Soluble in ammonia and dilute acids.	Decomposes above 200 °C to form nickel monoxide and water. The CAS Registry database lists "green nickel oxide" as a synonym for only this compound. Extremely insoluble in water.	Budavari (1996); Weast (1980); Antonsen (1996)

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel monoxide; Nickel(II) oxide; Nickel protoxide; Nickelous oxide; Nickel(II) oxide, green [or black]	1313-99-1	84269	NiO	74.69	Green (yellow when hot), green-black powder or green cubic crystals	1984; 2090		6.67; 7.45	Insoluble in hot or cold water.	Soluble in acids; slightly soluble in ammonium hydroxide	Color depends on precursor Ni species. Green NiO is formed in Ni refining. Black NiO has slightly more oxygen than the formula indicates (76-77% Ni vs. 78.5% Ni). Black NiO is chief nickel species used to make simple Ni salts.	Budavari (1996); Weast (1990); Rodnan (1997); Antonsen (1985)
Nickel naphthenate; Naphthenic acid(s), nickel salt; Nickel naphthenates	61788-71-4	83650	Unspecified	N/A							Sold as "Nickel naphthenate, -60 in toluene (6-8%)."	ChemFinder database (1998
Nickel nitrate	13138-45-9	50480	N_2NiO_6; $Ni(NO_3)_2$	182.70								Budavari (1996); Rodnan (1997
Nickel nitrate hexahydrate	13478-00-7		$H_{12}N_2NiO_{12}$; $Ni(NO_3)_2 \cdot 6H_2O$	290.81	Green monoclinic, deliquescent crystals	56.7	137	2.05	~8.2 M (238.5 g/L cold water)	Soluble in ammonium hydroxide and ethanol.	The pH of an aqueous solution is about 4.	Budavari (1996); Weast (1980); Rodnan (1997
Nickel octanoate; Nickel(II) octanoate; Nickel bis(2-ethylhexanoate); Nickel octoate	4995-91-9	82957	$C_{16}H_{30}NiO_4$; $[CH_3(CH_2)_6CO_2]_2Ni$	345.10						At least 78% in 2-ethylhexanoic acid.		
Nickel oxalate; Ethanedioic acid, nickel(2^+) salt (1:1)	547-67-1	X7105	C_2NiO_4; NiC_2O_4	146.71								
Nickel oxalate dihydrate	6018-94-6		$C_2H_4NiO_6$; $NiC_2O_4 \cdot 2H_2O$	182.76	Light green powder				Insoluble	Soluble in mineral acids and solutions of ammonium chloride, nitrate, or sulfate; very slightly soluble in oxalic acid.		
Nickel oxide	11099-02-8	50495	Unspecified	N/A							NIOSH lists as "nickel oxides."	

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel phosphate; Nickel phosphate ($Ni_3(PO_4)_2$); Nickel orthophosphate; Phosphoric acid, nickel(2+) salt (2:3)	10381-36-9	M1709	$N_3O_8P_2$; $Ni_3(PO_4)_2$	366.02							Ignition of nickel phosphate gives the pigment "nickel yellow."	
Nickel phosphate octahydrate; Nickel(2+) orthophosphate octahydrate	19033-89-7		$H_{16}Ni_3O_{16}P_2$; $Ni_3(PO_4)_2 \bullet 8H_2O$	510.20	Apple- or emerald-green plates or granules	Decomposes			Insoluble in hot or cold water	Soluble in acids, ammonia, and ammonium salts.		
Nickel potassium cyanide; Potassium tetracyanonickelate(II); Dipotassium tetrakis(cyano-C)nickelate(2-)	14220-17-8	E0851	$C_4K_2N_4Ni$; $K_2Ni(CN)_4$	240.96	Orange				Soluble	Treating an aqueous solution with hydrogen sulfide will not precipitate nickel sulfide. No CASRN was identified for the orange-yellow, water-soluble monohydrate listed by Budavari (1996).		
Nickel sesquioxide; Nickel oxide (Ni_2O_3); Nickel(III) oxide; Nickelic oxide; Black nickel oxide; Nickel trioxide	1314-06-3		Ni_2O_3	165.39	Gray-black powder				Insoluble	Dissolves in hot sulfuric or nitric acid with oxygen release and in hot hydrochloric acid with chlorine release.	Decomposes at about 600 °C to NiO and O_2.	
Nickel strontium phosphate; Strontium nickel phosphate	34755-21-0	T0477b	$Ni_xSr_xPO_4$	N/A								

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel subsulfide; Nickel sulfide (3:2); Heazlewoodite (mineral); Trinickel disulfide	12035-72-2		Ni_3S_2	240.25	Black powder; pale yellow-bronze metallic lustrous crystals	790		5.82	Insoluble (< 0.1 g/100 mL water)	Soluble in acids. < 0.1 g/100 mL DMSO or ethanol.		
Nickel sulfamate; Sulfamic acid, nickel(2+) salt (2:1)	13770-89-3	50470; Z0110	$H_4N_2NiO_6S_2$; $Ni(OSO_2NH_2)_2$	250.85							Crystalline entity is never isolated from the reaction mixture of Ni or NiO plus hot aqueous sulfamic acid. Forms a tetrahydrate (CASRN 124594-15-6).	
Nickel sulfate	7786-81-4	50510	NiO_4S; $NiSO_4$	154.76	Yellow cubic crystals	Decom-poses		3.68	1.9 M (29.3 g/100 mL)	Insoluble in acetic acid, diethyl ether, and ethanol.	Decomposes at 848 °C.	
Nickel sulfate hexahydrate, "-form	10101-97-0	X4349	$H_{12}NiO_{10}S$; $NiSO_4 \bullet 6H_2O$	262.85	Blue to blue-green tetragonal crystals	Decom-poses		2.07	2.4 M (62.52 g/100 mL)	Soluble in ammonium hydroxide, ethanol, and methanol.	The "-form makes its transition to the $-form at 53.3 °C (the triple point).	
Nickel sulfate hexahydrate, $-form	10101-97-0	X4349	$H_{12}NiO_{10}S$; $NiSO_4 \bullet 6H_2O$	262.85	Opaque blue at room temp.; transparent monoclinic green crystals at 40 °C	Decom-poses		2.07	Soluble	Sparingly soluble in ethanol; more soluble in methanol.	The hexahydrate loses 5 water molecules at about 100 °C. Anhydrous nickel sulfate forms at 280 °C. The aqueous solution has a pH of about 4.5.	
Nickel sulfide; Nickel monosulfide; Millerite (mineral)	11113-75-0	83744	NiS	90.77	Black trigonal crystals or amorphous; yellow metallic luster	797		5.3-5.65	34.8 :M (0.000316 g/100 mL) at 18 °C	Insoluble in acetic acid, diethyl ether, and ethanol.		

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel tetrafluoroborate; Nickel fluoroborate; Nickel fluoborate; Borate(1$^-$), tetrafluoro-, nickel(2$^+$)	14708-14-6	50460	B_2F_8Ni; $Ni(BF_4)_2$	232.32				1.454	Soluble		Sold in 45% aqueous solution (55-gal drums; tank cars)	R (A
Nickel titanate; Nickel titanium oxide	12653-76-8		NiTiO	154.61								R
Nickel titanate; Nickel titanium oxide ($NiTiO_3$)	12035-39-1	M0778	NiO_3Ti; $NiTiO_3$	154.56								R
Raney Nickel No.7®	7440-02-0		HNi_2; Ni_2H		Gray-black powder or cubic crystals				Insoluble	Insoluble in ethanol.	Note CASRN is that of nickel. 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.	E ((

Notes: M = molar mol. wt. = molecular weight N/A = Not applicable

NIOSH No. = The number used by the National Institute of Occupational Safety and Health (NIOSH) in its databases of the National Occupational Hazard Survey and the National Occupational Exposure Survey to identify substances to which workers were potentially exposed. See Table 2-4.

2.0 HUMAN EXPOSURE

2.1 Use

Nickel and its alloys are valued for their strength, corrosion resistance, high ductility, good thermal and electric conductivity, magnetic characteristics, and catalytic properties (NiDI, 1997). In the United States, approximately 200,000 metric tons of nickel (primary plus secondary nickel) are used per year. The use of primary nickel (Table 2-1) is divided into six sectors: (1) stainless steels, (2) alloy steels, (3) nickel alloys, (4) foundry, (5) plating, and (6) other. In 1996, approximately 46% of U.S. primary nickel consumption was for stainless steel and alloy steel production, 33% went into nonferrous alloys and superalloys, 14% into electroplating, and 7% into other uses such as chemicals, catalysts, batteries, coins, pigments, ceramics, eating utensils, and jewelry (Kuck, 1997a; NiDI, 1997).

2.2 Production

2.2.1 Product Classification and Processes

Metallic nickel is produced from sulfide ore and silicate-oxide ore. Neither type of ore contains more than three percent nickel. Sulfide ores are extracted by flotation and magnetic separation into preparations containing nickel and other metals, while silicate-oxide ores are extracted by chemical means. Other ways of obtaining nickel are through the recycling process, consumer scrap, and through the refining of other metals, such as copper and platinum (IARC, 1990).

Nickel products are classified by the amount of nickel they contain. Class I products are defined as containing ≥99.7 percent nickel, whereas Class II products vary in their nickel content (NiDI, 1997). The nickel used in Class I nickel products is refined using a variety of processes to decrease impurities such as antimony, cobalt, arsenic, zinc, copper, iron, and lead. Cobalt closely resembles the physical and chemical properties of nickel and is often difficult to remove completely from the mined ores, therefore many Class I products may contain high levels of cobalt. Nickel products designated as Class II products such as nickel oxide, metallized nickel oxide, and ferronickel are produced directly by smelting and roasting and are sufficiently pure to be used without refining in applications like stainless steel production (Ullman, 1985). Ammonium nickel sulfate is produced by reacting nickel sulfate with ammonium sulfate and crystallizing the salt from a water solution (Antonsen, 1981; Sax and Lewis, 1987; both cited by IARC, 1990). It is produced by three companies in the United Kingdom, two in the United States, and one in Japan (Chemical Information Services, Ltd., 1988; cited by IARC, 1990).

Two commercial processes are used to manufacture nickel carbonyl. The atmospheric method, practiced in the United Kingdom, produces nickel carbonyl by passing carbon monoxide over freshly reduced nickel. In Canada, high-pressure carbon monoxide is used in the formation of iron and nickel carbonyl. These two products are later separated by distillation. The second method, also practiced in the United States, prepares nickel carbonyl by reacting carbon monoxide with nickel sulfate solution (Antonsen, 1996). Nickel carbonyl is manufactured by

Table 2-1. Uses of Nickel and Nickel Compounds

Nickel Compound	Use	Reference
Nickel	Nickel plating for various alloys, for coins, electrotypes, storage batteries, magnets, lightning rod tips, electrical contacts and electrodes, spark plugs, and machinery parts. Also used for hydrogenation of oils and other organic substances.	Budavari (1996); Sax and Lewis (1987; cited by IARC, 1990)
Ammonium nickel sulfate	Electroplating metals, a dye mordant, and in metal finishing compositions.	Budavari (1996); Sax and Lewis (1987; cited by IARC, 1990)
Nickel acetate	Catalyst, mordant for textiles, an intermediate in the formation of other nickel compounds, a sealer for anodized aluminum, and in nickel electroplating.	Budavari (1996); Antonsen (1981; cited by IARC, 1990)
Nickel acetylacetonate	Catalyst	Budavari (1996)
Nickel carbonate hydroxide	Nickel plating, a catalyst for hardening fats, and an ingredient of ceramic colors and glazes.	Budavari (1996)
Nickel carbonyl	Organic synthesis, production of high-purity nickel powder, and continuous nickel coatings on steel and other metals.	Mond et al. (1890); Wilke et al. (1966; both cited by Budavari, 1996)
Nickel chloride	Nickel plating cast zinc, manufacturing sympathetic ink. The anhydrous salt of nickel chloride is used in gas masks to absorb ammonia.	Budavari (1996)
Nickel cyanide	Nickel plating	Budavari (1996)
Nickel dimethylglyoxime	Sun-fast pigment in paints, used in lacquers, cellulose compounds, and cosmetics.	Budavari (1996)
Nickel formate	Manufacturing nickel and preparation of nickel catalysts for organic reactions (mainly hydrogenation catalysts).	Budavari (1996)
Nickel monoxide	Painting on porcelain, manufacturing magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes.	Budavari (1996); Antonsen (1981; cited by IARC, 1990)
Nickel nitrate	Nickel plating and manufacturing brown ceramic colors.	Budavari (1996)
"Nickel yellow" (yield after nickel phosphate is ignited)	Pigment in oil paints and water colors.	Budavari (1996)
Nickel sulfate	Nickel plating, a mordant in dyeing and printing fabrics, and blackening zinc and brass.	Budavari (1996)
Raney nickel®	Catalyst for hydrogenation of unsaturated organic compounds.	Budavari (1996)

two companies in the Federal Republic of Germany, two in the United States, and one in Japan (Chemical Information Services Ltd., 1988; cited by IARC, 1990).

The compound nickel chloride hexahydrate is produced by the reaction of nickel powder or nickel oxide with hot aqueous hydrochloric acid (Antonsen, 1996). It is produced by eight

companies in the United States, six in India, four in the Federal Republic of Germany, four in Japan, four in the United Kingdom, three in Mexico, two in Brazil, two in France, two in Italy, and one in Spain, Switzerland, and Taiwan (Chemical Information Services, Ltd., 1988; cited by IARC, 1990).

Nickel hydroxide is prepared by three processes: 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; 3) extraction with hot alcohol of the gelatinous precipitate formed by nickel nitrate solution and potassium hydroxide (Antonsen, 1996).

Nickel monoxide is produced by firing a mixture of pure nickel powder and water in air at 1000 °C or by firing a mixture of high purity nickel powder, nickel oxide, and water in air (Antonsen, 1996). This nickel compound is produced by two companies in the United States, six in Japan, two in the United Kingdom, and one in the Federal Republic of Germany (Chemical Information Services Ltd., 1988; cited by IARC, 1990).

Nickel nitrate hexahydrate is prepared by reacting dilute nitric acid and nickel carbonate. Three methods of manufacturing nickel nitrate hexahydrate on a commercial basis include: 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; 3) adding nitric acid to a mixture of black nickel oxide powder and hot water. Anhydrous nickel nitrate is produced by treating the hexahydrate with fuming nitric acid (Antonsen, 1981; cited by IARC, 1990). Nickel nitrate is produced by six companies in the United States, four in Brazil, four in Japan, four in the United Kingdom, two in the Federal Republic of Germany, two in France, two in India, two in Italy, two in Spain, one in Argentina, Australia, Belgium, Mexico, and Switzerland (Chemical Information Services Ltd., 1988; cited by IARC, 1990).

Nickel subsulfide is prepared by the direct fusion of nickel with sulfur. Nickel sulfide and nickel subsulfide are produced in large quantities as intermediates in the processing of sulfidic and silicate-oxide ores (IARC, 1990).

Anhydrous nickel sulfate is produced by a gas-phase reaction of nickel carbonyl with sulfur dioxide and oxygen at 100 °C or in a closed-looped reactor that recovers the solid product in sulfuric acid. The hydrates are prepared by treating nickel powder, nickel carbonate, or nickel oxide with dilute sulfuric acid (Antonsen, 1981; cited by IARC, 1990). Historically, most nickel sulfate has been produced in Belgium, Czechoslovakia, the Federal Republic of Germany, Finland, Japan, Taiwan, the United Kingdom, the United States, and the Union of Soviet Socialist Republics (ERAMET-SLN, 1989b; cited by IARC, 1990).

2.2.2 Production Volumes

In 1995, the Glenbrook Nickel Company, a subsidiary of Cominco, Ltd., produced 8,300 metric tons of nickel contained in ferronickel from imported ores. In 1996, Glenbrook processed 719,000 metric tons of nickel ore, producing 15,000 metric tons of nickel contained in ferronickel (Cominco, 1998).

The United States imported approximately 3,070 metric tons of metallurgical-grade nickel oxide in 1994, but only 530 metric tons in 1995. The nickel imported in 1995 was approximately

59% of the net nickel consumed. This amount was lower than the amount imported in 1994 because Glenbrook resumed production of ferronickel in 1995 (Kuck, 1997b). U.S. exports of nickel products have increased in recent years because of increased demand for stainless steel in the Far East and Western Europe.

In 1996, 164 facilities reported consumption of nickel (Kuck, 1997a). In the Western World, demand for primary nickel reached an all-time high in 1995 when it increased by 15% (from 786,000 to 900,000 metric tons) over the previous year (Kuck, 1997b).

2.3 Nickel Refining

2.3.1 Refining Processes

Nickel refining is a complex process involving many steps and intermediate compounds. Sulfide ores are initially concentrated mechanically and the concentrates are treated by a series of processes, including roasting, smelting, and converting to produce a copper-nickel matte. The matte is further treated to produce a copper-nickel alloy and nickel sulfide. These are then refined to nickel by electrolysis or the carbonyl process. Lateritic ores may be treated by pyrometallurgical processes followed by reduction or electrolysis. Hydrometallurgical processes involving leaching with ammonia or sulfuric acid may be used also (Tien and Howson, 1985).

Carbonyl refining involves the use of nickel carbonyl as an intermediate. High purity nickel pellets are used for melting and dissolving and are a product of the process. Nickel powders used in chemical syntheses and for making nickel alkaline-battery electrodes and powder-metallurgical parts are also derived from the carbonyl-refining process (Antonsen, 1996). This process is based on the selective action of carbon monoxide gas which reacts with nickel occurring in previously metallized materials or with nickel concentrates separated from copper-nickel matte. At 50 °C, the reaction results in the formation of nickel carbonyl which is easily separated from other metals, such as copper, cobalt, and iron. The carbonyl is brought into contact with surfaces heated to around 200 °C at which point it decomposes, releasing carbon monoxide and yielding pure nickel (Carson, 1980; ICNCM, 1990).

2.3.2 Types of Ores

The type of nickel ore processed varies from region to region. There are two types of nickel ores—sulfide ores and silicate-oxide ores (laterites/garnierites) (IARC, 1990). Sulfide deposits, which are formed far beneath the earth's surface by the reaction of sulfur with nickel-bearing rocks, account for most of the nickel that is produced worldwide. The most common nickel sulfide is pentlandite ($Fe_9Ni_9S_{16}$), which is frequently found in association with chalcopyrite ($CuFeS_2$) and pyrrhotite (Fe_7S_8). Lateritic ores, which are formed over long periods of time as a result of weathering of nickel-containing rocks and found in the form of oxides or silicates (Tien and Howson, 1985) exist in tropical regions and regions that once were tropical, such as parts of the Pacific Northwest (IARC, 1990). Canadian and European refineries process mainly copper-sulfidic nickel ores, whereas refineries that operated in the United States processed silicate and lateritic nickel ores. Sources of ores processed in the United States were Cuban laterites at Port Nickel, Louisiana, laterites found near the California-Oregon border, nickel silicate ores processed near Riddle, Oregon, and ores from the Duluth gabbro of northeastern

Minnesota. The nickel silicate mineral mined by Hanna Nickel Smelting Company at Nickel Mountain near Riddle, Oregon, was garnierite. Garnierite is a complex nickel magnesium silicate associated with iron, cobalt, chromium, and aluminum and was refined at the Hanna facility by dephosphorizing and deoxidizing to produce ferronickel (Carson, 1980). More recently, the Glenbrook (formerly the Hanna Nickel Smelting Co.) smelter produced ferronickel from domestic and imported lateritic ores (Kuck, 1997a,b).

2.3.3 Refining Operations in the United States

Since the first nickel refinery was first successfully operated in 1902, there have been several refineries established in the United States involved in primary nickel production. Amax Nickel, a division of Amax, Inc., refined primary cobalt and pure nickel at Port Nickel (Braithwaite), Louisiana, beginning in 1974. The facility had a capacity of 36,000 metric tons of nickel when operable. Nickel-copper mattes from Botswana, New Caledonia, Australia, and South Africa were processed. LeClerc et al. (1987) and Langer et al. (1980) note that the soil in the French territory of New Caledonia, where nickel has been mined and smelted for more than one hundred years also, contains large amounts of chrysotile asbestos. Crude nickel sulfate was produced by ASARCO electrolytic copper refineries in Washington, Maryland, and Perth Amboy, New Jersey. Beginning in 1954, crude nickel sulfate was refined at Perth Amboy by hot water leaching, air oxidizing, and adjusting the pH with calcium carbonate solution to precipitate iron, precipitating copper and zinc as the sulfides, and crystallizing the purified solution (Busch et al., 1961; cited by Carson 1980).

In 1972, a plant at SEC Corporation in El Paso, Texas, began operations to recover copper and nickel from the liquor discharged from the final evaporation stage in copper sulfate crystallization from copper-refining electrolytes that were bled for purification. At SEC, nickel and copper were extracted by organic solvents and the pH controlled by ammonia additions. After acid-stripping of the solvent extracts, nickel and copper were recovered by electrowinning (Carson, 1980).

Table 2-2 is a summary of operations that are involved in or have been involved in mining, milling, smelting, or refining of nickel that may have potentially exposed workers to nickel compounds. Currently, there are no nickel refining processes carried out in the United States. The nickel smelter, located near Riddle, Oregon, and operated by Glenbrook Nickel Company, had been the only one active in recent years (Kuck, 1997a,b; King, 1998). Glenbrook announced the closing of its nickel smelter and the associated port facility in Coos Bay, Oregon, in January 1998 (Cominco, 1998).

