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Occupational Toxicology of Nickel and Nickel Compounds

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Nickel and nickel compounds are widely used in industry. The high consumption of nickel products inevitably leads to occupational and environmental pollution. In occupational settings, exposure to nickel and nickel compounds occurs primarily during nickel refining, electroplating, and welding. The most common airborne exposures to nickel in the workplace are to insoluble nickel species, such as metallic nickel, nickel sulfide, and nickel oxides from dusts and fumes. The chemical and physical properties of nickel and nickel compounds strongly influence their bioavailability and toxicity. The lung and the skin are the principal target organs upon occupational exposure. Inhalation exposure is a primary route for nickel-induced toxicity in the workplace. The most important adverse health effects due to occupational exposure to nickel and its compounds are skin allergies, lung fibrosis, and lung cancer. The exact mechanisms of nickel-induced carcinogenesis are not clear. This review summarizes the current knowledge on occupational toxicology of nickel and its compounds. The subtopics include: chemical and physical properties, uses, occupational exposures, occupational exposure limits, toxicokinetics, biological monitoring, acute toxicity, chronic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, molecular mechanisms of carcinogenesis, and gaps in knowledge.

KEYWORDS: Nickel, nickel compounds, occupational exposure, toxicology, occupational exposure limits, toxicokinetics, biological monitoring, acute toxicity, chronic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, molecular mechanisms of carcinogenesis

Introduction

Nickel, a silvery-white hard metal, was discovered and named by Cronstedt in 1751. It has properties that make it very desirable for combining with other metals to form mixtures called alloys. Some of the metals that combine with nickel to make alloys are iron, copper, chromium, and zinc. Many other elements, such as chlorine, sulfur, and oxygen, can combine with nickel to form nickel compounds.

Due to their unique physical and chemical properties, nickel and its alloys have been in widespread commercial use for over one hundred years. The high consumption of nickel products leads to occupational and environmental pollution.[1] Several million workers worldwide are exposed to airborne fumes, dusts, and mists containing nickel and its compounds. Exposures by inhalation, ingestion, or skin contact can occur in nickel and nickel alloy production plants as well as in welding, electroplating, grinding, and cutting operations. Inhalation is the main route of nickel uptake. Occupational exposure has been shown to give rise to elevated levels of nickel in blood, urine, and body tissues. Nonoccupational sources of nickel

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exposure include food, air, and water. However, the levels found are usually much lower than those found in the workplace.[2] Accumulation of nickel and its compounds in the workplace or in the environment may represent a serious hazard to human health. Among the known health-related adverse effects of nickel are allergic dermatitis, pulmonary fibrosis, and increased risk of cancer.[3] Nickel is listed by the United States Environmental Protection Agency (U.S. EPA) as one of the 129 priority pollutants and is considered to be one of the 14 most noxious heavy metals. Nickel is listed among the 25 hazardous substances thought to pose the most significant potential threat to human health. The U.S. EPA has also classified nickel refinery dust and nickel subsulfide as human carcinogens (Group A) and nickel carbonyl as a probable human carcinogen (Group B2).[4,5] In its tenth report on carcinogens in 2002, the International Agency for Research on Cancer (IARC) determined that some nickel compounds are carcinogenic to humans and that metallic nickel may also be carcinogenic to humans.[6]

Because most human hazard effects related to nickel exposure occur in occupational settings, this review will focus mainly on current knowledge concerning the occupational toxicology of nickel and nickel compounds. The molecular mechanisms of carcinogenesis, especially the formation of reactive oxygen species (ROS) and alterations of signal transduction pathways, will also be summarized because carcinogenic activity is still the most serious concern for nickel and nickel compounds.