Table 2-2. U.S. & Foreign Mining, Milling, Smelting, and Refining Operations

FACILITY AND LOCATION	TYPE OF MATERIAL PROCESSED	TYPE OF PROCESS	NICKEL SPECIES
United States Operations			
Huntington Alloys, Inc. (nickel refinery), West Virginia	Nickel-copper matte from Canada and/or nickel matte from New Caledonia	ND	Total nickel, metallic nickel, oxidic nickel sulfidic nickel
Hanna Mining & Smelting Operations (later known as Glenbrook), Oregon	Garnierite (a complex nickel magnesium silicate associated with iron, cobalt, chromium, and aluminum)	Refined by dephosphorizing and deoxidizing	Oxidic nickel
Amax Port Nickel Refinery, Louisiana	Nickel-copper mattes from Botswana, New Caledonia, Australia, and South Africa (lateritic and silicate ores)	Hydrometallurgical process, atmospheric sulfuric acid leaching	ND
St. Louis Smelting and Refining Company, Fredricksburg, Missouri	Cobalt	Pressure leaching	Metallic nickel
ASARCO Refineries, Tacoma, Washington; Baltimore, Maryland; Perth Amboy, New Jersey	Copper containing nickel and cobalt	Electrolytic copper refining	Crude nickel sulfate
Foreign Operations			
Mond/INCO Nickel Refinery, Clydach Wales	Nickel-copper matte containing nickel subsulfide, copper sulfide, copper-nickel alloy particles, and minor amounts of cobalt, iron, arsenic and platinum	Carbonyl process	Metallic nickel, oxidic nickel, sulfidic nickel, and soluble nickel
Falconbridge Nickel Refinery, Kristiansand, Norway	Crude nickel-copper sulfides matte from Canada	Hybinette process (until 1978) then chlorine leach process	Nickel subsulfide, nickel-copper alloy, nickel-copper oxide, nickel-copper sulfate
INCO Mining, Smelting and Refining Operations, Ontario, Canada	Nickel-copper matte; sulfidic nickel ores	Electrolytic refining	Total nickel, metallic nickel, oxidic nickel, sulfidic nickel, soluble nickel
Outokumpu Oy Nickel Refinery, Finland	Nickel-copper ore consisting of nickel-copper alloy, nickel subsulfide, and copper sulfide	Atmospheric pressure leaching, electrolytic copper removal, cobalt removal, and nickel electrowinning	Soluble nickel
SocietJ le Nickel's Mining and Smelting Operations, New Caledonia	Lateritic ores including silicate and limonite ores (also contains asbestos)	Mining operations	Nickel silicate, oxidic nickel

ND = No data given Sources: Carson (1980); ICNCM (1990).

2.4 Exposure

2.4.1 Environmental Exposure

Nickel is ubiquitous in nature, occurring mainly in the form of sulfide, oxide, and silicate minerals. Nickel is an essential element in certain microorganisms, animals, and plants and is generally believed also to be an essential element for humans (NiDI, 1997). About 130 million metric tons of nickel have been identified in world resource deposits averaging one percent nickel or greater. Sixty percent of the nickel is in laterites and 40% in sulfide deposits. Additionally, deep-sea resources of nickel exist in manganese crusts and nodules covering large areas of the ocean floor, particularly in the Pacific Ocean (Kuck, 1997a). Small amounts of nickel can be emitted into the atmosphere from forest fires, volcanoes, wind-blown dusts, meteoric dusts, and extremely low amounts from sea spray (IARC, 1990).

Environmental exposures to nickel can occur by breathing air or smoking tobacco containing nickel. Very low levels of nickel can be found in ambient air as a result of releases from manufacturing facilities, oil and coal combustion, sewage sludge incineration, and other sources. Contact with many everyday items such as nickel-containing jewelry, cooking utensils, stainless steel kitchens, and clothing fasteners may expose individuals to nickel. Eating food containing nickel is a major source of exposure for most people. The U.S. Environmental Protection Agency (EPA) estimated that the average adult consumes 100 to 300 μg of nickel per day (USEPA, 1998). Drinking water also contains small amounts of nickel (ATSDR, 1997).

2.4.2 Occupational Exposure

The main route of occupational exposure to nickel is through inhalation and, to a lesser degree, skin contact. Nickel refinery dust is a mixture of many nickel species (IRIS, 1997). Exposure concentrations are in Table 2-3.

The National Institute of Occupational Safety and Health (NIOSH) compiled extensive data on potential occupational exposures to nickel, nickel compounds, and alloys in two surveys. The National Occupational Hazard Survey (NOHS) data (NIOSH, 1976) were collected during the period 1972 to 1974 from a sample of 4,636 businesses employing nearly 900,000 workers for the year 1970. The National Occupational Exposure Survey (NOES) data (NIOSH, 1990) were collected during the period 1981-1983 from a sample of 4,490 businesses employing nearly 1,800,000 workers.

The nickel species for which NIOSH collected data are listed in Table 2-4, presented as four groupings. List 14A includes forms of elemental nickel; 14B, nickel compounds and complexes; 14C, nickel alloys; and 14D, nickel alloys used in welding, soldering, and brazing.

Table 2-5 lists U.S. industries by Standard Industrial Classification (SIC) code in which employees were potentially exposed to the nickel compounds of List B in Table 2-1. The 1972-1974 NOHS estimated that 97,192 employees in 9,351 plants were potentially exposed to nickel compounds. The 1981-1983 NOES estimated that 139,779 employees (of which 30,833 were female) of 7,153 plants were potentially exposed to nickel compounds.

Table 2-6 lists those industries in which employees were potentially exposed specifically to nickel sulfate(s): 13,210 total in 2,205 plants in the NOHS and 57,395 total (12,211 females) in 3,509 plants in the NOES.

Table 2-7 lists those industries in which employees were potentially exposed specifically to nickel oxide(s): 4,916 total in 311 plants (nickel oxide; nickel monoxide) and 51,809 total in 1,800 plants ("nickel oxides") in the NOHS and 18,166 total (5,820 females) in 702 plants in the NOES (nickel oxide).

The NOHS provided an estimate of 116 total employees who were potentially exposed to nickel monosulfide at 14 plants producing steel wire and related products (SIC code 3315).

Potential nickel metal and alloy exposure data for species in Lists A, C, and D of Table 2-1 were also compiled by NIOSH. The NOHS estimated that 163,174 total employees in 12,297 plants were exposed to metallic forms of nickel. The NOES estimated that 901,533 total employees (62,776 females) in 51,007 establishments were exposed to nickel metals and alloys.

Although there are no refineries in operation in the United States at present, there is still concern regarding the effects that past exposures in the nickel refining industry have had or are having on the health of former workers. No estimates of the number of former nickel refinery workers exposed were found for inclusion in this background document.

TABLE 2-3. SUMMARY OF CURRENT NICKEL EXPOSURES IN NICKEL-PRODUCING AND -USING INDUSTRIES

Industry Sector	Range of Exposure Concentrations (mg Ni/m^3)[1]	Range of Mean Aerosol Exposure Concentrations (mg Ni/m^3)[1]	Predominant Species[2]
Mining	0-<1.0	0.003-0.15	SU, O[3]
Milling	0.001-4.0	0.01-<0.70	SU
Smelting	0.001-77.0[4]	0.01-<3.0	SU,O[3]
Refining	0.001-20.0[5]	0.003-~1.50[6]	SU,O,M,SO[7]
Stainless and alloy steels	0-<1.0	0.001-0.10	O,M
Nickel alloy steels	0.001-9.0[8]	0.002-~0.50[9]	O,M
Welding and hot cutting	Trace-7.0[8]	0.001-~0.5[10]	O,M[11]
Nickel plating	Trace-~3.0[12]	0.0004-~0.10	SO[13]
Production of chemicals	0.001-~3.0	0.02-~1.50	SO,O,M
Nickel catalysts	0-26.0[14]	0.004-~1.0[15]	SO,O,M[16]
Ni-cadmium batteries	0-~2.0	0.005-~0.50	O,M,SO
Others	Trace-14.0	Trace-0.5[17]	Mixed

1 'Total' nickel, unless otherwise indicated.
2 M=metallic nickel, O=oxidic nickel, NC=nickel carbonyl, SU=sulphidic nickel, SO=solublenickel salts.
3 Dependent upon the type of ore.
4 Upper limits of ranges for most data sources did not exceed 2.0 mg Ni/m^3.
5 Upper limits of ranges for most data sources did not exceed 5.0 mg Ni/m^3.
6 A few mean aerosol concentrations exceeded 1.5 mg Ni/m^3. The highest mean value reported was 4.84 mg Ni/m^3.
7 Dependent upon the operation and job.
8 Upper limits of ranges for most data sources did not exceed 1 mg Ni/m^3.
9 A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest mean value reported was 3.2 mg Ni/m^3.
10 A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest mean value reported was 3.58 mg Ni/m^3.
11 In some instances, soluble nickel was noted to be present, although it was not the pre-dominant form of nickel found.
12 Upper ranges for most data sources did notexceed 1.0 mg Ni/m^3.
13 In instances where speciation was conducted,insoluble nickel compounds were noted to be present although they were not thepredominant forms of nickel found.
14 Upper ranges for most data sources did notexceed 4.0 mg Ni/m^3.
15 A few mean aerosol concentrations exceeded 1.0 mg Ni/m^3. The highest mean value reported was 1.55 mg Ni/m^3.
16 In addition to potential exposures to oxidic and/or metallic nickel species, sulfidic nickel is also believed to be present in the spent nickel catalyst
17 A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest value meanreported was 4.1 mg Ni/m^3

Table derived from NiPERA (1996)

TABLE 2-4. GROUPINGS FOR NIOSH SURVEY DATA (NIOSH Number and Name)

NICKEL, METAL, ORE (LIST 14A)

X5986	NI, NICKEL POWDER-MF UNKNOWN
X5918	NI, NICKEL-PURE *
X5096	NICKEL, DUST
X3242	NICKEL, ISOTOPE OF MASS 63

NICKEL COMPOUNDS/COMPLEXES (LIST 14B)

50460	BORATE(1-), TETRAFLUORO-, NICKEL(2+); Nickel tetrafluoroborate *
X4331	CHROMIC ACID, NICKEL(2+) SALT (1:1); Nickel chromate *
X7105	ETHANEDIOIC ACID, NICKEL(2+) SALT (1:1); Nickel oxalate *
M4033	FORMIC ACID, NICKEL(2+) SALT; Nickel formate *
M0101	INORGANIC NICKEL COMPOUNDS
M1990	MAGNESIUM-NICKEL
M3818	NB.NI, NICKEL COMPD. WITH NIOBIUM
81906	NICKEL ACETATE *
X3677	NICKEL ALUMINIDE
T1988	NICKEL AMMONIUM FERROCYANIDE **
81907	NICKEL AMMONIUM SULFATE *
83009	NICKEL BROMIDE *
81905	NICKEL CARBONATE *
50440	NICKEL CHLORIDE *
X7161	NICKEL CHLORIDE (NICL2) *
X4330	NICKEL CHLORIDE (NICL2), HEXAHYDRATE *
82846	NICKEL CYANIDE *
83311	NICKEL DITHIOCARBAMATE *
T0483	NICKEL DITHIOOXYAMIDE **
T1625	NICKEL FERROCYANIDE *
50450	NICKEL FLUORIDE *
X7142	NICKEL HYDROXIDE (NI(OH)2) *
T1660	NICKEL NAPHTHALENE SULFONATE **
83650	NICKEL NAPHTHENATE *
50480	NICKEL NITRATE *
84269	NICKEL OXIDE *
50495	NICKEL OXIDES *
X3115	NICKEL PLATED BRASS
81904	NICKEL SALTS
50470	NICKEL SULFAMATE *
50510	NICKEL SULFATE *
83744	NICKEL SULFIDE *
W0002	NICKEL SULFONATE **
M0778	NICKEL TITANATE *
M1782	NICKEL-ANTIMONY TITANATES *
E0714	NICKEL, (CARBONATO(2-))TETRAHYDROXYTRI-; Nickel carbonate hydroxide *
X9871	NICKEL, AMMINE(2,3-BUTANEDIONE OXIME THIOSEMICARBAZONATE)(2-))- *
84025	NICKEL, BIS(DIBUTYLDITHIOCARBAMATO)- *
X4332	NICKEL, BIS(DIMETHYLCARBAMODITHIOATO-S,S")- *
X5635	NICKEL, BIS(2,4-PENTANEDIONATO-O,O')-, (SP-4-1)-; Nickel acetylacetonate *
E0851	NICKELATE(2-), TETRAKIS(CYANO-C)-, DIPOTASSIUM, (SP-4-1)-; Potassium tetracyanonickelate(II) *
82957	OCTANOIC ACID, NICKEL(2+) SALT; Nickel octanoate *
84725	ORGANIC NICKEL COMPOUNDS
E0671	PHOSPHONIC ACID, ((3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL)METHYL)-, MONOETHYL ESTER, NICKEL(2+) SALT (2:1) **
M1709	PHOSPHORIC ACID, NICKEL(2+) SALT (2:3); Nickel phosphate *
Z1115	SODIUM HYDROXIDE-TUNGSTEN-MOLYBDENUM-NICKEL-ALUMINUM OXIDE SOLUTION
X2836	SPINELS, CHROMIUM IRON NICKEL BLACK
T0477	STRONTIUM NICKEL PHOSPHATE; Nickel strontium phosphate *
Z0110	SULFAMATE NICKEL ACID COMPOUND; Nickel sulfamate *
X4948	SULFURIC ACID, AMMONIUM NICKEL(2+) SALT (2:2:1); Nickel ammonium sulfate * (see no. 81907 above)
X4349	SULFURIC ACID, NICKEL(2+) SALT (1:1), HEXAHYDRATE; Nickel sulfate hexahydrate *
M3188	TITANIUM, NICKEL, ANTIMONY COMPLEX

TABLE 2-4. GROUPINGS FOR NIOSH SURVEY DATA (NIOSH Number and Name) (continued)

NICKEL ALLOYS (LIST 14C)

X7858	AG.NI, ALLOY MF-UNKNOWN
X8061	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI.W, INCOLOY-MF UNKNOWN
X6385	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI, ASTM A637-718
X4908	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI, INCONEL-MF UNKNOWN
X6380	AL.C.CO.CR.FE.MN.MO.NB.NI.SI.TI, ASTM B443
X7808	AL.C.CO.CR.FE.MO.NI.TI, AISI 687
X7805	AL.C.CR.FE.MN.MO.NB.NI.SI.TI.ZR,ASTM A567-7V
X7388	AL.CU.FE.MG.MN.NI.SI.SN.ZN-AA 360
X7392	AL.CU.FE.MG.MN.NI.SI.TI.ZN-AA 319
X7394	AL.CU.FE.MG.MN.NI.SI.TI.ZN-AA 333
X7829	AL.CU.FE.MN.NI.PB.SI.SN.ZN, ALLOY MF-UNKNOWN
X6951	AL.CU.FE.MN.NI.SI., CDA 958
X6384	AL.NI, ALLOY-MF UNKNOWN
X7837	AU.NI, ALLOY MF-UNKNOWN
A1278	B.C.CR.FE.N.NI.SI, FERROCHROMIUM-VAN
X6401	C.CO.CR.FE.MN.MO.NI.SI.V.W, HASTELLOY A,B&C
X6378	C.CO.CR.FE.MN.MO.NI.SI.V, AMS 5755
X8048	C.CO.CR.FE.MN.MO.NI.SI.W, AISI 680
X8055	C.CO.CR.FE.MN.MO.NI.SI, HASTELLOY-MF UNKNOWN
X5951	C.CO.CR.FE.MN.NI.SI.W, AISI 670
X7810	C.CO.CR.FE.MN.NI.SI.W, ASTM A567-2
X5905	C.CO.CU.NI.TA.TI.W, ALLOY-MF UNKNOWN
X6391	C.CR.CU.FE.MN.MO.NI.SI, AISI 4140
X7580	C.CR.CU.FE.MN.MO.NI.SI, AISI 4145
X5944	C.CR.CU.FE.MN.MO.NI.SI, AISI 4340
X5953	C.CR.CU.FE.MN.MO.NI.SI, AISI 8620
X7717	C.CR.CU.FE.MN.MO.NI.SI, ASTM A296-CN-7M
X6358	C.CR.CU.FE.MN.MO.NI.SI, STEEL, AISI 4130
X6358	C.CR.CU.FE.MN.MO.NI.SI, STEEL, AISI 4130
X7794	C.CR.CU.FE.MN.NB.NI.SI, AMS 5679
X8124	C.CR.CU.FE.MN.NI.P.SI.ZR, ASTM A242-1
X7796	C.CR.CU.FE.MN.NI.SI.TI, AMS 5675
X5054	C.CR.CU.FE.MN.NI.SI, ASTM B163-600
X7881	C.CR.FE.MB.MN.NI, ALLOY MF-UNKNOWN
X7814	C.CR.FE.MN.MO.N.NI.SI, M2-VAN
X5932	C.CR.FE.MN.MO.NI.SI, AISI E9310
X6377	C.CR.FE.MN.MO.NI.SI, AISI 316
X6361	C.CR.FE.MN.MO.NI.SI, AISI 4330-VAN
X5930	C.CR.FE.MN.NI.P.S.SI, AISI 303
X6379	C.CR.FE.MN.NI.SI.TI, AISI 321
X5938	C.CR.FE.MN.NI.SI, AISI 301
X5937	C.CR.FE.MN.NI.SI, AISI 302
X6376	C.CR.FE.MN.NI.SI, AISI 304
X7800	C.CR.FE.MN.NI.SI, AISI 308
X7871	C.CR.FE.MN.NI.SI, ASTM B344-60NI,16CR.
X8026	C.CR.FE.MN.NI, ALLOY-MF UNKNOWN
X7651	C.CR.FE.MN, ALLOY-MF UNKNOWN
69715	C.CR.FE.MN, STAINLESS STEEL-MF UNKNOWN
X6905	C.CR.FE,MN,MO,NI,SI.V, L6 MF-UNKNOWN
X5936	C.CU.FE.MN.NI.SI, ASTM B160-200
X4282	C.CU.FE.MN.NI.SI, ASTM B164-A
X6373	C.FE.MN.NI.SI.V, AISI W2
X5902	C.FE.MN.NI.SI, DIN 1.3917
X7530	C.FE.MN.NI, STEEL, NICKEL-MF UNKNOWN
M2286	C.I. PIGMENT YELLOW 53
X9111	C.MN.P.S.SI.CR.NI.MO, AISI 316L
X8289	C.NI, NICKEL ALLOY
X7873	CO.FE.NI, ASTM F15
X5059	COBALT ALLOY, CO 46-58,CR 19-21,W 14-16,NI 9-11,FE 0-3,MN 0-2,SI 0-1,C 0-0.2 (AISI 670)
X5061	COBALT ALLOY, CO,C,CR,FE,MN,MO,NI,SI,W (STELLITE)
X6395	CR.FE.MO, ALLOY-MF UNKNOWN
X6371	CR.NI, ALLOY-MF UNKNOWN
X6350	CU.NI.SN, BRONZE, NICKEL-MF UNKNOWN
X6722	CU.NI.ZN, GERMAN SILVER
X6368	CU.NI, ALLOY-MF UNKNOWN
X6398	FE.NI, ALLOY-MF UNKNOWN
X8291	NI.ZN, ALLOY MF-UNKNOWN
X8297	NI.ZR, ALLOY MF-UNKNOWN
50675	NI-HARD STEEL
X8294	NI, NICKEL-FUME-MF UNKNOWN
50420	NI, NICKEL-MF UNKNOWN
X9567	SPINELS, IRON NICKEL BROWN
50676	STEEL, NI-HARD, OXIDES OF

TABLE 2-4. GROUPINGS FOR NIOSH SURVEY DATA (NIOSH Number and Name) (continued)

NICKEL IN WELDING, SOLDERING, BRAZING (LIST 14D)

X7849	AG.NI, ALLOY MF-UNKNOWN, SOLDERING
X7868	AG.NI,ALLOY, MF-UNKNOWN, WELDING
X7743	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI, ASTM A637-718, WELDING
X7809	AL.C.CO.CR.FE.MO.NI.TI, AISI 687, WELDING
X7806	AL.C.CR.FE.MN.MO.NB.NI.SI.TI.ZR, ASTM A567-7V, WELDING
X7830	AL.CU.FE.MN.NI.PB.SI.SN.ZN, ALLOY MF-UNKNOWN, WELDING
S2013	ARW NICKEL
S2344	ARW NICKEL ALLOY STEEL
S2222	ARW NICKEL COPPER ALLOYS
S2216	ARW NICKEL/CHROMIUM ALLOY
X7838	AU.NI, ALLOY MF-UNKNOWN, BRAZING
S1026	BRT GOLD/NICKEL
X8132	C.CO.CR.FE.MN.MO.NI.SI.V.W, HASTELLOY A,B&C, WELDING
X7739	C.CO.CR.FE.MN.MO.NI.SI.V, AMS 5755, WELDING
X7741	C.CO.CR.FE.MN.MO.NI.SI.W, AISI 680, WELDING
X7732	C.CO.CR.FE.MN.NI.SI.W, AISI 670, WELDING
X7811	C.CO.CR.FE.MN.NI.SI.W, ASTM A567-2, WELDING
X8119	C.CR.CU.FE.MN.MO.NI.SI., AISI 4140-BRAZING
X8134	C.CR.CU.FE.MN.MO.NI.SI, AISI 4140-WELDING
X7755	C.CR.CU.FE.MN.MO.NI.SI, AISI 8620, WELDING
X7714	C.CR.CU.FE.MN.MO.NI.SI, ASTM A296-CN-7M, WELDING
X7795	C.CR.CU.FE.MN.NB.NI.SI, AMS 5679, WELDING
X8125	C.CR.CU.FE.MN.NI.P.SI.ZR, ASTM A242-1, WELDING
X7797	C.CR.CU.FE.MN.NI.SI.TI, AMS 5675, WELDING
X7781	C.CR.CU.FE.MN.NI.SI, ASTM B163-600, BRAZING
X7766	C.CR.CU.FE.MN.NI.SI, ASTM B163-600, WELDING
X7882	C.CR.FE.MB.MN.NI, ALLOY MF-UNKNOWN, WELDING
X7815	C.CR.FE.MN.MO.N.NI.SI, M2-VAN, WELDING
X7801	C.CR.FE.MN.MO.NI.P.S.SI, AISI 303, WELDING
X7748	C.CR.FE.MN.MO.NI.SI, AISI 316, WELDING
X7876	C.CR.FE.MN.NI.SI.TI, AISI 321, WELDING
X7750	C.CR.FE.MN.NI.SI, AISI 302, WELDING
X7802	C.CR.FE.MN.NI.SI, AISI 304, WELDING
X7798	C.CR.FE.MN.NI.SI, AISI 308, WELDING
X7872	C.CR.FE.MN.NI.SI, ASTM B344-60NI,16CR, WELDING
X8136	C.CU.FE.MN.NI.SI, ASTM B164-A, WELDING
X7826	C.FE.MN.NI, ALLOY MF-UNKNOWN, WELDING
X8128	C.FE.MN.NI, STEEL, NICKEL-MF UNKNOWN, WELDING
X7874	CO.FE.NI, ASTM F15, WELDING
X7745	CR.NI, ALLOY-MF UNKNOWN, WELDING
X7746	CU.NI, ALLOY-MF UNKNOWN, WELDING
S2345	FCA NICKEL ALLOY STEEL
S2223	MIG COPPER-NICKEL ALLOY
S2014	MIG NICKEL
S2217	MIG NICKEL CHROMIUM ALLOYS
X6669	NI, NICKEL-MF UNKNOWN, WELDING
S2015	OFC NICKEL
S2579	OFC NICKEL STEEL
S2218	OFC NICKEL/CHROMIUM ALLOY
S2016	OFW NICKEL
S2219	OFW NICKEL CHROMIUM ALLOYS
S2224	OFW NICKEL COPPER ALLOYS
S2017	OWP NICKEL
S2220	PAC NICKEL/CHROMIUM ALLOY
S2225	REW COPPER/NICKEL
S2018	REW NICKEL
S0039	SOE NICKEL SILVER
S2335	TIG AMS 5679 NICKEL
S2609	TIG AMS 5837 NICKEL
S2019	TIG NICKEL
S2221	TIG NICKEL CHROMIUM ALLOYS
S2226	TIG NICKEL COPPER ALLOYS
S2580	TIG NICKEL STEEL
S2203	TIG, HAST X STEEL (IRON BASED STEEL ALLOY ABOUT 60% IRON, 40% NICKEL)

Notes: * Indicates a nickel compound included in Table 1-1.
** Indicates a compound for which no CASRN was identified; it is not included in Table 1-1.

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS

NATIONAL OCCUPATIONAL HAZARD SURVEY (NOHS) (1972-1974) (NIOSH, 1976)

NICKEL AGGREGATE (LIST 14B IN TABLE 2-4)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1311	CRUDE PETROLEUM AND NATURAL GAS	29	43	
1511	GENERAL BUILDING CONTRACTORS	43	172	
1711	PLUMBING, HEATING, AIR CONDITIONING	256	9,988	
2052	COOKIES AND CRACKERS	41	41	
2256	KNIT FABRIC MILLS	10	10	
2259	KNITTING MILLS, NEC	8	8	
2284	THREAD MILLS	10	10	
2295	COATED FABRICS, NOT RUBBERIZED	10	80	
2512	UPHOLSTERED HOUSEHOLD FURNITURE	16	16	
2514	METAL HOUSEHOLD FURNITURE	31	94	
2542	METAL PARTITIONS AND FIXTURES	16	16	
2591	VENETIAN BLINDS AND SHADES	37	1,511	
2599	FURNITURE AND FIXTURES, NEC	10	100	
2621	PAPER MILLS, EXCEPT BUILDING PAPER	6	30	
2647	SANITARY PAPER PRODUCTS	27	491	
2711	NEWSPAPERS	126	327	
2721	PERIODICALS	17	291	
2731	BOOK PUBLISHING	90	90	
2741	MISCELLANEOUS PUBLISHING	20	40	
2751	COMMERCIAL PRINTING, EX LITHOGRAPIC	75	150	
2752	COMMERCIAL PRINTING, LITHOGRAPHIC	591	1,464	
2816	INORGANIC PIGMENTS	16	32	
2818	INDUSTRIAL ORGANIC CHEMICALS, NEC	41	187	
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	71	1,202	
2821	PLASTICS MATERIALS AND RESINS	43	1,462	
2822	SYNETHTIC RUBBER	82	815	
2833	MEDICINALS AND BOTANICALS	19	38	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2844	TOILET PREPARATIONS	47	141	
2851	PAINTS AND ALLIED PRODUCTS	151	4,796	
2871	FERTILIZERS	54	54	
2893	PRINTING INK	43	1,032	
2911	PETROLEUM REFINING	34	888	
3011	TIRES AND INNER TUBES	6	23	
3069	FABRICATED RUBBER PRODUCTS, NEC	19	733	
3079	MISCELLANEOUS PLASTICS PRODUCTS	40	100	
3161	LUGGAGE	3	45	
3211	FLAT GLASS	75	226	
3231	PRODUCTS OF PURCHASED GLASS	21	21	
3269	POTTERY PRODUCTS, NEC	75	3,123	
3273	READY-MIXED CONCRETE	21	21	
3291	ABRASIVE PRODUCTS	173	720	
3312	BLAST FURNACES AND STEEL MILLS	219	4,518	
3315	STEEL WIRE AND RELATED PRODUCTS	14	116	
3321	GRAY IRON FOUNDRIES	86	6,612	
3323	STEEL FOUNDRIES	43	5,237	
3339	PRIMARY NONFERROUS METALS, NEC	26	1,179	
3341	SECONDARY NONFERROUS METALS	14	130	
3351	COPPER ROLLING AND DRAWING	14	327	
3352	ALUMINUM ROLLING AND DRAWING	14	144	
3356	NONFERROUS ROLLING AND DRAWING, NEC	54	499	
3357	NONFERROUS WIRE DRAWING AND INSULATING	11	97	
3362	BRASS, BRONZE, AND COPPER CASTINGS	28	951	
3421	CUTLERY	21	67	
3423	HAND AND EDGE TOOLS, NEC	52	52	
3425	HANDS SAWS AND SAW BLADES	24	48	
3429	HARDWARE, NEC	63	365	
3432	PLUMBING FITTINGS AND BRASS GOODS	35	35	
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	52	259	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3442	METAL DOORS, SASH, AND TRIM	24	24	
3443	FABRICATED PLATE WORK (BOILER SHOPS)	112	2,030	
3444	SHEET METAL WORK	14	196	
3452	BOLTS, NUTS, RIVETS, AND WASHERS	28	85	
3461	METAL STAMPINGS	183	493	
3471	PLATING AND POLISHING	934	7,665	
3479	METAL COATING AND ALLIED SERVICES	8	24	
3481	MISC. FABRICATED WIRE PRODUCTS	11	76	
3494	VALVES AND PIPE FITTINGS	52	1,141	
3499	FABRICATED METAL PRODUCTS, NEC	64	2,218	
3511	STEAM ENGINES AND TURBINES	39	944	
3522	FARM MACHINERY	11	23	
3533	OIL FIELD MACHINERY	20	40	
3534	ELEVATORS AND MOVING STAIRWAYS	33	198	
3544	SPECIAL DIES, TOOLS, JIGS & FIXTURES	75	276	
3545	MACHINE TOOL ACCESSORIES	50	545	
3554	PAPER INDUSTRIES MACHINERY	78	233	
3559	SPECIAL INDUSTRY MACHINE, NEC	28	284	
3561	PUMPS AND COMPRESSORS	60	4,434	
3569	GENERAL INDUSTRIAL MACHINERY, NEC	11	42	
3573	ELECTRONIC COMPUTING EQUIPMENT	32	54	
3585	REFRIGERATION MACHINERY	17	264	
3589	SERVICE INDUSTRY MACHINES, NEC	14	14	
3599	MISC. MACHINERY, EXCEPT ELECTRICAL	121	242	
3611	ELECTRIC MEASURING INSTRUMENTS	61	683	
3622	INDUSTRIAL CONTROLS	28	313	
3623	WELDING APPARATUS	11	65	
3632	HOUSEHOLD REFRIGERATORS AND FREEZERS	24	141	
3641	ELECTRIC LAMPS	7	382	
3642	LIGHTING FIXTURES	44	267	
3643	CURRENT-CARRYING WIRING DEVICES	50	207	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3644	NONCURRENT-CARRYING WIRING DEVICES	11	11	
3651	RADIO AND TV RECEIVING SETS	6	12	
3652	PHONOGRAPH RECORDS	17	17	
3661	TELEPHONE AND TELEGRAPH APPARATUS	67	2,182	
3662	RADIO AND TV COMMUNICATION EQUIPMENT	26	190	
3673	ELECTRON TUBES, TRANSMITTING	14	650	
3679	ELECTRONIC COMPONENTS, NEC	183	3,689	
3694	ENGINE ELECTRICAL EQUIPMENT	12	2,842	
3711	MOTOR VEHICLES	14	378	
3713	TRUCK AND BUS BODIES	5	5	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	37	173	
3721	AIRCRAFT	34	778	
3722	AIRCRAFT ENGINES AND ENGINE PARTS	5	10	
3729	AIRCRAFT EQUIPMENT, NEC	12	201	
3742	RAILROAD AND STREET CARS	8	32	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	56	576	
3821	MECHANICAL MEASURING DEVICES	81	1,039	
3841	SURGICAL AND MEDICAL INSTRUMENTS	20	78	
3843	DENTAL EQUIPMENT AND SUPPLIES	10	188	
3851	OPHTHALMIC GOODS	36	411	
3871	WATCHES AND CLOCKS	36	222	
3911	JEWELRY, PRECIOUS METAL	32	158	
3912	JEWELERS' FINDINGS AND MATERIALS	18	35	
3914	SILVERWARE AND PLATED WARE	25	225	
3941	GAMES AND TOYS	25	150	
3952	LEAD PENCILS AND ART GOODS	11	55	
3961	COSTUME JEWELRY	11	88	
3963	BUTTONS	25	100	
3964	NEEDLES, PINS, AND FASTENERS	58	517	
3999	MANUFACTURES, NEC	96	224	
4212	LOCAL TRUCKING, WITHOUT STORAGE	220	220	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
4411	DEEP SEA FOREIGN TRANSPORTATION	31	31	
4511	CERTIFICATED AIR TRANSPORTATION	5	375	
4619	PIPE LINES, NEC	8	30	
4721	ARRANGEMENT OF TRANSPORTATION	76	76	
4811	TELEPHONE COMMUNICATION	7	7	
5013	AUTOMOTIVE EQUIPMENT	415	415	
5022	DRUGS, PROPRIETARIES, AND SUNDRIES	282	564	
5211	LUMBER AND OTHER BUILDING MATERIALS	107	107	
5252	FARM EQUIPMENT DEALERS	222	667	
5511	NEW AND USED CAR DEALERS	178	178	
5921	LIQUOR STORES	86	86	
5999	MISCELLANEOUS RETAIL STORES, NEC	232	3,248	
6023	STATE BANKS, NOT FED. RESERVE, FDIC	199	199	
6711	HOLDING COMPANIES	73	146	
7391	RESEARCH & DEVELOPMENT LABORATORIES	668	703	
8061	HOSPITALS	37	37	
TOTAL		9,351	97,192	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

NATIONAL OCCUPATIONAL EXPOSURE SURVEY (NOES) (1981-1983) (NIOSH, 1990)

NICKEL AGGREGATE (LIST 14B IN TABLE 2-4)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1542	NONRESIDENTIAL CONSTRUCTION, NEC	5	100	25
1743	TERRAZZO, TILE, MARBLE, MOSAIC WORK	464	4,274	
1793	GLASS AND GLAZING WORK	76	227	
2075	SOYBEAN OIL MILLS	18	321	
2079	SHORTENING AND COOKING OILS	17	51	
2091	CANNED AND CURED SEAFOODS	31	31	
2211	WEAVING MILLS, COTTON	166	1,331	832
2221	WEAVING MILLS, SYNTHETICS	23	23	
2241	NARROW FABRIC MILLS	26	385	
2491	WOOD PRESERVING	96	192	
2531	PUBLIC BUILDING & RELATED FURNITURE	12	60	
2751	COMMERCIAL PRINTING, LETTERPRESS	146	1,460	438
2771	GREETING CARD PUBLISHING	20	336	173
2791	TYPESETTING	5	5	
2812	ALKALIES AND CHLORINE	38	383	115
2822	SYNTHETIC RUBBER	15	679	139
2831	BIOLOGICAL PRODUCTS	46	511	325
2841	SOAP AND OTHER DETERGENTS	11	723	
2869	INDUSTRIAL ORGANIC CHEMICALS, NEC	3	3	3
2899	CHEMICAL PREPARATIONS, NEC	97	1,201	54
3069	FABRICATED RUBBER PRODUCTS, NEC	180	6,869	156
3079	MISCELLANEOUS PLASTICS PRODUCTS	304	2,338	102
3229	PRESSED AND BLOWN GLASS, NEC	66	2,415	1,660
3264	PORCELAIN ELECTRICAL SUPPLIES	5	43	
3312	BLAST FURNACES AND STEEL MILLS	22	2,566	
3315	STEEL WIRE AND RELATED PRODUCTS	33	658	
3341	SECONDARY NONFERROUS METALS	14	1,334	14
3351	COPPER ROLLING AND DRAWING	3	3	
3356	NONFERROUS ROLLING AND DRAWING, NEC	10	58	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3369	NONFERROUS FOUNDRIES, NEC	91	1,066	75
3412	METAL BARRELS, DRUMS, AND PAILS	10	21	
3421	CUTLERY	72	360	
3423	HAND AND EDGE TOOLS, NEC	120	698	41
3429	HARDWARE, NEC	35	484	57
3432	PLUMBING FITTINGS AND BRASS GOODS	27	460	54
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	21	42	
3442	METAL DOORS, SASH, AND TRIM	31	123	
3443	FABRICATED PLATE WORK (BOILER SHOPS)	5	268	
3444	SHEET METAL WORK	21	62	
3446	ARCHITECTURAL METAL WORK	23	136	
3465	AUTOMOTIVE STAMPINGS	35	366	10
3471	PLATING AND POLISHING	1,177	21,023	3,955
3484	SMALL ARMS	7	163	7
3494	VALVES AND PIPE FITTINGS	53	452	114
3495	WIRE SPRINGS	7	85	
3496	MISC. FABRICATED WIRE PRODUCTS	29	88	29
3511	TURBINES AND TURBINE GENERATOR SETS	3	145	
3519	INTERNAL COMBUSTION ENGINES, NEC	44	15,486	4,352
3523	FARM MACHINERY AND EQUIPMENT	4	103	21
3541	MACHINE TOOLS, METAL CUTTING TYPES	21	270	
3546	POWER DRIVEN HAND TOOLS	19	171	
3547	ROLLING MILL MACHINERY	22	132	44
3549	METALWORKING MACHINERY, NEC	25	279	
3551	FOOD PRODUCTS MACHINERY	65	130	
3552	TEXTILE MACHINERY	11	45	
3554	PAPER INDUSTRIES MACHINERY	7	2,995	22
3555	PRINTING TRADES MACHINERY	27	189	81
3561	PUMPS AND PUMPING EQUIPMENT	60	4,771	8
3562	BALL AND ROLLER BEARINGS	3	259	29
3563	AIR AND GAS COMPRESSORS	43	86	
3572	TYPEWRITERS	4	29	
3573	ELECTRONIC COMPUTING EQUIPMENT	96	2,031	481
3579	OFFICE MACHINES, NEC	14	251	44

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3585	REFRIGERATION AND HEATING EQUIPMENT	12	601	301
3612	TRANSFORMERS	50	1,115	87
3621	MOTORS AND GENERATORS	43	444	315
3622	INDUSTRIAL CONTROLS	38	227	76
3629	ELECTRICAL INDUSTRIAL APPARATUS, NEC	80	1,603	240
3631	HOUSEHOLD COOKING EQUIPMENT	35	209	
3634	ELECTRIC HOUSEWARES AND FANS	53	695	84
3635	HOUSEHOLD VACUUM CLEANERS	6	53	6
3643	CURRENT-CARRYING WIRING DEVICES	177	779	623
3652	PHONOGRAPH RECORDS	163	347	
3661	TELEPHONE AND TELEGRAPH APPARATUS	17	793	272
3662	RADIO AND TV COMMUNICATION EQUIPMENT	38	543	188
3671	ELECTRON TUBES, RECEIVING TYPE	17	256	146
3672	CATHODE RAY TELEVISION PICTURE TUBES	2	9	5
3673	ELECTRON TUBES, TRANSMITTING	37	1,174	217
3674	SEMICONDUCTORS AND RELATED DEVICES	39	2,740	2,011
3678	ELECTRONIC CONNECTORS	9	233	28
3679	ELECTRONIC COMPONENTS, NEC	244	1,888	704
3691	STORAGE BATTERIES	27	485	27
3693	X-RAY APPARATUS AND TUBES	17	17	
3694	ENGINE ELECTRICAL EQUIPMENT	6	470	24
3699	ELECTRICAL EQUIPMENT & SUPPLIES, NEC	55	718	
3711	MOTOR VEHICLES AND CAR BODIES	54	4,820	172
3713	TRUCK AND BUS BODIES	33	69	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	219	2,146	26
3721	AIRCRAFT	22	637	40
3724	AIRCRAFT ENGINES AND ENGINE PARTS	56	830	84
3728	AIRCRAFT EQUIPMENT, NEC	108	877	19
3731	SHIP BUILDING AND REPAIRING	3	28	3
3743	RAILROAD EQUIPMENT	8	278	
3761	GUIDED MISSILES AND SPACE VEHICLES	10	81	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	24	410	
3822	ENVIRONMENTAL CONTROLS	19	970	155
3825	INSTRUMENTS TO MEASURE ELECTRICITY	21	7,296	3,593

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3829	MEASURING & CONTROLLING DEVICES, NEC	10	709	21
3851	OPHTHALMIC GOODS	55	3,917	3,144
3861	PHOTOGRAPHIC EQUIPMENT AND SUPPLIES	35	411	
3873	WATCHES, CLOCKS, AND WATCHCASES	25	198	148
3911	JEWELRY, PRECIOUS METAL	365	3,654	932
3914	SILVERWARE AND PLATED WARE	10	392	90
3949	SPORTING AND ATHLETIC GOODS, NEC	7	609	217
3953	MARKING DEVICES	11	121	
3961	COSTUME JEWELRY	112	448	
3964	NEEDLES, PINS, AND FASTENERS	87	857	181
4226	SPECIAL WAREHOUSING AND STORAGE, NEC	77	687	303
4511	CERTIFICATED AIR TRANSPORTATION	3	139	
4582	AIRPORTS AND FLYING FIELDS	6	244	
4583	AIRPORT TERMINAL SERVICES	3	131	
7391	RESEARCH & DEVELOPMENT LABORATORIES	97	8,723	1,143
8062	GENERAL MEDICAL & SURGICAL HOSPITALS	318	2,849	1,749
TOTAL		7,153	139,779	30,833

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS

NATIONAL OCCUPATIONAL HAZARD SURVEY (NOHS) (1972-1974) (NIOSH, 1976)

CAS #	RTECS #	HAZ	DESCRIPTION
7786-81-4	QR9350000	50510	NICKEL SULFATE

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2295	COATED FABRICS, NOT RUBBERIZED	10	80	
2514	METAL HOUSEHOLD FURNITURE	16	47	
2542	METAL PARTITIONS AND FIXTURES	16	16	
2599	FURNITURE AND FIXTURES, NEC	10	100	
2721	PERIODICALS	17	291	
2818	INDUSTRIAL ORGANIC CHEMICALS, NEC	21	166	
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	14	532	
3161	LUGGAGE	3	45	
3269	POTTERY PRODUCTS, NEC	11	44	
3291	ABRASIVE PRODUCTS	152	678	
3339	PRIMARY NONFERROUS METALS, NEC	11	133	
3421	CUTLERY	21	62	
3423	HAND AND EDGE TOOLS, NEC	52	52	
3429	HARDWARE, NEC	63	365	
3432	PLUMBING FITTINGS AND BRASS GOODS	35	35	
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	52	207	
3442	METAL DOORS, SASH, AND TRIM	24	24	
3444	SHEET METAL WORK	14	196	
3452	BOLTS, NUTS, RIVETS, AND WASHERS	28	85	
3461	METAL STAMPINGS	161	471	
3471	PLATING AND POLISHING	641	4,065	
3479	METAL COATING AND ALLIED SERVICES	8	24	
3481	MISC. FABRICATED WIRE PRODUCTS	11	76	
3499	FABRICATED METAL PRODUCTS, NEC	17	168	
3511	STEAM ENGINES AND TURBINES	13	53	
3534	ELEVATORS AND MOVING STAIRWAYS	33	66	
3559	SPECIAL INDUSTRY MACHINE, NEC	28	284	
3585	REFRIGERATION MACHINERY	17	264	