Chemical and Physical Properties

Nickel is a lustrous silvery, hard, ferromagnetic metal or a gray powder. It has a vapor pressure of 1 mm Hg at 1810°C and a specific gravity of 8.91 g/cc. Nickel possesses relatively high thermal and electrical conductivity as well as ferromagnetic properties. However, the conductive and magnetic properties are less than silver and iron, respectively.[7] Metallic nickel is soluble in dilute nitric acid, slightly soluble in hydrochloric acid and sulfuric acid, and insoluble in water and ammonia. It is resistant to attack by air, water, and alkali at standard temperatures. Powdered nickel is reactive in air and may ignite spontaneously.[8] Nickel is a natural element of the earth's crust. Therefore, small amounts are found in food, water, soil, and air. In the environment, it is found primarily combined with oxygen or sulfur.

Nickel has properties that make it desirable for combining with other metals to form alloys. Metals that nickel can be alloyed with include iron, copper, chromium, and zinc. These alloys are used in making metal coins and jewelry and in industry for making metal items. Nickel can also combine with other substances, such as chlorine, sulfur, and oxygen, to form nickel compounds. Many of these compounds dissolve fairly easily in water and have a characteristic green color. Nickel and its compounds have no characteristic odor or taste.[6]

Nickel salts of strong acids and organic acids are soluble in water, whereas nickel salts of weak inorganic acids are insoluble in water. In contrast to the soluble nickel salts (chloride, nitrate, sulfate), nickel sulfides and nickel oxides are poorly soluble in water. Nickel carbonates and nickel hydroxides are moderately soluble in water.

Nickel carbonyl is the most toxic nickel compound encountered in occupational settings. It occurs as a colorless, volatile, and highly flammable liquid. It is practically insoluble in water but soluble in alcohol, benzene, chloroform, acetone, and carbon tetrachloride. Nickel carbonyl may decompose violently when exposed to heat or flame in the presence of air or oxygen. When heated or in contact with acid or acid fumes, nickel carbonyl emits toxic carbon monoxide fumes. It decays spontaneously in air.[9]

Both the soluble and less-soluble nickel compounds are important with regard to all relevant routes of exposure. Generally, the soluble compounds are considered to be more toxic than the less-soluble compounds, although the less-soluble compounds are more likely to be carcinogenic at the site of deposition.

The chemical and physical properties of nickel and nickel compounds strongly influence their bioavailability and toxicity. Table 1 lists the chemical and physical properties and industrial uses of nickel and some of its compounds, which are frequently encountered in occupational settings or used in experimental studies.[7,10]

Uses

Nickel is refined from either sulfide or silicate-oxide ore. These ores generally contain no more than 3% nickel.[8] Major deposits of nickel ores are located in

TABLE 1. Physical and Chemical Properties, and Industrial Uses of Nickel and Nickel Compounds

Name	Molecular formula	Molecular weight	CAS registry no.	Density (g/cm^3)	Appearance	Melting point (°C)	Boiling point (°C)	Solubility (water; other solvents)	Industrial uses
Nickel	Ni	58.69	7440-02-0	8.91	Lustrous, white, face-centered cubic crystals	1453	2732	Insoluble; soluble in dilute nitric acid, slightly soluble in hydrochloric acid	Electrode materials, catalysts of chemical industry, magnetic materials, contact materials and powder metallurgy of diamond tools, hard alloys and high-temperature alloys
Nickel acetate	Ni $(CH_3COO)_2$	176.80	373-02-4	1.744	Green crystalline powder	NA	NA	Soluble; soluble in acid and alcohol	Precise plating, surface treatment of aluminum profile and ceramic glazing
	Ni $(CH_3COO)_2.4H_2O$	248.84	6018-89-9	1.798	Green monoclinic crystal	Decomposes	NA	Soluble; soluble in acid and alcohol	Catalyst production, nickel electroplating, aluminum sealing
Nickel arsenate	$Ni_3(AsO_4)_2$	453.97	27016-75-7	4.982	Yellow-green powder	NA	NA	Insoluble; soluble in acids	Fat-hardening catalyst in soap making
Nickel (II) arsenate octahydrate	$Ni_3(AsO_4)_2.$ $8H_2O$	598.04	7784-48-7	4.98	Yellow-green powder	NA	NA	Insoluble; soluble in acid	Selective fat-hardening hydrogenation catalyst
Nickel bromide	$NiBr_2$	218.53	13462-88-9	5.098	Yellow-green deliquescent crystals	963	NA	Soluble; soluble in alcohol	Nickel electroplating
Nickel carbonate	$NiCO_3$	118.70	3333-67-3	2.60	Light-green powder	Decomposes before melting	NA	Insoluble; soluble in acids	Nickel catalysts, electroplating, ceramic color, drying agent for glazed colored porcelain
Nickel(II) carbonate hydroxide tetrahydrate	$2NiCO_3 \cdot$ $3Ni(OH)_2 \cdot 4H_2O$	587.59	1224-51-8	2.6	Green powder	NA	NA	Insoluble in water; soluble in diluted acid	Nickel catalysts, electroplating, ceramic color, drying agent for glazed colored porcelain
Nickel carbonyl	$Ni(CO)_4$	170.73	13463-39-3	1.318	Colorless, volatile liquid	−19	43	Insoluble; soluble in organic solvents	Mond process and for continuous nickel coatings, vapor plating of nickel and depositing of nickel in semiconductor manufacturing
Nickel chloride	$NiCl_2$	129.61	7718-54-9	3.55	Yellow, deliquescent crystals	1001	1783	Soluble in water, alcohol, and ammonium hydroxide; insoluble in ammonia	Electroplating, electroforming, electroplating, tea and coffee plantation, dye mordant, insecticides