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3599	MISC. MACHINERY, EXCEPT ELECTRICAL	96	192	
3611	ELECTRIC MEASURING INSTRUMENTS	44	178	
3622	INDUSTRIAL CONTROLS	11	33	
3632	HOUSEHOLD REFRIGERATORS AND FREEZERS	24	47	
3643	CURRENT-CARRYING WIRING DEVICES	50	190	
3661	TELEPHONE AND TELEGRAPH APPARATUS	61	1,061	
3662	RADIO AND TV COMMUNICATION EQUIPMENT	26	190	
3673	ELECTRON TUBES, TRANSMITTING	14	41	
3679	ELECTRONIC COMPONENTS, NEC	19	245	
3694	ENGINE ELECTRICAL EQUIPMENT	12	37	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	13	40	
3721	AIRCRAFT	8	32	
3729	AIRCRAFT EQUIPMENT, NEC	12	201	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	17	87	
3821	MECHANICAL MEASURING DEVICES	57	660	
3841	SURGICAL AND MEDICAL INSTRUMENTS	20	78	
3871	WATCHES AND CLOCKS	36	219	
3912	JEWELERS' FINDINGS AND MATERIALS	18	35	
3914	SILVERWARE AND PLATED WARE	25	225	
3961	COSTUME JEWELRY	11	88	
3963	BUTTONS	25	100	
3964	NEEDLES, PINS, AND FASTENERS	47	506	
3999	MANUFACTURES, NEC	51	61	
4511	CERTIFICATED AIR TRANSPORTATION	5	30	
7391	RESEARCH & DEVELOPMENT LABORATORIES	5	5	
TOTAL		2,205	13,210	

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

NATIONAL OCCUPATIONAL EXPOSURE SURVEY (NOES) (1981-1983) (NIOSH, 1990)

NICKEL SULFATE AGGREGATE
(HAZ CODES 50510, X4349 & X4948)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2091	CANNED AND CURED SEAFOODS	31	31	
2491	WOOD PRESERVING	96	192	
2531	PUBLIC BUILDING & RELATED FURNITURE	12	60	
2791	TYPESETTING	5	5	
2831	BIOLOGICAL PRODUCTS	46	511	325
2841	SOAP AND OTHER DETERGENTS	11	723	
3079	MISCELLANEOUS PLASTICS PRODUCTS	253	759	
3229	PRESSED AND BLOWN GLASS, NEC	37	441	
3264	PORCELAIN ELECTRICAL SUPPLIES	5	43	
3351	COPPER ROLLING AND DRAWING	3	3	
3369	NONFERROUS FOUNDRIES, NEC	91	1,066	75
3412	METAL BARRELS, DRUMS, AND PAILS	10	21	
3421	CUTLERY	72	360	
3423	HAND AND EDGE TOOLS, NEC	120	645	41
3429	HARDWARE, NEC	35	451	57
3432	PLUMBING FITTINGS AND BRASS GOODS	27	460	54
3471	PLATING AND POLISHING	940	16,041	3,701
3484	SMALL ARMS	7	163	7
3494	VALVES AND PIPE FITTINGS	53	452	114
3496	MISC. FABRICATED WIRE PRODUCTS	29	88	29
3511	TURBINES AND TURBINE GENERATOR SETS	3	145	
3523	FARM MACHINERY AND EQUIPMENT	4	62	
3546	POWER DRIVEN HAND TOOLS	19	171	
3547	ROLLING MILL MACHINERY	22	132	44
3554	PAPER INDUSTRIES MACHINERY	7	2,995	22
3561	PUMPS AND PUMPING EQUIPMENT	8	40	8

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS(continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3563	AIR AND GAS COMPRESSORS	43	43	
3572	TYPEWRITERS	4	29	
3573	ELECTRONIC COMPUTING EQUIPMENT	85	1,048	441
3579	OFFICE MACHINES, NEC	14	251	44
3621	MOTORS AND GENERATORS	2	35	28
3622	INDUSTRIAL CONTROLS	38	227	76
3631	HOUSEHOLD COOKING EQUIPMENT	35	209	
3634	ELECTRIC HOUSEWARES AND FANS	53	695	84
3635	HOUSEHOLD VACUUM CLEANERS	6	53	6
3661	TELEPHONE AND TELEGRAPH APPARATUS	14	212	50
3662	RADIO AND TV COMMUNICATION EQUIPMENT	12	265	52
3671	ELECTRON TUBES, RECEIVING TYPE	6	126	108
3673	ELECTRON TUBES, TRANSMITTING	22	133	88
3674	SEMICONDUCTORS AND RELATED DEVICES	14	584	311
3678	ELECTRONIC CONNECTORS	9	233	28
3679	ELECTRONIC COMPONENTS, NEC	81	1,535	701
3693	X-RAY APPARATUS AND TUBES	17	17	
3694	ENGINE ELECTRICAL EQUIPMENT	6	470	24
3711	MOTOR VEHICLES AND CAR BODIES	3	511	11
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	189	2,017	26
3721	AIRCRAFT	16	316	17
3724	AIRCRAFT ENGINES AND ENGINE PARTS	6	141	3
3728	AIRCRAFT EQUIPMENT, NEC	106	840	19
3731	SHIP BUILDING AND REPAIRING	3	10	
3743	RAILROAD EQUIPMENT	3	3	
3761	GUIDED MISSILES AND SPACE VEHICLES	7	72	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	24	410	
3822	ENVIRONMENTAL CONTROLS	19	970	155
3825	INSTRUMENTS TO MEASURE ELECTRICITY	21	6,157	3,069
3829	MEASURING & CONTROLLING DEVICES, NEC	10	709	21
3851	OPHTHALMIC GOODS	55	55	
3861	PHOTOGRAPHIC EQUIPMENT AND SUPPLIES	8	38	
3873	WATCHES, CLOCKS, AND WATCHCASES	25	198	148
3911	JEWELRY, PRECIOUS METAL	317	3,199	886

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS(continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3861	PHOTOGRAPHIC EQUIPMENT AND SUPPLIES	8	38	
3873	WATCHES, CLOCKS, AND WATCHCASES	25	198	148
3911	JEWELRY, PRECIOUS METAL	317	3,199	886
3914	SILVERWARE AND PLATED WARE	10	392	90
3953	MARKING DEVICES	11	121	
3961	COSTUME JEWELRY	112	448	
3964	NEEDLES, PINS, AND FASTENERS	23	544	181
4511	CERTIFICATED AIR TRANSPORTATION	3	65	
4582	AIRPORTS AND FLYING FIELDS	3	162	
7391	RESEARCH & DEVELOPMENT LABORATORIES	53	6,853	895
8062	GENERAL MEDICAL & SURGICAL HOSPITALS	72	940	172
TOTAL		3,509	57,395	12,211

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS

NATIONAL OCCUPATIONAL HAZARD SURVEY (NOHS) (1972-1974) (NIOSH, 1976)

CAS #	RTECS #	HAZ	DESCRIPTION
1313-99-1	QR8400000	84269	**NICKEL OXIDE**

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	14	350	
2821	PLASTICS MATERIALS AND RESINS	43	1,462	
2851	PAINTS AND ALLIED PRODUCTS	47	1,744	
3269	POTTERY PRODUCTS, NEC	49	98	
3339	PRIMARY NONFERROUS METALS, NEC	26	210	
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	52	104	
3673	ELECTRON TUBES, TRANSMITTING	14	14	
3679	ELECTRONIC COMPONENTS, NEC	19	697	
3911	JEWELRY, PRECIOUS METAL	32	158	
3952	LEAD PENCILS AND ART GOODS	11	55	
7391	RESEARCH & DEVELOPMENT LABORATORIES	5	25	
TOTAL		311	4,916	

CAS #	RTECS #	HAZ	DESCRIPTION
		50495	**NICKEL OXIDES**

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1711	PLUMBING, HEATING, AIR CONDITIONING	256	9,988	
2816	INORGANIC PIGMENTS	16	32	
2818	INDUSTRIAL ORGANIC CHEMICALS, NEC	21	21	
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	45	431	
2822	SYNTHETIC RUBBER	20	79	
2911	PETROLEUM REFINING	19	151	
3079	MISCELLANEOUS PLASTICS PRODUCTS	11	23	

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3269	POTTERY PRODUCTS, NEC	26	2,981	
3312	BLAST FURNACES AND STEEL MILLS	185	4,328	
3321	GRAY IRON FOUNDRIES	75	6,568	
3323	STEEL FOUNDRIES	43	5,237	
3339	PRIMARY NONFERROUS METALS, NEC	11	564	
3341	SECONDARY NONFERROUS METALS	14	130	
3351	COPPER ROLLING AND DRAWING	14	327	
3356	NONFERROUS ROLLING AND DRAWING, NEC	54	360	
3362	BRASS, BRONZE, AND COPPER CASTINGS	28	951	
3443	FABRICATED PLATE WORK (BOILER SHOPS)	112	2,030	
3494	VALVES AND PIPE FITTINGS	52	1,141	
3499	FABRICATED METAL PRODUCTS, NEC	48	2,050	
3511	STEAM ENGINES AND TURBINES	25	891	
3533	OIL FIELD MACHINERY	20	40	
3544	SPECIAL DIES, TOOLS, JIGS & FIXTURES	14	42	
3545	MACHINE TOOL ACCESSORIES	50	495	
3554	PAPER INDUSTRIES MACHINERY	78	233	
3561	PUMPS AND COMPRESSORS	60	4,413	
3569	GENERAL INDUSTRIAL MACHINERY, NEC	11	42	
3599	MISC. MACHINERY, EXCEPT ELECTRICAL	25	50	
3611	ELECTRIC MEASURING INSTRUMENTS	34	505	
3622	INDUSTRIAL CONTROLS	28	280	
3623	WELDING APPARATUS	11	65	
3632	HOUSEHOLD REFRIGERATORS AND FREEZERS	24	94	
3641	ELECTRIC LAMPS	7	382	
3642	LIGHTING FIXTURES	44	267	
3651	RADIO AND TV RECEIVING SETS	6	12	
3661	TELEPHONE AND TELEGRAPH APPARATUS	13	1,072	
3673	ELECTRON TUBES, TRANSMITTING	14	581	
3679	ELECTRONIC COMPONENTS, NEC	28	148	
3694	ENGINE ELECTRICAL EQUIPMENT	12	2,805	
3711	MOTOR VEHICLES	7	28	

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3713	TRUCK AND BUS BODIES	5	5	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	23	133	
3721	AIRCRAFT	26	693	
3722	AIRCRAFT ENGINES AND ENGINE PARTS	5	10	
3742	RAILROAD AND STREET CARS	8	32	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	31	80	
3821	MECHANICAL MEASURING DEVICES	57	238	
3851	OPHTHALMIC GOODS	36	383	
3999	MANUFACTURES, NEC	45	90	
4511	CERTIFICATED AIR TRANSPORTATION	5	310	
TOTAL		1,800	51,809	

NATIONAL OCCUPATIONAL EXPOSURE SURVEY (NOES) (1981-1983) (NIOSH, 1990)

CAS #	RTECS #	HAZ	DESCRIPTION
1313-99-1	QR8400000	84269	**NICKEL OXIDE**

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1743	TERRAZZO, TILE, MARBLE, MOSAIC WORK	317	2,217	
2075	SOYBEAN OIL MILLS	18	321	
2079	SHORTENING AND COOKING OILS	17	51	
2899	CHEMICAL PREPARATIONS, NEC	42	170	
3229	PRESSED AND BLOWN GLASS, NEC	17	1,962	1,660
3312	BLAST FURNACES AND STEEL MILLS	14	1,174	
3315	STEEL WIRE AND RELATED PRODUCTS	33	658	
3429	HARDWARE, NEC	7	13	
3465	AUTOMOTIVE STAMPINGS	3	18	
3612	TRANSFORMERS	44	1,089	87

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3672	CATHODE RAY TELEVISION PICTURE TUBES	2	9	5
3673	ELECTRON TUBES, TRANSMITTING	22	88	44
3674	SEMICONDUCTORS AND RELATED DEVICES	2	67	42
3691	STORAGE BATTERIES	27	485	27
3711	MOTOR VEHICLES AND CAR BODIES	23	2,824	52
3713	TRUCK AND BUS BODIES	3	11	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	13	65	
3825	INSTRUMENTS TO MEASURE ELECTRICITY	3	1,056	483
3851	OPHTHALMIC GOODS	55	3,861	3,144
3911	JEWELRY, PRECIOUS METAL	12	116	46
4226	SPECIAL WAREHOUSING AND STORAGE, NEC	16	81	
7391	RESEARCH & DEVELOPMENT LABORATORIES	14	1,828	230
TOTAL		702	18,166	5,820

2.5 Regulations and Criteria

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 Authorization Act (SARA). The nickel salt of an organo compound containing nitrogen is regulated under the Toxic Substances Control Act (TSCA). 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, while a value 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. 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; cited by IARC, 1990). 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). 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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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 (NESHAP) established pursuant to section 112 of the CAA, which regulate 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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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 washoff solvents. Nickel carbonyl is listed as a VHAP 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 1000 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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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 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.	
	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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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 are also 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 2.1×10^{-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).
	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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	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.
	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.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	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.
E P A	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 fluoborate, the limits for total nickel are 0.0060 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 fluoborate, 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.).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	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.
E P A	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.).
	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 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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	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.	
EPA	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.
FDA	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.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
O S H A	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.	
	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.
O S H A	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, open vessel operations restricted, 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.	PEL for nickel carbonyl (as Ni) $\leq$ 0.007 mg/m^3, as an 8-hr TWA. PEL for nickel insoluble and soluble compounds (as Ni) $\leq$ 1 mg/m^3, as an 8-hr 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.	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program to include labels, materials safety data sheets, and worker training.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	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.	
OSHA	29 CFR 1915.1000—Sec. 1915.1000 Air contaminants. Promulgated: 61 FR 31430, 06/20/96.	The requirements applicable to shipyard employment under this section are identical to those set forth in section 1910.1000.
	29 CFR 1926—PART 1926—SAFETY AND HEALTH REGULATIONS FOR CONSTRUCTION. Promulgated: 44 FR 8577, 02/09/79; 44 FR 20940, 04/06/79.	
	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.

[a]The regulations in this table have been updated through the following 1998 Code of Federal Regulations: 21, 19, and 40 in February 1999.

3.0 HUMAN STUDIES

3.1 Review of Nickel Compound Epidemiology (IARC, 1990, and ICNCM, 1990)

The IARC Working Group for consideration of nickel and nickel compounds concluded nickel compounds are carcinogenic to humans. The reviewed studies evaluated the risk from occupational exposure to nickel and nickel compounds. There is sufficient evidence for the carcinogenicity of nickel sulfate in humans, and of combinations of nickel sulfides and oxides encountered in the nickel refining industry. Carcinogenicity of the respiratory tract is the main chronic effect reported in relation to nickel and its compounds. The risks were highest for lung and nasal cancers among calcining workers who were heavily exposed to sulfidic, oxidic, and metallic nickel.

The separate effects of oxides and sulfides could not be estimated as high exposure was always either to both, or to oxides together with soluble nickel. In addition, the presence of many potential confounders (sulfuric acid mists, oxide and sulfide ores other than nickel, and smoking) increased the difficulty in identifying the causative agent(s). Also, an increased cancer incidence was reported only in workers employed prior to 1955, when exposure levels were estimated to be 1-10 mg Ni/m^3 (consisting mainly of Ni-Cu oxides). Since 1955, levels are estimated to be between 1-5 mg Ni/m^3 (consisting mainly of impure NiO).

A comprehensive review of the epidemiological studies of cancer and human exposure to nickel was also performed in 1990 by the International Committee on Nickel Carcinogenesis in Man (ICNCM, see Appendix A). This review, including a recent analysis of one case-control study and nine cohort studies, concludes that cancers of the lung and nasal cavities are significantly higher in nickel refinery workers than the general population (Steenland et al., 1996). However, causal relationships between cancer and nickel exposure in U.S. refineries are confounded by other factors.

Mortality studies of exposed workers in the nickel alloy industry demonstrate no consistent association with lung cancer. The few studies reporting positive results could not separate the cancer risk associated with nickel from other confounding factors, such as exposure to known carcinogens like chromium (Steenland et al., 1996). According to the ICNCM report, when operations at the Riddle, Oregon, refinery were in progress, analysis of the epidemiological data for the refinery found only a modest excess of lung cancer mortality. No malignancies of the nasal passages or sinuses, and no significant excess of any other type of cancer were reported (ICNCM, 1990). The excess in the incidence of lung cancers was found in a subgroup of short-term workers exposed for less than one year, whereas workers with chronic exposure had no significant excess in mortality due to lung cancer. In contrast, workers in Canadian and European refineries, which process sulfidic ores, had increased incidences of respiratory cancer (ICNCM, 1990).

3.2 Studies Post-IARC (1990)

Full design details and results for the studies described in this section are presented in **Table 3-1**. To facilitate comparison, Standardized Mortality Ratios (SMRs), Odds Ratios (ORs), and Relative Risk Ratios (RRs) reported in this section have all been converted to base 1.

3.2.1 Metallic Nickel

Two studies (published without information regarding levels of nickel exposure) of stainless steel and ferrochromium production workers and welders in France found no significant excess risk of lung cancer. The first study involved a cohort of 2269 men followed from 1952 to 1982 (Moulin et al., 1990). Stainless steel production began in 1958. Causes of death were obtained from general practitioners or hospital records. The SMR for lung cancer was not statistically raised in the overall cohort (SMR = 1.40, 95% CI = 0.72-2.45). The higher rate of lung cancer (SMR = 2.04, 95% CI = 1.02-3.64) seen in workers exposed for at least one year in workshops producing stainless steel or ferrochromium could have been due to confounding exposures to polycyclic aromatic hydrocarbons (PAHs).

The second study (Moulin et al., 1993) examined welders in French factories. The cohort consisted of 2721 welders, and mortality was followed from 1975 to 1988. There was no significant excess of lung cancer in all welders compared to controls, but the lung cancer incidence was increased in mild steel welders compared to other subgroups of welders. The lung cancer mortality among mild steel welders was also significantly increased with an exposure duration and latency period of $\geq$ 20 years.

3.2.2 Nickel Carbonyl

The only epidemiological study specifically investigating the possible carcinogenic effect of nickel carbonyl provided no conclusive results. The study focused on 69 men who died between 1933 and 1966 in Wales whose work history included absence from the refinery due to accidental exposure to nickel carbonyl. Their SMR for lung cancer was not statistically significant at 1.52 (95% CI = 0.56-3.31) (Morgan, 1992).

3.2.3 Oxidic Nickel

A European study of 11,092 welders that compared the mortality experiences of shipyard welders, mild steel welders, and those who had ever welded stainless steel provided no definitive evidence of increasing cancer mortality with higher cumulative exposure to nickel (Simonato et al., 1991), although the SMR for all malignant neoplasms for the overall cohort was significantly increased at 1.13 (95% CI = 1.00-1.26). There were no carcinomas of the nose or nasal cavities. The SMR for carcinoma of the trachea, bronchus, and lung was 1.34 (95% CI = 1.10-1.60).

Stainless steel welders would have been exposed to a much higher level of nickel and chromium than those welding mild steel. The lung cancer SMR for mild steel welders was 1.78 (95% C I= 1.27-2.43), 1.28 (95% CI = 0.91-1.75) for those who ever welded stainless steel, and 1.23 (95% CI = 0.75-1.90) for those who predominantly welded stainless steel. Within this last group, there was a non-significant increase in lung cancer SMR with duration of employment: <9 years, SMR = 0.98 (95% CI = 0.40-2.02); >10 years, SMR=1.43 (95% CI = 0.76-2.44). There was no information on the smoking habits or the previous occupational exposure of the cohort (Simonato et al., 1991).

3.2.4 Soluble Nickel

A cohort study of 418 (369 male and 49 female) workers employed at a Finnish nickel refinery (1960-1987) reported a two-fold increased incidence of lung cancer (CI = 0.3-7.4) and a large increase for sinonasal cancer (SIR = 53.8; CI = 1.4-300), however, these estimates were based on only 2 and 1 observed cases, respectively (Karjalainen et al., 1992). The small size of the study and follow-up period limit the conclusions that can be drawn.

Exposures in the refinery were principally to soluble nickel compounds, mainly nickel sulfate, and to a lesser extent, nickel chloride. No nickel oxides were reported to be present, although low levels (between 0.05 and 0.2 mg Ni/m^3) of nickel subsulfide and nickel hydroxide (levels not reported) were noted to be present in certain areas of the refinery. Overall, average levels of nickel ranged between 0.1-0.5 mg Ni/m^3. Copper/nickel smelter workers and maintenance workers were followed from 1953-1987 and nickel refinery workers from 1960-1987. There were ten cases of lung cancer observed while 9.2 were expected. In the original follow-up period, there was one case of sinonasal cancer, but two further cases of sinonasal cancer were diagnosed after the closing date of follow-up.