continued

TABLE 1. (Continued)

Nickel chloride hexahydrate	$NiCl_2 \cdot 6H_2O$	237.70	7791-20-0	3.55	Yellow or light-green deliquescent crystals	1001	1783	Soluble; soluble in alcohol; deliquescent in moist air	Electroplating, antiseptic, ammonia absorbent and other chemicals
Nickel fluoride	NiF_2	96.69	10028-18-9	4.72	Yellow-green tetragonal crystals	1450	1750	Slightly soluble	Surface treatment of aluminum profile and printing ink making, fluorescence lamp, fluidizer and catalyzer for organic synthesis
	$NiF_2.4H_2O$	168.75	13940-83-5	4.63	Grass-green crystal	Decomposes in boiling water	NA	Freely soluble in water and inorganic acid, slightly soluble in alcohol	
Nickel hydroxide	$Ni(OH)_2$	92.72	12054-48-7	4.15	Green powder	230 Decomposes	NA	Insoluble; soluble in acids and ammonia	Batteries, manufacture of nickel salts
Nickel nitrate	$Ni(NO_3)_2$	182.72	13138-45-9	2.05	Green, deliquescent crystals	56.7	137	Soluble; soluble in alcohol	Electroplating of nickel, glazed color of ceramics, other nickel salts and catalyst
	$Ni(NO_3)_2$-$6H_2O$	290.81	13478-00-7	2.05	Light green monoclinic crystal	56.7 Decomposes	137	Soluble; soluble in alcohol, and slightly soluble in acetone	
Nickel oxide	NiO	74.69	1313-99-1	6.67	Green or black powder	1894	NA	Insoluble; soluble in hot hydrochloric acid, hot sulfuric acid or nitric acid	Enamel, ceramics, glass industries, magnetic materials, thermo-sensors, stainless steel, nickel salt, secondary battery
Nickel (III) oxide	Ni_2O_3	165.39	1314-06-3	6.67	Black powder	NA	NA	Insoluble; soluble in vitriol and nitric acid	The cathode in many rechargeable batteries, including nickel-cadmium, nickel-iron nickel hydrogen and nickel-metal hydride, and used by certain manufacturers in Li-ion batteries, battery material, catalysts, ceramics, electroplating
Nickel phosphate	$Ni_3(PO_4)_2$	366.07	14396-43-1	2.85	Light green powder	NA	158	Insoluble; soluble in acid	Steel coatings, pigment for oil and water paints, electroplating and production of yellow nickel
Nickel sulfate	$NiSO_4$	154.77	7786-81-4	3.70	Blue-green tetragonal crystals	53.3 Loses water at 280	NA	Soluble, slightly soluble in acid and aqueous ammonia	Electroplating, nickel-cadmium battery, organic synthesis, catalyst in painting production, raw material of nickel salt for coloring of metals and additives of reduction dye

continued

TABLE 1. (Continued)