Exposure to sulfuric acid (and allied) mists has been associated with increased risk of various respiratory cancers and is identified as a possible confounder in this study. The workers in this study showed no significant increase in standard incidence rates (SIR) of non-respiratory cancer.

A follow-up to this study reports an updated analysis of cancer incidence among the Finnish worker cohort (Anttila et al., 1998). A total of 1,155 workers were presumed to have potential nickel exposure based upon dates of employment (after January 1, 1960 which corresponds to the start of nickel smelting and refining). The vital status of nearly all cohort members (99.4%) was determined. Linkage with the national cancer registry of Finland ascertained incident cases of cancer among the cohort. Follow-up was extended from the end of 1987 to December 31, 1995. An elevated risk of nasal cancer was found among refinery workers (SIR = 41.1; CI = 4.9- 148) with a greater increased risk among workers with a longer latency (20+ years; SIR = 67.1) and duration of employment (5+ years; SIR = 75.2). An increased risk of lung cancer was also found for nickel refinery workers (latency of 20+ years SIR = 3.4).

The additional follow-up provided a relatively complete latency period, although the size of the cohort limits the precision of many risk estimates. For example, the association with nasal cancer is quite suggestive, but is based upon only 2 cases among the exposed nickel workers. Other aspects of the study design are strengths such as the excellent tracing and linkage with a national cancer registry. The potential confounding effects of other workplace and exposures is of concern. Examination of the risk estimates for the unexposed (to nickel) cohort shows a 1.5-fold increased risk for lung cancer raising the possibility that some of the excess risk attributed to nickel exposure may be due to other factors.

Another European study (Andersen et al., 1996) suggests an association between work in a nickel refinery and an increased incidence of cancers. This cohort cancer incidence study of 4764 Norwegian nickel refinery workers found an elevated incidence for nose and nasal cavity cancer (SIR = 18.0; CI = 12.3-25.4) and lung cancer (SIR = 3.0; CI = 2.6-3.4). A moderately increased risk of laryngeal cancer was also found (SIR = 1.6; CI = 0.8- 2.8). An analysis of nickel

compounds showed a dose-response gradient for lung cancer with cumulative exposure to soluble nickel after adjustment for nickel oxide, smoking, and age, in addition to a multiplicative interaction between smoking and total nickel exposure.

3.3 Other Occupational Exposure Studies

The largest body of epidemiological data linking increased incidences of cancer and nickel exposures is from the European and Canadian communities, where the source of nickel is mainly from copper-sulfidic nickel ores. Exposures were mainly to the more dust-generating nickel processes, and those primarily occurring prior to the 1930's. No recent epidemiologic data exists for U.S. nickel refinery workers, who were mainly exposed to either lateritic ores (oxides or silicates, with much lower copper content than European varieties), or to garnierite (a complex nickel magnesium silicate associated with iron, cobalt, chromium, and aluminum, and containing about 0.5 percent cobalt) (Carson, 1980). Since the possible contribution of copper to potential carcinogenicity has not been extensively investigated, caution may be needed when making comparisons between U.S. and non-U.S. studies.

One European study which might be relevant to the United States is an update to an earlier study of French refinery workers in New Caledonia, using lateritic ores similar to those used in U.S. processes (Goldberg et al., 1994). The study did not find an increased incidence of respiratory and upper aerodigestive tract cancers among male nickel workers compared with the incidence among the general male population of New Caledonia for a ten-year period (1978-1987). Further, there was no increased incidence of these cancers when stratified by duration of exposure. A nested case-control study using a job-exposure matrix to classify workers according to 20 specific exposure groups did not show a pattern of association with lung, larynx, or pharynx cancer for nickel-related exposures. Many of the risk estimates for the exposure-based analysis were imprecise with wide confidence intervals.

Recent studies in the United States which suggest an association between occupational nickel exposure and cancer, like their European counterparts, cannot attribute the increased incidence of cancer to any one specific form of nickel. Additionally, none of the studies examined U.S. refinery workers specifically. Two of the studies (Wortley et al., 1992; Horn-Ross et al., 1997), while conducted in the United States, did not specify the type of nickel exposure, nor even the industry. A link between laryngeal cancer and occupational exposure to nickel (n = 235; RR = 1.6; CI = 0.4-6.7) was reported in a study of cases in the western Washington region (Wortley et al., 1992). In this analysis, patients were assigned numerical risk ratings, based upon self-reported occupations and the potential risk of nickel exposure; comparisons were made between the incidence of laryngeal cancer and exposure scores.

Another study (Horn-Ross et al., 1997) of patients diagnosed with cancer of the salivary glands found a substantial dose-dependent association between cumulative hours of worker exposure to nickel compounds or alloys and an increased risk of cancer of the salivary glands. A major criticism of the study, aside from the small number of patients in the "high" risk group, is the potential misclassification of nickel exposure using job title and a job-exposure matrix. In addition, neither of these studies attempted to qualify the type of nickel exposure, combining all nickel compounds and alloys into one group.

Some of the more recent studies suggesting a link between incidence of cancer and nickel exposure (Karjalainen et al., 1992; Wortley et al., 1992; Horn-Ross et al., 1997) are limited by the relatively small number of subjects studied. In addition, exposure to nickel was largely self-reported, and potential exposure to other potential carcinogens (e.g., mists of sulfuric acid) were not taken into account in some studies. The recent study by Anderson et al (1996) does suggest an association between nickel exposure, in particular soluble nickel, and an increased risk of lung and nasal cancer. The risk estimate for lung cancer was relatively precise and the study did account for smoking and utilized cumulative exposure measures based upon available direct measurements of nickel concentrations.

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Cohort	2,269 male stainless steel and ferrochromium production workers in France followed from 1952 to 1982	Metallic nickel no data regarding levels of nickel exposure.	Significant excess in lung cancer; SMR for workers exposed for ≥ 1 yr in stainless steel or ferrochromium shops = 2.04, 95% CI = 1.02-3.64.	Nested case-control study of lung cancer cases showed elevated OR for welders exposed only to nickel and/or chromium and not PAHs (OR = 3.4; CI= 0.4-32.4). Smoking similar in exposed and non-exposed groups		Moulin et al. (1990)
Cohort	69 male refinery workers who died between 1933 and 1966	Nickel carbonyl effects of accidental exposure caused work absences in this cohort	Lung cancer SMR not significant at 1.52			Morgan (1992)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Reference
Cohort	11,092 welders (shipyard, mild steel, stainless steel) from 135 companies in nine European countries	Oxidic nickel Stainless steel workers would have been exposed to a much higher level of nickel and chromium than those welding mild steel.	SMR for all malignant neoplasms for the overall cohort was significantly increased at 1.13 (95% CI = 1.00-1.26). The SMR for carcinoma of the trachea, bronchus, and lung was 1.34 (95% CI = 1.10-1.60). SMRs (95% CI) Mild steel = 1.78 (1.27-2.43) Stainless steel (ever) = 1.28 (0.91-1.75) Stainless steel (predominantly) = 1.23 (0.75-1.90)	No data on smoking habits or previous occupational exposure of cohort.	Simonato et al. (1991)
Cohort	2,721 welders in 13 factories in France; internal comparison group of 6,683 manual workers; mortality determined 1975-1988	Oxidic nickel no data on levels of exposure to nickel	No significant excess of lung cancer in all welders compared to controls; increased lung cancer in mild steel welders compared to stainless steel welders Overall SMR for lung cancer in all welders = 1.24, 95% CI = 0.75-1.94. Stainless steel welders (SMR = 1.1; 95% CI = 0.4-2.6); non-shipyard mild steel welders (SMR=1.59, 95% CI = 0.73-3.02) and significant increase for $\geq$ 20 yr duration and latency	Smoking; no significant difference between exposed and non-exposed groups	Moulin et al. (1993)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Cohort	418 workers (369 M, 49 W) in a Finnish nickel refinery after 1960; cancer incidence followed up from 1960-1987.	Soluble nickel Measured levels of 0.1-0.5 mg/m^3 from personal sampling in the 1970s; 1.1 mg Ni/m^3 highest recorded single concentration in electrowinning dept.; urine conc. < 0.85 :mol/L in leaching workers and 1.5-2 :mol/L in electrowinning workers	Calculated standardized incidence ratios (SIRs): Sinonasal cancer SIR (95% CI; no. obsd/no. exp) 53.8 (1.4-300. 1/0.018) Stomach cancer SIR (95% CI; no. obsd/no. exp) 4.3 (0.5-16; not given) Lung cancer SIR (95% CI; no. obsd/no. exp) 2.0 (0.3-7.4; 2/1)	Effects of smoking could not be evaluated due to lack of historical information.	Overall cancer risk among workers exposed to nickel was the same as in the reference population. Increased incidence of lung and nasal cancers indicates that even moderate or low nickel exposures can be hazardous.	Karjalainen et al. (1992)
Cohort	418 workers (369 M, 49 W) in a Finnish nickel refinery continuously employed at least 3 mo 1945-1985; cancer incidence followed up through 1995.	Soluble nickel Measured levels of 0.2-0.8 mg/m^3 from stationary samplers 1967-1988; 0.1-0.4 mg /m^3 in breathing zone samples taken 1979-1981; 1.2 mg /m^3 highest recorded single concentration measured at stationary sites in electrowinning work area; most exposure to Ni sulfate after 1973	Calculated standardized incidence ratios (SIRs): Sinonasal cancer SIR (95% CI; no. obsd/no. exp) 41.1 (4.97-148; 2/0.05) Stomach cancer SIR (95% CI; no. obsd/no. exp) 4.98 (1.62-11.6; 5/1.0) Lung cancer SIR (95% CI; no. obsd/no. exp) 2.61 (0.96-5.67; 6/2.3)	Effects of smoking could not be evaluated due to lack of historical information.	Overall cancer risk among workers exposed to nickel was the same as in the reference population. Increased incidence of lung and nasal cancers indicates that even moderate or low nickel exposures can be hazardous.	Anttila et al. (1998)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Cohort	4,764 nickel refinery workers; 379 workers with first employment 1916-1940, with at least 3 yr of employment, and 4,385 workers with at least 1 yr of employment 1946-83.	Soluble nickel Measurement of atmospheric nickel in most process areas in 1973; few measurements in 1952-1953 and 1964 Concentrations of total airborne nickel and different forms estimated by experts (engineers, medical personnel, others with refinery experience) Assumed that nickel species occurred in respirable dust in same proportion as in material handled in work areas; species divided into four categories: metallic, oxidic, soluble, sulfidic	Two analyses: 1) SIR 2) Poisson regression for RR SIR (95% CI; no. obsd/no. exp.) 18 (12-25; 32/1.8) for nasal cancer 3 (2.6-3.4; 203/68) for lung cancer RR (95% CI) of lung cancer 1.1 (0.2-5.1) for exposed workers (never smoked): 5.1 (1.3-20.5) for exposed workers (smoked) *Soluble nickel:* Mean Exposure mg/m^3, (n) — RR — 95% CI 0.1 (86) — 1.0 — referent 2.3 (36) — 1.2 — (0.8-1.9) 8.8 (23) — 1.6 — (1.0-2.8) 28.9 (55) — 3.1 — (2.1-4.8) *Nickel oxide:* Mean Exposure mg/m^3, (n) — RR — 95% CI 0.4 (53) — 1.0 — referent 2.5 (49) — 1.0 — (0.6-1.5) 8.3 (53) — 1.6 — (1.0-2.5) 44.3 (45) — 1.5 — (1.0-2.2)	RR adjusted for smoking, age; RRs for soluble nickel and nickel oxide adjusted for each other		Andersen et al. (1996)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Case-control nested in nickel workers cohort	Cases: 112 male workers at a New Caledonia, France nickel refinery; all cases of cancer were diagnosed between 1978 and 1987, and each had worked at the company >10 yr. Controls: 298 non-exposed males from the general population in New Caledonia.	Established a job-exposure matrix for various categories of nickel compounds and agents considered to be potential confounders; levels of exposure evaluated by industrial hygienists based on measurements and chemical analyses	Calculated age-adjusted ORs and 95% CI for cumulative exposure and total duration of exposure (considering latency and lag periods); no significant increase in respiratory cancer risk, including pleural, upper respiratory tract, and nasal cancers.	Alcohol and tobacco consumption reported for 3-yr period (1978-81), no change in ORs adjusted for these factors		Goldberg et al. (1994)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Case-control	Cases: 235 patients diagnosed with laryngeal cancer between Sept. 1983 and Feb. 1987 in western Washington area. Controls: 547 men and women, identified by random-digit dialing.	Personal interviews to obtain lifetime occupational histories; prepared a job exposure matrix that included potential nickel exposure; no actual measurements	Odds ratios and 95% CI were for laryngeal cancer estimated using unconditional logistic regression analyses, controlling for alcohol use, cigarette smoking, age and education. Suggestion of increased risk of laryngeal cancer with exposure scores of ≥ 20 Odds Ratio (95% CI): 1.6 (0.4-6.7)	Chromium exposure, age, alcohol use, education, smoking	Strengths: use of a population-based design for the ID of cases and controls, adjusted for smoking, alcohol use, major risk factors for laryngeal cancer; analyses based on latency, peak, duration and intensity of exposure. Weaknesses: potential misclassifica-tion of nickel exposure using job title, a job-exposure matrix, and a small number of subjects	Wortley et al. (1992)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Case-control	Cases: 141 men and women diagnosed with salivary gland tumors in one area of California Controls: 191 men and women, identified by random-digit dialing, and from the Health Care Finance Administration Files; frequency-matched to cases by 5-yr age group and sex	Self-reported occupational exposure from telephone interviews.	Odds ratios and 95% CI were estimated using unconditional logistic regression analyses, controlling for age and sex. Odds Ratio (95% CI): 6.0 (1.6-22.0) for ever-exposed 3.7 (0.71-19.8) for lifetime exposure > 3,000 hr 9.0 (1.1-77.2) for lifetime exposure ≤ 3,000 hr	Age, sex	Exposure to Ni compounds & alloys associated with a substantial risk, evidence of a dose-response relation for cumulative hrs of exposure.	Horn-Ross et al. (1997)

adj. = adjusted; exp = expected; obsd = observed

4.0 EXPERIMENTAL CARCINOGENESIS

4.1 Studies Reviewed in IARC (1990)

IARC (1990) found sufficient evidence for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides, and crystalline nickel sulfides in experimental animals. Numerous studies confirm the carcinogenic potential of these compounds at various sites in rodents. IARC found limited evidence in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonides, nickel selenides, and nickel telluride. There was not adequate evidence for the carcinogenicity of nickel trioxide, amorphous nickel sulfide, and nickel titanate in experimental animals.

4.2 Animal Carcinogenicity Studies Post-IARC (1990)

4.2.1 NTP (1996) Studies of Nickel Oxide, Nickel Sulfate Hexahydrate, and Nickel Subsulfide

The National Toxicology Program (NTP) selected nickel oxide and nickel sulfate hexahydrate, compounds commonly found in the workplace in the United States, and nickel subsulfide, linked by an earlier study to lung cancer in rats, for chronic inhalation two-year studies in $B6C3F_1$ mice and F344/N rats (NTP, 1996a, b, and c).

Rats were exposed to nickel oxide concentrations of 0, 0.62, 1.25, or 2.5 mg/m^3 for six hours per day, five days per week for 104 week. Mice were exposed to nickel oxide concentrations of 0, 1.25, 2.5, or 5 mg/m^3 for six hours per day, five days per week for 104 weeks. The results indicated significantly ($p< 0.05$) increased rates of alveolar/bronchiolar adenoma or carcinoma (combined) for male and female rats in 1.25 and 2.5 mg/m^3 exposure groups. An increased incidence of benign pheochromocytoma of the adrenal medulla was observed in both sexes, but an increase in malignant pheochromocytomas was observed only in males. This study did not find that nickel oxide was carcinogenic in male mice, but found some evidence of carcinogenic activity in female mice based on increased incidence of alveolar/bronchiolar adenoma in the 2.5 mg/m^3 exposure group, and increased incidence of alveolar/bronchiolar adenoma or carcinoma in the 1.25 mg/m^3 exposure group.

Rats were exposed to nickel sulfate hexahydrate concentrations of 0, 0.12, 0.25, or 0.5 mg/m^3 for six hours per day, five days per week for 104 weeks. Mice were exposed to nickel sulfate hexahydrate concentrations of 0, 0.25, 0.5, or 1 mg/m^3 for six hours per day, five days per week for 104 weeks. Results did not indicate that nickel sulfate hexahydrate was carcinogenic in rats or mice.

Rats were exposed to nickel subsulfide concentrations of 0, 0.15, or 1 mg/m^3 for six hours, five days per week for 104 weeks. Mice were exposed to nickel subsulfide concentrations of 0, 0.6, or 1.2 mg/m^3 for six hours, five days per week for 105 weeks. Nickel subsulfide caused exposure-related increases in the incidence of alveolar/bronchiolar adenomas, alveolar/ bronchiolar carcinoma, alveolar/bronchiolar adenoma or carcinoma. In addition, benign and malignant pheochromocytomas of the adrenal medulla were significantly increased in male rats. With the exception of malignant pheochromocytomas, similar effects were seen in the female rats (NTP, 1996a, b, and c). Nickel subsulfide was not shown to be carcinogenic in mice.

4.2.2 Nickel Subsulfide

In a study of the effect of local inflammation on nickel subsulfide carcinogenesis in male F344/NCr rats, *Mycobacterium bovis* (MB) injected at the same injection site as nickel subsulfide inhibited localized tumor development (Kasprzak and Ward, 1991). The prevention of nickel sulfide tumors by local MB might result from the localization of numerous natural killer (NK) cells and macrophages and the formation of giant cells observed at the injection site of nickel subsulfide 1-14 days post injection. Presumably, enhanced macrophage activity would cause increased solubilization of the insoluble nickel subsulfide and thereby enhance tumor response. However, the results of the experiment showed that augmentation of the inflammatory response at the site of nickel subsulfide injection was followed by the nearly complete prevention of nickel-induced muscle tumor development (Kasprzak and Ward, 1991). Treatment with anti-inflammatory agents, which would hypothetically reduce solubilization of the nickel and thus reduce tumor formation, had no significant effect on nickel subsulfide tumor incidence, but actually shortened the latency of tumors as compared to treatment with nickel subsulfide alone.

In another investigation, magnesium basic carbonate (MgCarb) was an antagonist and metallic iron powder was a promoter of nickel carcinogenesis in rat kidney (Kasprzak et al., 1994). F344/NCr rats were injected in the renal cortex of each pole of the right kidney with either nickel subsulfide alone or with equimolar doses of MgCarb or metallic iron powder. The results showed that MgCarb inhibited and iron enhanced nickel carcinogenesis. Previous experimentation with the skeletal muscles of F344/NCr rats showed that both MgCarb and iron suppressed nickel subsulfide carcinogenicity, apparently by affecting local inflammatory/phagocytic response towards nickel subsulfide particles (Kasprzak et al., 1987; Kasprzak and Rodriguez, 1992; both cited by Kasprzak et al., 1994). Within the kidney, magnesium seemed to attenuate the uptake of nickel subsulfide by macrophages and tubular epithelial cells, as it did in skeletal muscle, while iron tended to enhance that uptake. No clear reason for the difference in activity of iron in the skeletal muscles versus the kidneys of rats was identified.

An investigation of the genetic factors involved in nickel carcinogenicity versus toxicity demonstrated a reverse order of susceptibility in three strains of male mice dosed with nickel subsulfide (Rodriguez et al., 1996). C57BL, C3H, and $B6C3F_1$ mice were injected with a single dose of nickel subsulfide at concentrations of 0, 0.5, 1.0, 2.5, 5.0, or 10.0 mg in the thigh muscle and observed for up to 78 weeks. The final incidence of local sarcomas in the 5 mg nickel subsulfide dose groups was C3H (97%)> $B6C3F_1$ (76%) > C57BL (40%). C3H mice developed more injection site tumors with a shorter latency period than mice of the other two strains. The results of this experiment suggest that the acute toxicity and carcinogenicity of nickel subsulfide and nickel subsulfide-derived soluble nickel(II) in mice depends on genetic background.

4.2.3 Nickel Acetate

Soluble nickel(II) acetate tetrahydrate was an effective initiator of renal cortical epithelial tumors at a dose of 90 μmol/kg body weight administered by single intraperitoneal (i.p.) injection to male F344/NCr rats at 5 weeks of age (Kasprzak et al., 1990). Renal cortical epithelial tumors

occurred after dosing with sodium barbital, a known renal tumor promoter. One rat given the nickel injection without the promoter developed a single renal cortical adenoma, while multiple tumors, some of which were metastatic to the lung, liver, and spleen, were common in rats given nickel and barbital. These results indicate that soluble nickel is an effective initiator of the carcinogenic process.

Diwan et al. (1992) investigated the transplacental carcinogenic effects of nickel(II) acetate in rats. Two groups of 24 F344/NCr rats were given nickel(II) acetate i.p. Group 1 received 90 μmol/kg body weight once a day on day 17 of gestation. Group 2 received 45 μmol/kg body weight/day twice on gestation days 16 and 18. Offspring were divided into four groups (1A, 1B, 2A, 2B). The A groups received tap water while the B groups received drinking water containing 500 ppm sodium barbital during weeks 4-85 of age. Malignant pituitary tumors occurred in rats given nickel(II) acetate with or without the barbital promoter, and pituitary tumor incidence was elevated in both sexes given nickel(II) acetate prenatally. These pituitary tumors induced with nickel were malignant, in marked contrast to the benign nature of most spontaneous pituitary tumors in rats. The male rats given nickel and barbital developed renal cortical epithelial and renal pelvic transitional epithelial tumors. No renal tumors occurred in female rats or in rats given nickel(II) acetate only. This study provided evidence that the soluble nickel compound, nickel acetate, is a potent transplacental initiator of epithelial tumors in the fetal rat kidney and a complete transplacental carcinogen for the rat pituitary.

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
NTP (1996) Studies						
Rat, F344/N, both sexes	Normal atmospheric conditions both sexes	Nickel subsulfide	0, 0.15, or 1 mg/m^3 by inhalation	6hr/day, 5 day/wk, 104 wk	The mortality rate of experimental rats was not significantly different from that of control rats. **Male:** Lung: alveolar/bronchiolar adenoma (0/53, 3/53, 6/53*); alveolar/bronchiolar carcinoma (0/53, 3/53, 7/53*); alveolar/bronchiolar adenoma or carcinoma (0/53, 6/53*, 11/53**) Adrenal Medulla: benign pheochromocytoma (13/53, 30/52**, 37/53**); malignant pheochromocytoma (0/53, 2/52, 11/53**); all pheochromocytoma (14/53, 30/52**, 42/53**) **Female:** Lung: alveolar/bronchiolar adenoma (2/53, 5/53, 5/53); alveolar/bronchiolar carcinoma (0/53, 0/53, 4/53); alveolar/bronchiolar adenoma or carcinoma (2/53, 5/53, 9/53*) Adrenal Medulla: benign pheochromocytoma (2/53, 7/53, 36/53**); benign or malignant pheochromocytoma (3/53, 7/53, 36/53**) *p<0.05 vs. controls; **p<0.01	NTP (1996b)
Mice, $B6C3F_1$, both sexes	Normal atmospheric conditions both sexes	Nickel subsulfide	0, 0.6, or 1.2 mg/m^3 by inhalation	6 h/day, 5 day/wk, 105 wk	The mortality rate of experimental mice was not significantly different from that of control mice. There were no neoplastic effects in experimental groups of 60 male or 60 female mice.	NTP (1996b)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
Rats, F344/N, both sexes	Normal atmospheric conditions both sexes	Nickel oxide	0, 0.62, 1.25, or 2.5 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental rats was not significantly different from that of control rats. **Male:** Lung: alveolar/bronchiolar adenoma (0/54, 1/53, 3/53, 2/52); alveolar/bronchiolar carcinoma (0/54, 0/53, 3/53, 2/52); alveolar/bronchiolar adenoma or carcinoma (0/54, 1/53, 6/53*, 4/52*); Adrenal medulla: benign pheochromocytoma (27/54, 24/52, 26/53, 32/52); malignant pheochromocytoma (0/54, 0/52, 1/53, 6/52*); benign or malignant pheochromocytoma (27/54, 24/52, 27/53, 35/52*) **Female:** Lung: alveolar/bronchiolar adenoma (1/53, 0/53, 1/53, 4/54); alveolar/bronchiolar carcinoma (0/53, 0/53, 5/53*, 1/54); alveolar/bronchiolar adenoma or carcinoma (1/53, 0/53, 6/53, 5/54) Adrenal medulla: benign pheochromocytoma (4/51, 7/52, 6/53, 18/53**) *p<0.05 vs. controls; **p<0.01	NTP (1996a)
Mice, B6C3F$_1$, both sexes	Normal atmospheric conditions both sexes	Nickel oxide	0, 1.25, 2.5, or 5 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental mice was not significantly different from that of control mice. **Male**: No neoplastic effects. **Female**: (Uncertain Findings) Lung: alveolar/bronchiolar adenoma (2/64, 4/66, 10/63*, 3/64); alveolar/bronchiolar carcinoma (4/64, 11/66, 4/63, 5/64); alveolar/bronchiolar adenoma or carcinoma (6/64, 15/66*, 12/63, 8/64) *p<0.05 vs. controls	NTP (1996a)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first)	Reference
Rats, F344/N, both sexes	Normal atmospheric conditions both sexes	Nickel sulfate hexahydrate	0, 0.12, 0.25, 0.5 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental rats was not significantly different from that of control rats. There were no neoplastic effects in experimental groups of 53-55 male or female rats.	NTP (1996c)
Mice, B6C3F$_1$, both sexes	Normal atmospheric conditions both sexes	Nickel sulfate hexahydrate	0, 0.25, 0.5, or 1 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental mice was not significantly different from that of control mice. There were no neoplastic effects in experimental groups of 60-62 male or female mice.	NTP (1996c)
Nickel subsulfide						
Mice, CH3, male Mice, B6C3F1, male Mice, C57BL, male	Injection vehicle alone	Nickel subsulfide	0, 0.5, 1.0, 2.5, 5.0, or 10.0 mg/site injected into the thigh musculature of both hind limbs	Single dose at age 6 to 8 wk and observed for 78 wk.	The mortality rate of C3H and B6C3F$_1$ mice injected with 5 mg/site and over was greater than that of control mice as was the mortality rate of C57BL mice at any dose of nickel subsulfide. **C3H:** Injection site sarcomas: 0/30, 5/30, 10/30, 20/27, 28/29, 14/14, respectively **B6C3F1:** Injection site sarcomas: 0/30, 2/29, 8/30, 15/30, 16/20, 5/6, respectively **C57BL:** Injection site sarcomas: 0/24, 1/27, 4/28, 6/21, 6/15, 0/2, respectively	Rodriguez et al. (1996)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form and Dose, Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
Rats, F344/NCr, male	1) 0.1 mL water 2) 0.5 mg *Mycobacterium Bovis* antigen (MB) 3) 1.0 mg cortisol 4) 1.0 mg indomethacin	**Group 1**: 2.5 mg Ni_3S_2 i.m. injection alone **Group 2**: 2.5 mg Ni_3S_2 + 0.5 mg MB i.m. injection **Group 3**: 2.5 mg Ni_3S_2 + 1.0 mg cortisol i.m. injection **Group 4**: 2.5 mg Ni_3S_2 + 1.0 mg indomethacin i.m. injection **Group 5**: 2.5 mg Ni_3S_2 i.m. injection + 1.0 mg MB sc. injection **Group 6**: 2.5 mg Ni_3S_2 i.m. injection + 2.0 mg indomethacin s.c. injection	Single injection at 8 wk of age and obsderved for up to 71 wk	The mortality rate of experimental rats was not significantly different from that of control rats. **Group 1:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 17/20) **Group 2:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 1/20) **Group 3:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 17/20) **Group 4:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 16/20) **Group 5:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 20/20) **Group 6:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 19/20)	Kasprzak and Ward (1991)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
Rats, F344/NCr, male	6.2 mg MgCarb (n = 20), 3.4 mg Fe^0 (n = 20), 0.1 mL water inj. vehicle (n = 20)	5 mg Ni_3S_2 (Group 1, n = 40) 5 mg Ni_3S_2 + 6.2 mg MgCarb (Group 2, n = 20) 5 mg Ni_3S_2 + 3.4 mg Fe^0 (Group 3, n = 20)	2 intrarenal injections	Observation began 24 wk post injection and lasted until week 109	The mortality rate of experimental rats was not significantly different from that of control rats. **Group 1:** Cumulative number of rats with renal tumors: (0/20, 0/20, 0/20, 25/40) **Group 2:** Cumulative number of rats with renal tumors: (0/20, 0/20, 0/20, 4/20) **Group 3:** Cumulative number of rats with renal tumors: (0/20, 0/20, 0/20, 12/20) First 3 incidences in parentheses are control groups	Kasprzak et al. (1994)
Nickel acetate						
Rats, F344/NCr, male (n = 23, 24)	Saline (n = 24)	Nickel acetate tetrahydrate (NiAcet), or NiAcet followed by sodium barbital (NaBB)	NiAcet = 90 µmol/ kg body weight, i.p. NaBB; 500 ppm in drinking water	Single injection at 5 wk of age, or single injection at 5 wk of age + exposure to NaBB through drinking water 2 wk later. Survivors sacrificed at 101 wk of age.	Mortality was significantly greater in rats given NaBB following NiAcet injection than in rats given only NiAcet. **NiAcet only:** Renal cortical lesions: Adenomas (0/24, 1/23), carcinomas (0/24, 0/23) Renal pelvic tumors: Papillomas (0/24, 0/23), carcinomas (0/24, 0/23) **NiAcet + NaBB:** Renal cortical tumors: Adenomas (0/24, 13/24*), carcinomas (0/24, 4/24) *$p<0.0002$ compared to NiAcet-only rats Renal pelvic tumors: Papillomas (0/24, 8/24), carcinomas (0/24, 0/24)	Kasprzak et al. (1990)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Chemical Form	Dose, Route	Exposure Duration	Results/Comments (Control group incidence listed first)	Reference
Rats, F344/NCr, sex n.p.	Nickel acetate (NiAcet) in distilled water Sodium barbital (NaBB)	**Group 1:** pregnant rats given NiAcet 90 µmol/kg i.p.; offspring divided into groups given tap water as drinking water (**Group 1A**) or 0.05% NaBB in drinking water (**Group 1B**) **Group 2**: pregnant rats given NiAcet 45 µmol/kg i.p.; offspring divided into groups given tap water as drinking water (**Group 2A**) or 0.05% NaBB in drinking water (**Group 2B**) control group given sodium acetate	**Group 1:** pregnant rats treated once/day on day 17 of gestation **Group 2:** pregnant rats treated twice on days 16 and 18 of gestation male and female offspring observed until age 85 wk	Neoplastic lesions in offspring: **Group 1A males**: total renal tumors (0/15, 0/17) total pituitary tumors (1/15, 9/17[a]) **Group 1B males:** total renal tumors (1/15, 8/15*) total pituitary tumors (2/15, 6/15) **Group 1A females:** total renal tumors (0/16, 0/16) total pituitary tumors (3/16, 5/16[a]) **Group 1B females:** total renal tumors (0/14, 0/15) total pituitary tumors (4/14, 5/15) **Group 2A males**: total renal tumors (0/15, 0/15) total pituitary tumors (1/15, 6/15[b]) **Group 2B males:** total renal tumors (1/15, 7/15*) total pituitary tumors (2/15, 7/15) **Group 2A females:** total renal tumors (0/16, 0/16) total pituitary tumors (3/16, 8/16[b]) **Group 2B females:** total renal tumors (0/14, 0/15) total pituitary tumors (4/14, 6/15) *p<0.01 vs. controls [a] p=0.012 vs. controls; both sexes combined b p=0.008 vs. controls; both sexes combined	Diwan et al. (1992)

5.0 GENOTOXICITY

5.1 Review of Animal Genotoxicity Studies (IARC, 1990)

IARC (1990) reviewed data on the genotoxic effects of nickel compounds. The summary of results for studies in mammalian systems is presented as follows: metallic nickel; nickel oxides and hydroxides; crystalline nickel sulfide and subsulfide, amorphous nickel sulfide; nickel chloride, nickel sulfate, nickel acetate, nickel nitrate; and, nickel carbonate, nickel subselenide, nickel potassium cyanide, and nickelocene.

5.1.1 Metallic Nickel

Nickel powder induced a dose-dependent increase in morphological transformations of Syrian hamster embryo cells *in vitro* (Costa et al., 1981).

5.1.2 Nickel Oxides and Hydroxides

The cell-transforming activity of nickel monoxide was correlated with its ability to induce preneoplastic changes in rats (Sunderman et al., 1987). Nickel trioxide transformed Syrian hamster embryo cells at twice the rate of nickel monoxide (Costa et al., 1981).

5.1.3 Crystalline Nickel Sulfide, Crystalline Nickel Subsulfide, and Amorphous Nickel Sulfide

In cultured Chinese hamster ovary cells, DNA repair (Robison et al.,1983), single-strand breaks (Robison and Costa, 1982), a dose-dependent increase in SCE, and a dose- and time-dependent increase in the frequency of chromosomal aberrations (Sen and Costa; 1985,1986) occurred after treatment with crystalline nickel sulfide. Crystalline nickel sulfide induced chromosomal aberrations, including gaps, breaks, and exchanges, in Chinese hamster ovary cells (Nishimura and Umeda, 1979; Umeda and Nishimura, 1979). Crystalline nickel sulfide induced DNA strand breaks in rat primary hepatocytes (Sina et al., 1983). Single-strand breaks and DNA protein cross-links were the two main lesions induced by crystalline nickel sulfide (Costa et al.,1982; Patierno and Costa, 1985).

Particulate crystalline nickel subsulfide induced resistance to 8-azaguanine in cultured rat liver cells, but neither particulate nor dissolved nickel subsulfide induced unscheduled DNA synthesis in primary rat hepatocytes (Swierenga and Mclean, 1985). Crystalline nickel subsulfide induced a dose-dependent increase in the frequency of morphological transformations in primary Syrian hamster embryo cells (DiPaolo and Casto, 1979). Robison et al. (1982, 1983) showed that crystalline nickel subsulfide induced strand breaks in hamster embryo cells, but amorphous nickel sulfide, which is not phagocytized by cells, had no effect on Syrian or Chinese hamster embryo cells. Crystalline nickel subsulfide and amorphous nickel sulfide induced a weak mutation response at the *hprt* locus in Chinese hamster ovary cells (Costa et al., 1980). Amorphous nickel sulfide had no effect on Chinese hamster ovary cells or Syrian hamster embryo cells (Robison et al., 1983).

5.1.4 Nickel Chloride, Nickel Sulfate, Nickel Acetate, and Nickel Nitrate

In Chinese hamster ovary cells, nickel chloride increased the frequency of strand breaks (Robison and Costa, 1982), SCE, and chromosomal aberrations (Sen and Costa, 1985, 1986; Sen

et al., 1987), and induced single-strand breaks, DNA-protein cross-links (Patierno and Costa, 1985), and DNA repair synthesis (Robison et al. 1983, 1984). Nickel chloride also induced chromosomal aberrations (Larramendy et al.,1981) and morphological transformations (Pienta et al., 1977; DiPaolo and Casto, 1979) in Syrian hamster embryo cells. Nickel chloride increased the frequency of chromosomal aberrations in bone-marrow cells of Chinese hamsters (Chorvatovicová, 1983) and Swiss mice (Mohanty, 1987).

In Chinese hamster V79 cells, nickel chloride induced 8-azaguanine-resistant mutations (Miyaki et al., 1979), a dose-related increase in the frequency of mutation to 6-thioguanine resistance (Hartwigg and Beyersmann, 1989), and a dose-dependent depression of proliferation and mitotic rate (Skreb and Fischer, 1984). It did not induce polychromatic erythrocytes or dominant lethal mutations in BALB/c mice (Deknudt and Léonard, 1982). Nickel chloride inhibited DNA synthesis in embryo cells (Basrur and Gilman, 1967) and liver epithelial cells (Swierenga and McLean, 1985) of rats.

Nickel sulfate caused an increased frequency of SCE in Chinese hamster Don cells (Ohno et al., 1982), Chinese hamster ovary cells (Deng and Ou, 1982), and in Syrian hamster embryo cells (Larramendy et al., 1981) Nickel sulfate hexhydrate induced a concentration-dependent increase in morphological transformation of Syrian hamster cells (Pienta et al., 1977; DiPaolo and Casto, 1979; Zhang and Barrett, 1988). Increased frequencies of chromosomal aberrations were seen in Syrian hamster embryo cells exposed to nickel sulfate hexahydrate (Larramendy et al., 1981). The frequency of chromosomal aberrations was not increased in bone-marrow cells and spermatogonia of male albino rats after intraperitoneal injections of nickel sulfate (Mathur et al., 1978).

5.1.5 Nickel Carbonate, Nickelocene, Nickel Potassium Cyanide, and Nickel Subselenide

Nickel carbonate induced DNA damage in rat kidney cells *in vivo* (Ciccarelli et al., 1981). Crystalline nickel subselenide transformed cultured primary Syrian hamster embryo cells (Costa et al., 1981; Costa and Mallenhauer, 1980), and nickel potassium cyanide increased the frequency of chromosomal aberrations in mouse mammary carcinoma cells (Nishimura and Umeda, 1979; Umeda and Nishimura, 1979). Bacterial gene mutations were not induced by nickelocene (Haworth et al., 1983). Nickel (II) and nickel (III) tetraglycine complexes induced DNA damage in calf thymus nucleohistone (Kasprzak and Bare, 1989).

5.2 Review of Human Genotoxicity Studies (IARC, 1990)

5.2.1 Metallic Nickel

Nickel powder did not induce chromosomal aberrations in cultured human peripheral lymphocytes (Paton and Allison, 1972).

5.2.2 Nickel Oxides and Hydroxides

Nickel monoxide did not induce chromosomal aberrations in cultured human peripheral lymphocytes (Paton and Allison, 1972), but did induce anchorage-independent growth in primary human diploid foreskin fibroblasts (Biedermann and Landolph, 1987).

5.2.3 Nickel Sulfides

Crystalline nickel subsulfide and amorphous nickel sulfide increased the frequency of SCE in cultured human lymphocytes (Saxholm et al., 1981), and induced anchorage-independent growth in human skin fibroblasts (Biedermann and Landolph, 1987).

5.2.4 Nickel Sulfate and Nickel Chloride

Dose-dependent increases in the frequency of SCE were seen in human blood peripheral lymphocytes exposed to nickel sulfate (Larramendy et al., 1981). Nickel sulfate did not induce DNA single-strand breaks in human fibroblasts (Fornace, 1982). Nickel sulfate reduced average chromosomal length in human lymphocytes (Andersen, 1985), transformed normal human bronchial epithelial cells (Lechner et al., 1984), and induced transformation to anchorage-dependent growth of primary human foreskin fibroblasts (Biedermann and Landolph, 1987). Human fetal kidney cortex explants did not become tumorigenic after 70-100 days of exposure to nickel sulfate (Tveito et al., 1989). In two human cell lines, exposure to nickel chloride *in vitro* resulted in a dose-dependent depression of proliferation and mitotic rate (Skreb and Fischer, 1984).

5.2.5 Mixed Exposures

A study of two groups of nickel refinery workers employed at the same Norwegian plant showed no increase in the frequency of SCE in mitogen-stimulated peripheral blood lymphocytes of workers exposed to nickel compounds during processing operations, though there was a statistically significant ($p<0.003$) increase in chromosomal aberrations in comparison to controls (Waksvik and Boysen, 1982). In the first group, nine workers who had similar nickel exposures (average air concentration of 0.5 mg Ni/m^3) for an average of 21.2 years showed an increased frequency of gaps (11.9%) compared to a control group of unexposed workers (3.7%). In the second group, 11 workers who had similar nickel exposures (average air concentration of 0.2 mg/m^3) for an average of 25.2 years also showed an increased frequency of gaps (18.3%) as compared to the control group (Waksvik and Boysen, 1982). Breaks in the two groups did not differ significantly from controls and the difference in the percentage of gaps between the nickel-exposed workers was not statistically significant.

In a study of retired nickel workers who had been employed at the same plant as the workers in the studies described above, an increased frequency of gaps (7.6%, $p<0.05$) and breaks (4.1%, $p<0.001$) was detected in comparison to controls (5.3%, 0.5%, respectively). These workers had been exposed to an air nickel concentration higher than 1.0 mg/m^3 for more than 25 years (Waksvik et al., 1984).

An increased frequency of chromosomal gaps, breaks, and fragments (4.3% versus 0.8% in controls) was observed in a study of seven electroplating workers exposed to nickel and chromium compounds (Deng et al., 1983, 1988). These workers were exposed to an air nickel

concentration of 0.0053-0.094 mg/m^3 for 2-27 years. The Working Group noted a small increase in the frequency of SCE in exposed workers.

5.3 Animal Genotoxicity Studies Published Post-IARC (1990)

[Excludes (with the exception of Higinbotham et al., 1992) those studies reviewed by NTP (1996)]

In calf thymus DNA, Ni^{2+} was effective in causing 8-hydroxy-2'-deoxyguanosine (8-OH-dG) formation and double-strand DNA breaks. A mechanism of 8-OH-dG formation was suggested by the involvement of free radicals in this formation, and inhibition by chelating agents (Shi et al., 1995).

In another study of DNA base damage, male F344/NCr rats were injected i.p. with 90 mmoles Ni(II) acetate tetrahydrate/kg body weight. The results indicated a tissue-specific response to Ni(II)-mediated oxidative DNA base damage, with apparently greater lesion persistence in the kidney than in the liver, consistent with the kidney as a primary target of Ni(II) carcinogenicity from soluble salts (Kasprzak et al., 1997). In rat kidney, the frequency of transforming mutations in the K-*ras* oncogene induced by an injection of nickel subsulfide was increased by coadministration of iron (Higinbotham et al., 1992). These findings are consistent with the known ability of nickel, in the presence of an oxidizing agent, to catalyze formation of 8-OH-dG, which leads to misincorporation of dATP opposite the oxidized guanine residue.

DNA damage (single-strand breaks) was not seen in cultured lung, liver, or kidney cells of rats administered 44.4 mg nickel chloride/kg s.c., either alone or in combination with cadmium chloride administered i.p. just prior to treatment with nickel chloride (Saplakoglu et al., 1997).

5.4 Human Genotoxicity Studies Published Post-IARC (1990)

Kiilunen et al. (1997) found that the frequency of micronucleated epithelial cells in the buccal mucosa of nickel refinery workers in the Helsinki area was not significantly elevated versus controls. Furthermore, there was no correlation between micronucleus frequencies and levels of nickel in the air in the refinery, or in the urine or blood of refinery workers.

Gennart et al. (1993), in an investigation of 24 male workers occupationally exposed for at least two years to varying concentrations of iron, nickel, chromium, and cobalt metal powders, found the mean SCE score of the group to be significantly increased versus the control group (23 male clerical workers matched for age, smoking habits, and alcohol consumption). Nine exposed workers had a mean score above the highest score observed in the controls. Since studies on cobalt have shown the metal to be weakly mutagenic, the investigators concluded that solubilized nickel (and chromium) probably induced the increase in SCE.

5.5 Cogenotoxicity

The details of this study (Lynn et al., 1994) are presented in Table 5-2. The genotoxic effects of nickel chloride were investigated in the presence and absence of UV light, methyl methane sulfonate (MMS), and buthionine sulfoxamine (BSO). Results indicate that UV-induced cyto- and genotoxicity is enhanced by the presence of nickel which may be due to its inhibition of DNA repair.

Table 5-1. Genotoxicity of Nickel Studies Published Post-IARC (1990)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
5.1.1 *Acellular Systems*							
Calf thymus DNA	Liberation of 8-hydroxy-2'-deoxyguanosine (8-OH-dG). Detection via HPLC.	-	$NiCl_2$	Incubation of 1 mM Ni^{2+}, 0.75 mM dG (purified from residues in calf thymus DNA), 10 mM *t*-butyl hydroperoxide, and 2 mM glutathione (GSH)	positive	Generation of 8-OH-dG (approx. 0.2% yield). Ni^{2+} is capable of causing 8-OH-dG and DNA double-strand breaks. Lipid peroxide free radicals are involved in the mechanism of 8-OH-dG formation. Chelating agents inhibit 8-OH-dG formation.	Shi et al. (1995)

Table 5-1. Genotoxicity of Nickel Studies Published Post-IARC (1990) (Continued)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
5.1.2 *In Vivo Mammalian Systems*							
Male F344/NCr rats (5 wk old) 48 animals	DNA damage in renal and hepatic chromatin	n.p.	Ni(II) acetate tetrahydrate (purity n.p.)	Treatment group: 90 µmol Ni(II) acetate/kg injected i.p. Control group: 180 µmol sodium acetate/kg injected i.p.	positive	Rats sacrificed at 12 hr and 1, 3, 7, and 14 days post-treatment. Ni(II) acetate-induced oxidative DNA base damage detected in the kidneys and livers. Lesions showed a greater persistence in the kidney than in the liver, consistent with the kidney as a major target of carcinogenesis from soluble nickel salts.	Kasprzak et al. (1997)
Male albino rats (local strain, 8-12 wk old); no. of animals n.p.	DNA damage (single-strand breaks) in rat lung, liver and kidney	n.p.	$CdCl_2$ or $NiCl_2$ (purity n.p.)	Treatment group: $CdCl_2$: 4 mg/kg bw, injected i.p. $NiCl_2$: 44.4 mg/kg bw, injected s.c.	$NiCl_2$: negative	No single-strand breaks were evident in $NiCl_2$-treated tissues, alone or in combination with prior administration of $CdCl_2$.	Saplakoglu et al. (1997)

Table 5-1. Genotoxicity of Nickel Studies Published Post-IARC (1990) (Continued)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
Male Fischer F344/NCr rats (6 wk old) 100 animals	mutational activation of K-*ras* in rat kidney	n.p.	Ni_3S_2; Ni_3S_2/Fe^0; Fe^0 (purity n.p.); 50% aqueous glycerol	all groups injected intrarenally Treatment Group 1: 10 mg of Ni_3S_2 injected intrarenally. Treatment Group 2: Ni_3S_2/Fe^0 [equimolar amounts of nickel and iron (3.4 mg of Fe^0)] Control Group 1: Fe^0 alone Control Group 2: 0.1 mL of 50% aqueous glycerol	positive	The frequency of transforming mutations in the K-*ras* oncogene induced by nickel was increased in the presence of iron. These findings are consistent with the known ability of nickel, in conjunction with an oxidizing agent, to catalyze formation of 8-OH-dG, which leads to misincorporation of dATP opposite the oxidized guanine residue.	Higinbotham et al. (1992)

Abbreviations: i.p. = intraperitoneally; n.p. = not provided; s.c. = subcutaneously

Table 5-2. Cogenotoxicity of Nickel Studies Published Post-IARC (1990)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
Chinese Hamster Ovary Cells (CHO-K1)	Measurement of cellular GSH levels; colony forming efficiency, frequencies of SCE, and cell cycle progression; repair synthesis of supercoiled plasmid DNA; joining of oligo(dT) molecules by H-bonding to poly (dA) or poly (rA)	n.p.	$NiCl_2$, Ultraviolet (UV) light, methyl methane-sulfonate (MMS), buthionine sulfoxime (BSO)	CHO cells treated with: (1) 0.8 mM MMS (1 hr), then incubated for various times. (2) 0.2 mM MMS alone (20 hr) (3) 4 mM $NiCl_2$ alone (20 hr) (4) UV (24 hr) (5) 0.2 mM MMS (1 hr), followed by 4 mM $NiCl_2$ +500 μM BSO (4 hr) (6) 0.2 mM MMS (1 hr), followed by 4 mM $NiCl_2$ (4 hr) (7) 0.2 mM MMS (1 hr), followed by various doses of $NiCl_2$ (0-4 mM, 4 hr) (8) 6 J/m^2 UV light (irradiation time n.p.), followed by 4 mM $NiCl_2$ (4 hr)	positive	Cellular GSH increased by treatment with MMS or $NiCl_2$, but not UV. Post treatment with $NiCl_2$ synergistically increased GSH levels in MMS-treated cells, but not with UV-treated cells. Pretreatment with *N*-acetylcysteine (GSH precursor) increased clonogenic survival of cells treated with UV + nickel. Nickel inhibited oligonucleotide ligation repair syntheses of UV- or MMS-treated plasmids. GSH relieves nickel inhibition. Results indicate that UV-induced cyto- and geno-toxicity is enhanced by the presence of nickel, which may be due to its inhibition of DNA repair.	Lynn et al. (1994)

Abbreviation: n.p. = not provided

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, and Excretion in Experimental Animals

Various animal models for nickel absorption and biokinetics have been studied. Studies of rats reported that nickel chloride was excreted primarily in the urine, while the oxide was eliminated equally in urine and feces (English, 1981; Carvalho and Zeimer, 1982; cited by IARC, 1990). A biphasic pulmonary clearance (1-2 hours for the first and 120-300 hours for the second) was reported after intratracheal instillation of nickel subsulfide in mice (Valentine and Fisher, 1984; Finch et al., 1987; cited by IARC, 1990).

Half lives of 1-3 days for nickel sulfate, 5 days for nickel subsulfide, and more than 100 days for nickel oxide have been reported for inhaled or intratracheally instilled nickel compounds (Benson et al., 1987; Dunnick et al., 1989; cited by NTP, 1996). Also, in chronic exposure studies with rats and mice, nickel sulfate had the shortest half-life, followed by nickel subsulfide, and nickel oxide. Oral administration resulted in 1-10% absorption of the dose in mice, rats, and dogs. An absorption rate of 1% (in 24 hours) through guinea pig skin was reported (ATSDR, 1992; Neilson et al., 1993; cited by NTP, 1996a, b, and, c).

6.2 Toxicokinetics of Nickel in Humans

The primary routes for nickel exposure are dietary ingestion, dermal absorption, and inhalation. Inhalation is the most serious toxicological exposure concern in the workplace, followed by dermal exposure (NiDI, 1997). Almost 35% of inhaled nickel is absorbed into the blood from the respiratory tract (Bennet, 1984; Grandjean, 1984; Sunderman and Oskarsson, 1991; cited by NTP, 1996). The disposition, absorption, and elimination of nickel particles in the respiratory tract depend largely on particle size and concentration of nickel, minute volume of the individual, mode of breathing (nasal or oronasal), the use of personal protective equipment, personal hygiene, and the work process, among other factors. Additionally, not all particles are inhalable; humans only inhale about half of the particles larger than 30 μm, and this efficiency may be even less for particles of 100-200 μm. Of the inhaled particles, a small percent which are less than 10 μm (most of which are less than 4 μm), settle to the lower regions of the lung. Once inhaled, the particle solubility, concentration, and surface area all play a role in the amount of time required to absorb and excrete associated metals. Smaller, more soluble particles are more rapidly absorbed and excreted because of an increased surface area to volume (NiDI, 1997).

For dermal absorption, penetration through the skin is primarily dictated by the rate at which nickel can pass through the epidermis, with different species of nickel penetrating at markedly different rates. For example, nickel chloride has been shown to penetrate in amounts ranging from 0.23-3.5% of the applied dose, while nickel sulfate may penetrate at levels of up to 50 times lower (NiDI, 1997).

Excretion of systemically absorbed nickel is mainly through the urine. Human volunteers absorbed 25% of an oral dose of nickel sulfate when it was administered in water, as opposed to only 1% administered by food. Half-life values were around 28 hours. Within 4 days, 100% had been recovered in either urine or as unabsorbed nickel in the stool. Nickel may also be eliminated via sweat, the hair, or human breast milk (NiDI, 1997).

6.3 Biokinetics and Evidence of Exposure in Nickel Workers

The ability to predict exposure and related health risks varies depending upon the nickel species evaluated. Nickel compounds lose their original chemical identity upon entering the blood, making it difficult to identify the original source of exposure (Grant and Mushak, 1989). In blood and urine, soluble nickel compounds and nickel metal powder are more easily measured than less soluble nickel compounds (Sunderman et al., 1986). Nickel refinery workers excreted nickel in their urine for up to 6 months after ceasing to work at the plant (Morgan and Rouge, 1983; cited by NTP, 1996). Post-mortem studies of nickel workers show nickel disposition at the highest levels in the lungs, thyroid, and adrenal glands with lesser concentrations in the kidney, liver, heart, spleen, and other tissues (NiDI, 1997).

Nickel has a half-life ranging from 30 to 53 hours in urine for workers exposed to insoluble nickel particles of small diameter (Raithel et al 1982). Some studies have suggested that for workers exposed to insoluble nickel of large particle size, urinary nickel has a longer half-life ranging from months to years (Torjussen and Andersen, 1979; Boysen et al., 1984; Morgan and Rouge, 1984). Reported levels of urinary nickel range from approximately 0.2 to 10 μg Ni/L in non-exposed individuals (Sunderman et al, 1986). In one study (Bernacki et al., 1978), higher urinary concentrations were seen in workers exposed to soluble nickel compounds. The highest value was 813 μg Ni/L reported in a group of electrolytic refinery workers. Mean urinary nickel values ranged from 2.6 μg Ni/L in high nickel alloy production workers to 222 μg Ni/L in electrolytic refinery workers.

The reported half-life of nickel in serum is similar to that in urine. Tossavainen et al. (1980) reported values ranging from 20 to 34 hours in workers exposed to soluble nickel compounds by inhalation. In human volunteers exposed orally to soluble nickel sulfate hexahydrate, a half-life of 11 hours was observed (Christensen and Lagesson, 1981). Nickel concentrations in the serum of nonexposed individuals range from 0.05 to 1.1 μg Ni/L (Sunderman et al., 1986).

7.0 MECHANISMS OF CARCINOGENESIS

The genotoxic effects demonstrated in tests of soluble nickel compounds in a variety of systems suggest that ionic nickel may be the carcinogenic species. In human cells, nickel sulfate increased chromosomal aberrations, and both nickel sulfate and nickel chloride increased the frequencies of SCE. In an assay of calf thymus DNA, nickel chloride induced formation of 8-OH-dG (8-hydroxy-2'-deoxyguanosine) and double-strand DNA breaks (section 5).

Oxidative DNA base damage occurred in the kidneys and liver of male rats treated with Ni(II) acetate. Nickel chloride and nickel nitrate were inactive in assays for induction of dominant lethal mutations and micronuclei. Nickel sulfate did not induce chromosomal aberrations in bone marrow cells, but nickel chloride induced chromosomal aberrations in Chinese hamster and mouse bone marrow cells (section 5).

Animal bioassays indicate that ionic nickel initiates carcinogenesis (section 4). Brief transplacental exposure to soluble nickel was a complete carcinogen in the pituitary gland, inducing malignant neoplasms without additional treatments. Malignant pituitary tumors are rare and their occurrence serves to emphasize the carcinogenic potential of soluble nickel compounds. Renal neoplasms were identified in male rats given nickel acetate by i.p. injection followed by sodium barbital in drinking water. In another study, sodium barbital promoted neoplastic lesions in the offspring of rats exposed to nickel.

Many studies have focused on the mechanism(s) underlying the toxicity of nickel compounds. A 1997 investigation (Oller et al., 1997) concluded that nickel subsulfide is probably carcinogenic to man, but not nickel sulfate hexahydrate. Green nickel oxide may only be toxic at very high doses. The toxicity of these compounds may depend largely on the ability of the compounds to be incorporated into the cell (i.e., solubility); genetic propensity for tumor induction is also a factor.

This idea was recently expanded by Costa (1998) in a model for an epigenetic mechanism of action of non-genotoxic carcinogens. Studies have suggested that water insoluble crystalline nickel compounds were responsible for a high incidence of lung and nasal cancers seen in human and animal studies (IARC, 1990). However, since not all water-insoluble crystalline nickel salts could be shown to induce tumors, it was assumed that factors other than water solubility were involved. Tumor induction was thought to be related to the ability of the compound to enter the cell, or by the ability of the cell to incorporate the compound (i.e., phagocytosis). However, Kasprzak and Ward (1991) found that stimulated phagocytes, rather than enhancing carcinogenic response, actually strongly inhibited muscle tumor development in rats injected with nickel subsulfide.

An investigation with Syrian hamster embryo cells (Costa, 1980) showed that cells undergoing transformation selectively phagocytized the negatively charged crystalline nickel sulfide compounds over positively charged amorphous nickel sulfide particles. However, when a negative charge was induced on the amorphous nickel sulfide particles, they too were phagocytized and were able to exhibit transformation potency equivalent to that of the crystalline nickel sulfide particles (Costa, 1980). Once inside the cell, the compound particles dissolve in the intracellular space, a process which is enhanced by the acidic pH of the cytoplasm surrounding the particles. Thus, transformation appeared to be directly related to the ability of the compound to enter the cell and increase intracellular soluble nickel concentrations (Costa, 1991). However, enhanced phagocytosis actually reduces carcinogenic response of insoluble nickel compounds *in vivo* (Kasprzak and Ward, 1991).

Costa's model is based upon the known ability of carcinogenic nickel compounds to enhance DNA chromatin condensation (Costa, 1991; cited by Costa, 1995; Huang et al., 1994). Although oxygen free radicals may be produced, a high incidence of genetic mutations are not generally noted since most of the damage done by the soluble nickel is to genetically inactivate heterochromatic DNA (Sen et al., 1985; 1986, cited by Costa, 1995). Subsequent methylation of this DNA may suppress genetic activities that are essential for normal cell maintenance. In this model, nickel selectively interacts with heterochromatin and binds to histone H1 and core histone, making them more efficient. Nickel then binds in place of Mg^{2+}, increasing the chromatin

condensation state. This causes neighboring euchromatin to be converted to heterochromatin. The intracellular methylation system recognizes the newly formed, more condensed chromatin. The DNA incorporated into heterochromatin is now methylated, and the DNA methylation pattern is inherited in all daughter cells. DNA found in heterochromatin is hypermethylated to direct protein binding for increased condensation (Costa, 1995).

Because water-soluble nickel salts are not taken up into cells as readily as the particulate compounds previously discussed, they tend to be less toxic in animal models (Costa, 1991; cited by Costa, 1995). However, studies by Kasprzak et al. (1990) also showed that soluble nickel acetate, when administered with the promoter sodium barbital, initiated malignant renal cortical epithelial tumors in Fischer rats. Diwan et al. (1992) showed that soluble nickel acetate was a complete transplacental carcinogen that induced malignant pituitary tumors in rats. Furthermore, in combination with the promoter, the soluble nickel salt was found to be a potent transplacental initiator of epithelial tumors in fetal rat kidney (Diwan et al., 1992). These studies clearly indicate the carcinogenic potential of soluble forms of nickel at sites distant from the site of application and indicate macrophage solubilization is not required for carcinogenesis to occur with nickel.

The other widely proposed mechanism of nickel carcinogenesis is that damage to DNA occurs indirectly through reactive oxygen species (ROS) that are generated in response to the compound. This could occur through phagocytosis of crystalline nickel compounds (Zhong et al., 1990; Lin et al., 1991; both cited by McCoy and Kenney, 1992) allowing ROS-mediated genetic damage to take place (McCoy and Kenney, 1992). However, soluble forms of nickel can also induce lesions *in vivo* or *in vitro* in DNA that are indicative of ROS attack. This proposal is supported by evidence that the antioxidant vitamin E inhibits some chromosomal damage caused by nickel (Lin et al., 1991; cited by McCoy and Kenney, 1992).

Overall, it appears that the ionic form of nickel is the ultimate carcinogenic species, and biokinetic factors may dictate the carcinogenic potential of the various soluble or insoluble nickel compounds.

8.0 References

Aldrich. 1998. Catalog Handbook of Fine Chemicals. Sigma-Aldrich Fine Chemicals. St. Louis, MO.

Andersen, O. 1983. Effects of coal combustion products and metal compounds on sister chromatic exchange (SCE) in a macrophagelike cell line. Environ. Health Perspect. 47:2239-253.

Andersen, O. 1985. Evaluation of the spindle-inhibiting effect of Ni(II) by quantitation of chromosomal super-contraction. Res. Commun. Chem. Pathol. Pharmacol. 50:379-386.

Andersen, A., S. Berge, A. Engeland, and T. Norseth. 1996. Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. Occup. Environ. Med. 53:708-713.

Antonsen, D.H. 1996. Nickel Compounds. In: Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Vol. 17. Kroschwitz, J., Exec. Ed. An Interscience Publication, John Wiley and Sons, New York, pp. 18-42.

Anttila, A., E. Pukkala, A. Aitio, T. Rantanen, and S. Karjalainen. 1998. Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. Int. Arch. Occup. Environ. Health 71(4):245-250.

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Nickel. Update. (Final Report, September 1997). ATSDR, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. 262 pp.

Basrur, P., and J. Gilman. 1967. Morphologic and synthetic response of normal and tumor muscle cultures to nickel sulfide. Cancer Res. 27:1168-1177.

Bernacki, E., G. Parsons, B. Roy, M. Mikac-Devic, C. Kennedy, and F. Sunderman, Jr. 1978. Urine concentrations in nickel-exposed workers. Ann. Clin. Lab. Sci. 8:184-189.

Biedermann, K., and J. Landolph. 1987. Induction of anchorage independence in human diploid foreskin fibroblasts by carcinogenic metal salts. Cancer Res. 47:3815-3823.

Boysen, M., L. Solberg, W. Torjussen, S. Poppe, and A. Hogetveit. 1984. Histological changes, rhinoscopical findings and nickel concentrations in plasma and urine in retired nickel workers. Acta Oto-Laryngol. 97:105-115.

Budavari, S., Ed. 1996. The Merck Index, 12th ed., Merck & Co., Inc., Whitehall, NJ.

Carson, B. L. 1980. Primary and Secondary Processing of Cobalt-Bearing Materials. In: Trace Metals in the Environment, Vol. 6—Cobalt. Smith, I.C., and B.L. Carson, Eds. Ann Arbor Science Publishers, Inc., Ann Arbor, MI, pp. 663-765.

ChemFinder database. 1998. CambridgeSoft Corporation, distributor. Available at URL wysiwyg://6/http://chemfinder.camsoft.com/. Last accessed October 27, 1998.

Christensen, O.B., and Lagesson, V. 1981. Nickel concentration of blood and urine after oral administration. Ann. Clin. Lab. Sci. 11:119-125.

Ciccarelli, R., T. Hampton, and K. Jennette. 1981. Nickel carbonate induces DNA-protein crosslinks and DNA strand breaks in rat kidney. Cancer Lett. 12: 349-354.

Cominco, Ltd. 1998. Exploration and Operations—Glenbrook. Available at URL http://www.cominco.com/explore/glenbrook.html. Undated. Cominco Ltd. Glenbrook Nickel Smelter. News—Cominco to close Glenbrook Nickel Smelter. Available at URL http://www.cominco.com/news/98-005-c.html. Released January 29, 1998. Cominco Ltd. Glenbrook Nickel Smelter. Last accessed May 22, 1998.

Costa, M. 1995. Model for the epigenetic mechanism of action of nongenotoxic carcinogens. Am. J. Clin. Nutr. 61(Suppl.):6666S-6669S.

Costa, M. 1998. Letter to Dr. E. J. Zillioux, Manager, Risk Assessment, of Florida Power & Light Company, from M. Costa of NYU Medical Center. Re: Proposed change of category listing all forms of nickel as known carcinogens. Letter dated February 27, 1998.

Costa, M., and H. Mollenhauer. 1980. Phagocytosis of nickel subsulfide particles during the early stages of neoplastic transformation in tissue culture. Cancer Res. 40:2688-2694.

Costa, M., M. Jones, and O. Lindberg. 1980. Metal carcinogenesis in tissue culture systems. In: Inorganic Chemistry in Biology and Medicine (ACS Symposium Series No. 140), Martell, A.E., Ed. American Chemical Society, Washington, DC, pp. 45-73.

Costa, M., J. Simmons-Hansen, C. Bedrossian, J. Bonura, and R. Caprioli. 1981. Phagocytosis, cellular distribution, and carcinogenic activity of particulate nickel compounds in tissue culture. Cancer Res. 41:2868-2876.

Costa, M., J. Heck, and S. Robison. 1982. Selective phagocytosis of crystalline metal sulfide particles and DNA strand breaks as a mechanism for the induction of cellular transformation. Cancer Res. 42:2757-2763.

Deknudt, G., and A. Leonard. 1982. Mutagenicity tests with nickel salts in the male mouse. Toxicology 25:289-292.

DiPaolo, J., and B. Casto. 1979. Quantitative studies of *in vitro* morphological transformation of Syrian hamster cells by inorganic metal salts. Cancer Res. 39:1008-1013.

Diwan, B.A., K.S. Kasprzak, and J.M. Rice. 1992. Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. Carcinogenesis 13:1351-1357.

Fornace, A., Jr. 1982. Detection of DNA single-strand breaks produced during the repair of damage by DNA-protein cross-linking agents. Cancer Res. 42:145-149.

Gennart, J., C. Baleux, C.H. Verellen-Dumoulin, J. Buchet, R. De Meyer, and R. Lauwerys. 1993. Increased sister chromatid exchanges and tumor markers in workers exposed to elemental chromium-, cobalt-, and nickel- containing dusts. Mutat. Res. 299:55-61.

Goldberg, M., P. Goldberg, A. Leclerc, J. Chastang, M. Marne, and D. Dubourdieu. 1994. A 10-year incidence survey of respiratory cancer and a case-control study within a cohort of nickel mining and refining workers in New Caledonia. Cancer Causes Control 5(1):15-25.

Grant, L.D. and P. Mushak. 1989. Specification of metals and metal compounds: Implications for biological monitoring and development of regulatory approaches. Toxicol. Ind. Health 5:891-908.

Hartwig, A. and D. Beyersmann. 1989. Enhancement of UV-induced mutagenesis and sister-chromatid exchanges by nickel ions in V79 cells: Evidence for inhibition of DNA repair. Mutat. Res. 217:65-73.

Haworth, L., T. Lawlor, K. Mortelmans, W. Speck, and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5(Suppl. 1):3-142.

Higinbotham, K., J. Rice, B. Diwan, K. Kasprzak, C. Reed, and A. Perantoni. 1992. GGT to GTT transversions in codon 12 of the k-*ras* oncogene in rat renal sarcomas induced with nickel subsulfide or nickel subsulfide/iron are consistent with oxidative damage to DNA. Cancer Res. 52:4747-4751.

Horn-Ross, P., B. Ljung, and M. Morrow. 1997. Environmental factors and the risk of salivary gland cancer. Epidemiology 8(4):414-419.

HSDB (Hazardous Substances Data Bank). 1998. Profike for Nickel. Online database produced by the National Library of Medicine. Bethesda, MD. Last updated March 18, 1998.

Huang, X., Z. Zhuang, K. Frenkel, C.B. Klein, and M. Costa. 1994. The role of nickel and nickel-mediated reactive oxygen species in the mechanism of nickel carcinogenesis. Environ. Health Perspect. 102(Suppl. 3):281-284.

IARC (International Agency for Research on Cancer). 1990. Nickel and Nickel Compounds. IARC Monogr. Eval. Carcinog. Risks Hum. 49(Chromium, Nickel, and Welding):391-397.

ICNCM 1990. Report of the International Committee on Nickel Carcinogenesis in Man (ICNCM). Scand. J. Work Environ. Health 16:1-82.

IRIS (Integrated Risk Information System). 1997. Nickel Refinery Dust. Integrated Risk Information System (IRIS) Substance File. U.S. Environmental Protection Agency. Available at URL http://www.epa.gov/ngispgm3/iris/subst/0272.htm. Last updated March 1, 1997. Last accessed May 28, 1998.

Karjalainen, S., R. Kerttula, and E. Pukkala. 1992. Cancer risk among workers at a copper/nickel smelter and nickel refinery in Finland. Int. Arch. Occup. Environ. Health 63:547-551.

Kasprzak, K. and R. Bare. 1989. In vitro polymerization of histones by carcinogenic nickel compounds. Carcinogenesis 10:621-624.

Kasprzak, K., and J. Ward. 1991. Prevention of nickel subsulfide carcinogenesis by local administration of *Mycobacterium bovis* antigen in male F344/NCr rats. Toxicology 67:97-105.

Kasprzak, K., B. Diwan, N. Konishi, M. Misra, and J. Rice. 1990. Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. Carcinogenesis 11(4):647-652.

Kasprzak, K., B. Diwan, J. Rice, M. Misra, C. Riggs, R. Olinski, and M. Dizdaroglu. 1992. Nickel(II)-mediated oxidative DNA base damage in renal and hepatic chromatin of pregnant rats and their fetuses; possible relevance to carcinogenesis. Chem. Res. Toxicol. 5:809-815.

Kasprzak, K., B. Diwan, and J. Rice. 1994. Iron accelerates while magnesium inhibits nickel-induced carcinogenesis in the rat kidney. Toxicology 90:129-140.

Kasprzak, K., P. Jaruga, T. Zastawny, S. North, C. Riggs, R. Olinski, and M. Dizdaroglu. 1997. Oxidative DNA base damage and its repair in kidneys and livers of nickel(II)-treated male F344 rats. Carcinogenesis 18(2):271-277.

Kiilunen, M., A. Aitio, and A. Tossavainen. 1997. Occupational exposure to nickel salts in electrolytic plating. Ann. Occup. Hyg. 41:189-200.

King, N.J. 1998. Letter to Dr. C.W. Jameson of NIEHS from N.J. King of Wilmer, Cutler & Pickering. Representing: The Nickel Development Institue (NiDI), The Nickel Producers Environmental Research Association (NiPERA), and Inco United States, Incorporated (Inco). Re: Ninth Report on Carcinogens. March 13, 1998.

Kuck, P. 1997a. Nickel. U.S. Geological Survey, Mineral Commodity Summaries. Available at URL http://minerals.usgs.gov.

Kuck, P. 1997b. Nickel. U.S. Geological Survey—Minerals Information. 1995 Minerals Yearbook. Available at URL http://minerals.usgs.gov.

Langer, A.M., A.N. Rohl, I.J. Selikoff, G.E. Harlow, and M. Prinz. 1980. Asbestos as a cofactor in carcinogenesis among nickel processing workers. Science 209:420-422.

Larramendy, M., N. Popescu, and J. DiPaolo. 1981. Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster cell strains. Environ. Mutagen. 3:597-606.

Lechner, J., T. Tokiwa, I. McClendon, and A. Haugen. 1984. Effects of nickel sulfate on growth and differentiation of normal human bronchial epithelial cells. Carcinogenesis 5:1697-1703.

LeClerc, A., M. Goldberg, P. Goldberg, J. Deloumeaux, and R. Fuhrer. 1987. Geographical distribution of respiratory cancer in New Caledonia. Arch. Environ. Health 42:315-320.

Lynn, S., F. Yew, J. Hwang, M. Tseng, and K. Jan. 1994. Glutathione can rescue the inhibitory effects of nickel on DNA ligation and repair synthesis. Carcinogenesis 15 (12):2811-2816.

Mathur, A., T. Dikshith, M. Lal, and S. Tandon. 1978. Distribution of nickel and cytogenetic changes in poisoned rats. Toxicology 10:105-113.

McCoy, H., and M. Kenney. 1992. A review of biointeractions of Ni and Mg. II. Immune system and oncology. Magnesium Res. 5 (3):223-232.

Miyaki, M., N. Akamatsu, T. Ono, and H. Koyama. 1979. Mutagenicity of metal cations in cultured cells from Chinese hamster. Mutat. Res. 68:259-263.

Mohanty, P.K. 1987. Cytotoxic effect of nickel chloride on the somatic chromosomes of Swiss albino mice *Mus musculus.* Curr. Sci. 56:1154-1157.

Moulin, J., P. Portefaix, P. Wild, J.M. Mur, G. Smagghe, and B. Mantout. 1990. Mortality study among workers producing ferroalloys and stainless steel in France. Br. J. Ind. Med. 47:537-543.

Moulin, J., P. Wild, J. Haguenoer, D. Faucon, R. De Gaudemaris, J. Mur, M. Mereau, Y. Gary, J. Toamain, Y. Birembaut, et al. 1993. A mortality study among mild steel and stainless steel welders. Br. J. Ind. Med. 50(3):234-243.

Morgan, L. G., 1992. Problems in the toxicology, diagnosis, and treatment of nickel carbonyl poisoning. In: Nickel and Human Health: Current Perspectives. Nieboer, E., and J. O. Nriagu, Eds. John Wiley and Sons, Inc., New York, pp. 261-271.

Morgan, L.G., and P.J. Rouge. 1984. Biological monitoring in nickel refinery workers. IARC Sci. Publ. 53:507-520.

NiDI. 1997. Safe Use of Nickel in the Workplace. 2nd ed. Nickel Development Institute, Ontario, Canada.

NIOSH (National Institute for Occupational Safety and Health). 1976. National Occupational Hazard Survey database search results for potential occupational nickel exposures provided by CDC, September 1998. Data collected 1972-1974 for the reference year 1970. Available from NTIS: Vol. I (Survey Manual), DHEW/PUB/NIOSH-74/127, PB-274 241/9, November 1976, 203 pp.; Vol. II (Data Editing and Data Base Development), DHEW/PUB/NIOSH-77/213, PB-274 819/2, July 1977, 154 pp.; Vol. III (Survey Analysis and Supplemental Tables (Technical Report February 1972-June 1974), DHEW/PUB/NIOSH-78-114, PB82-229881, December 1977, 802 pp. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, OH.

NIOSH (National Institute for Occupational Safety and Health). 1990. National Occupational Exposure Survey (1981-1983) [database search results for potential occupational nickel exposures during the period 1981 to 1983 provided by CDC, September 1998]. Unpublished provisional data as of 7/1/90. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Surveillance Branch, Hazard Section, Cincinnati, OH. Phone contact (513) 841-4491.

NiPERA (Nickel Producers Environmental Research Association). 1996. Occupational Exposure Limits Criteria Document for Nickel and Nickel Compounds. Volume 1: Summary, Conclusions, and Recommendations. Final Document.

Nishimura, M., and M. Umeda. 1979. Induction of chromosomal aberrations in cultured mammalian cells by nickel compounds. Mutat. Res. 68:337-349.

NTP (National Toxicology Program). 1996a. Toxicology and carcinogenesis studies of nickel oxide (CAS No. 1313-99-1) in F344 rats and B6C3F$_1$ mice (Inhalation studies). Report No. TR-451. NIH Publication No. 96-3367. NTIS No. PB97-116701. 376 pp. National Toxicology Program, Research Triangle Park, NC.

NTP (National Toxicology Program). 1996b. Toxicology and carcinogenesis studies of nickel subsulfide (CAS No. 12035-72-2) in F344 rats and B6C3F$_1$ mice (Inhalation studies). Report No. TR-453. NIH Publication No. 96-339. NTIS No. PB97-116784. 360 pp. National Toxicology Program, Research Triangle Park, NC.

NTP (National Toxicology Program). 1996c. Toxicology and carcinogenesis studies of nickel sulfate hexahydrate (CAS No. 10101-97-0) in F344 rats and B6C3F$_1$ mice (Inhalation studies). Report No. TR-454. NIH Publication No. 96-3370. NTIS No. PB97-120216. 376 pp. National Toxicology Program, Research Triangle Park, NC.

Ohno, H., F. Hanaoka, and M. Yamada. 1982. Inducibility of sister-chromatid exchanges by heavy-metal ions. Mutat. Res.104:141-145.

Oller, A.R., M. Costa, and G. Oberd`rster. 1997. Carcinogenicity assessment of selected nickel compounds. Toxicol. Appl. Pharmacol. 143:152-166.

Patierno, S., and M. Costa. 1985. DNA-protein cross-links induced by nickel compounds in intact cultured mammalian cells. Chem.-Biol. Interact. 55:75-91.

Paton, G., and A. Allison. 1972. Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16:332-336.

Pienta, R., J. Poiley, and W. Lebherz III. 1977. Morphological transformation of early passage golden Syrian hamster embryo cells derived from cryopreserved primary cultures as a reliable in vitro bioassay for identifying diverse carcinogens. Int. J. Cancer 19:642-655.

Radian. 1991. Nickel Subsulfide profile from NTP Chemical Repository, Radian Corporation, August 29, 1991. NTP Chemical Health and Safety Database. Available at URL http://ntp-server.niehs.nih.gov/Main_Pages/Chem-HS.html. Last accessed October 27, 1998.

Raithel, H.J., K.H. Schaller, T. Kraus, and G. Lehnert. 1993. Biomonitoring of nickel and chromium in human pulmonary tissue. Int. Arch. Occup. Environ. Health 65(Suppl. 1):S197-S200.

Robison, S., and M. Costa. 1982. The induction of DNA strand breakage by nickel compounds in cultured Chinese hamster ovary cells. Cancer Lett. 15:35-40.

Robison, S., O. Cantoni, and M. Costa. 1982. Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. Carcinogenesis 3:657-662.

Robison, S., O. Cantoni, and M. Costa. 1984. Analysis of metal-induced DNA lesions and DNA-repair replication in mammalian cells. Mutat. Res. 131:173-181.

Robison, S., O. Cantoni, J. Heck, and M. Costa. 1983. Soluble and insoluble nickel compounds induce DNA repair synthesis in cultured mammalian cells. Cancer Lett. 17:273-279.

Rodnan, N., Ed. 1997. Chemcyclopedia 98. American Chemical Society, Washington, DC, pp. 156, 298-299.

Rodriguez, R., M. Misra, B. Diwan, C. Riggs, K. Kasprzak. 1996. Relative susceptibilities of C57BL/6, (C57BL/6 x C3H/He)F_1, and C3H/He mice to acute toxicity and carcinogenicity of nickel subsulfide. Toxicology 107:131-140.

Saplakoglu, U., M. Iscan, and M. Iscan. 1997. DNA single-strand breakage in rat lung, liver and kidney after single and combined treatments of nickel and cadmium. Mutat. Res. 394:133-140.

Saxholm, H., A. Reith, and A. Brogger. 1981. Oncogenic transformation and cell lysis in C3H/10$T^1/_2$ cells and increased sister chromatic exchange in human lymphocytes by nickel subsulfide. Cancer Res. 41:4136-4139.

Sen, P., and M. Costa. 1985. Induction of chromosomal damage in Chinese hamster ovary cells by soluble and particulate nickel compounds: Preferential fragmentation of the heterochromatic long arm of the c-chromosome by carcinogenic crystalline NiS particles. Cancer Res. 45:2320-2325.

Sen, P., and M. Costa. 1986. Pathway of nickel uptake influences its interaction with heterochromatic DNA. Toxicol. Appl. Pharmacol. 84:278-285.

Sen, P., K.Conway, and M. Costa. 1987. Comparison of the localization of chromosome damage induced by calcium chromate and nickel compounds. Cancer Res. 47:2142-2147.

Shi, X., Y. Mao, N. Ahmed, and H. Jiang. 1995. HPLC investigation on Ni(II)-mediated DNA damage in the presence of *t*-butyl hydroperoxide and glutathione. J. Inorg. Biochem. 57:91-102.

Simonato, L., A.C. Fletcher, A. Anderson, K. Anderson, N. Becker, J. Chang-Claude, G. Ferro, M. Gérin, C.N. Gray, K.S. Hansen, P-L. Kalliomaki, K. Kurppa, S. Langard, F. Merló, J.J. Moulin, M.L. Newhouse, J. Peto, E. Pukkala, B. Sjogren, P. Wild, R. Winkelman, and R. Saracci. 1991. A historical prospective study of European stainless steel, mild steel, and shipyard welders. Br. J. Ind. Med. 48:145-154.

Sina, J., C. Bean, G. Dysart, V. Taylor, and M. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113:357-391.

Sunderman, F.W., Jr., A. Aitio, L.O. Morgan, and T. Norseth. 1986. Biological monitoring of nickel. Toxicol. Ind. Health 2:17-78.

Sunderman, F.W., Jr., S. Hopfer, F. Knight, D. McCully, A. Cecutti, P. Thornhill, K. Conway, C. Miller, S. Patierno, and M. Costa. 1987. Physicochemical characteristics and biological effects of nickel oxides. Carcinogenesis 8:305-313.

Swierenga, S., and J. McLean. 1985. Further insights into mechanisms of nickel-induced DNA damage: Studies with cultured rat liver cells. In: Progress in Nickel Toxicology, S.S. Brown and F.W. Sunderman, Jr., Eds., Blackwell Scientific Publications, Oxford, pp. 101-104.

Tien, J.K., and T.E. Howson. 1985. Nickel and Nickel Alloys. In: Kirk-Othmer Concise Encyclopedia of Chemical Technology. Grayson, M., Ed. An Interscience Publication, John Wiley and Sons, New York, NY, pp. 781-783.

Torjussen, W., and J. Andersen. 1979. Nickel concentrations in nasal mucosa, plasma, and urine in active and retired workers. Ann. Clin. Lab. Sci. 9:289-298.

Tossavainen, A., M. Nurminen, P. Mutanen, and S. Tola, 1980. Application of mathematical modelling for assessing the biological half-times of chromium and nickel in field studies. Br. J. Ind. Med. 37:285-291.

Tsuchiyama, F., N. Hisanaga, E. Shibata, T. Aoki, H. Takagi, T. Ando, and Y. Takeuchi. 1997. Pulmonary metal distribution in urban dwellers. Int. Arch. Occup. Environ. Health 70:77-84.

Tveito, G., I.-L. Hansteen, H. Dalen, and A. Haugen. 1989. Immortalization of normal human kidney epithelial cells by nickel(II). Cancer Res. 49:1829-1835.

Ullman, F. 1985. Ullman's Encyclopedia of Industrial Chemistry. 5th ed. Vol. A17. VCH Publishers, Deerfield Beach, FL.

USEPA (U.S. Environmental Protection Agency). 1998. Nickel and Compounds. U.S. Environmental Protection Agency Technology Transfer Network. Available at URL wysiwyg://2/http://www.epa.gov/ttnuatw1/hlthef/nickel.html. Last updated May 26, 1998. Last accessed July 22, 1998.

Umeda, M., and M. Nishimura. 1979. Inducibility of chromosomal aberrations by metal compounds in cultured mammalian cells. Mutat. Res. 67:221-229.

Waksvik, H., and M. Boysen. 1982. Cytogenetic analyses of lymphocytes from workers in a nickel refinery. Mutat. Res. 103:185-190.

Waksvik, H., M. Boysen, and A. Hogetveit. 1984. Increased incidence of chromosomal aberrations in peripheral lymphocytes of retired nickel workers. Carcinogenesis 5:1525-1527.

Weast, R.C., Ed. 1980. Physical Constants of Inorganic Compounds. In: CRC Handbook of Chemistry and Physics, CRC Press, Inc., Boca Raton, FL, pp. B-123 to B-124 (nickel compounds).

Wortley, P., T. Vaughan, S. Davis, M. Morgan, and D. Thomas. 1992. A case-control study of occupational risk factors for laryngeal cancer. Br. J. Ind. Med. 49:837-844.

Zhang, Q., and J. Barrett. 1988. Dose-response studies of nickel-induced morphological transformation of Syrian hamster embryo fibroblasts. Toxicol. *In Vitro* 2: 303-307.

APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risks to Humans
Volume 49 (Chromium, Nickel and Welding)
Nickel and Nickel Compounds
pp. 257-445, 616-638, 1990

APPENDIX B

Report on Carcinogens (RoC), 9th Edition
Review Summary

Report on Carcinogens (RoC), 9th Edition
Review Summary

Nickel Compounds

NOMINATION
Review for possible listing as a *known to be human carcinogen* based on recent IARC reclassification of Nickel and Nickel Compounds as a known human carcinogen (IARC Vol. 49, 1990).

DISCUSSION
Nickel and Certain Nickel Compounds, which have many industrial and commercial applications (including use in stainless steels, nickel alloys, catalysts, batteries, pigments, ceramics, etc.), is currently listed in the RoC as *reasonably anticipated to be a human carcinogen.* Studies of workers exposed to various nickel compounds show the risks for death from lung cancer and nasal cancer are elevated. Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel compounds encountered in the nickel refining industries which included sulfates, which are soluble, and combinations of sulfides and oxides, which are insoluble, are carcinogenic to humans. Both soluble and insoluble nickel compounds are multi-species animal carcinogens by multiple routes of exposure and cause tumors both at the site of application and at distant sites. The combined results of epidemiological studies, carcinogenesis studies in rodents, and mechanistic data support the concept that nickel compounds act by the generation of nickel ions at critical sites in target cells of carcinogenesis and allow consideration and evaluation of these compounds as a single group. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as known to be human carcinogen	7 yes/0 no
NTP EC Working Group (RG2)	list as known to be human carcinogen	4 yes/3 no/1 a*
NTP Board RoC Subcommittee	list as known to be human carcinogen	12 yes/0 no

*a-abstentions

Public Comments Received:
A total of 17 public comments were received:

- 15 against upgrading to a known to be human carcinogen
- 1 recommending listing only insoluble Nickel Compounds as known human carcinogens
- 1 providing comments on the content of the background document prepared for the review of this nomination