Nickel sulfate hexahydrate	$NiSO_4 \cdot 6H_2O$	262.86	10101-97-0	2.03	Green crystals of cubic	100	103	Soluble, slightly soluble in acid and aqueous ammonia	Electroplating, nickel-cadmium battery, organic synthesis, catalyst in painting production, raw material of nickel salt for coloring of metals and additives of reduction dye
Nickel sulfide	NiS	90.77	16812-54-7	5.30	Black powder	797	NA	Insoluble	A major component in the mining and refining of certain nickel ores
Nickel subsulfide	Ni_3S_2	240.21	12035-72-2	5.82	Pale, yellowish bronze metallic	790	2967	Insoluble; soluble in nitric acid	Manufacture of lithium batteries, a major component in the mining and refining of certain nickel ores
Nickel(II) iodide	NiI_2	312.50	13462-90-3	5.83	Blue green, very deliquescent crystals	780	797	Soluble, soluble in alcohol	Catalyst in carbonylation reactions
Bis(1,5-cyclooctadiene) nickel	$C_{16}H_{24}Ni$	275.06	1295-35-8	4.78	Yellow solid	60 Decomposes	153.5	Insoluble; moderately soluble in benzene	Intermediate in organometallic chemistry, catalyst for isomerization and hydrosilyltion of unsaturated compounds. co-catalyst for oligomerization/ cyclo-oligomerization or polymerization of alkenes, butadiene

Note. CAS = chemical abstracts service; NA = not available.

Australia, Canada, Cuba, Indonesia, New Caledonia, and Russia. Australia, Canada, and Russia are the largest nickel-mining countries.[11,12] In 2004, world demand for primary nickel was at an all-time high, with most nickel producers operating at full capacity. Primary nickel demand in the Western World was reported to be 1.05 million tons. In the United States, apparent consumption of primary nickel was 129,000 tons.[13]

Nickel has many uses in industry because of its unique properties. The majority of nickel production is used for the creation of the following: stainless steel, nickel alloys, and nickel cast iron that comprise objects, such as coins, electrical equipment, tools, machinery, armaments, appliances, and household utensils.[7] The widespread use of nickel alloys in jewelry and associated products may cause contact dermatitis.[14] Other uses for nickel compounds include electroplating (black oxide [soluble form], carbonate, chloride, sulfate), electroforming (nickel sulfamate), nickel-cadmium alkaline batteries (hydroxide), dye mordant (ammonium chloride, acetate), catalysts (acetate, arsenate, carbonate, cyanide, formate, hydroxide), and electronic equipment (carbonates, ferrites). There is no specific commercial use for nickel sulfide, and exposure to this compound mainly occurs in mining and refining facilities.[7]

Pure nickel metal is used in electroplating, as a chemical catalyst, and in the manufacture of alkaline batteries, coins, welding products, magnets, electrical contacts and electrodes, spark plugs, machinery parts, and surgical and dental prostheses.

Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and for continuous nickel coatings on steel and other metals. Nickel carbonyl also has many small-scale applications, such as vapor plating of nickel and depositing of nickel in semiconductor manufacturing.[8]

Nickel nanoparticles are new products. Their characteristics include a high level of surface energy, high magnetism, low melting point, high surface area, and low burning point. Therefore, they are widely used in industry.[15,16] However, concern has been expressed that these same properties of nanoparticles may present unique bioactivity and challenges to health.[17] Although little is known about the effects of particle size relative to speciation, it should be borne in mind that the size of the nickel particles to which workers are exposed may play an important role in the biological effects of different nickel species.[18]

Various public and private statistical services track the production and end-use of nickel. Data on the world wide uses of nickel in 2006 indicate that 59% is used in stainless steel, 13% in nickel alloy, 11% in plating, 7% in alloy steel, and 10% in other uses.[18]

Occupational Exposures

Nickel is normally present in human tissues, and under conditions of high exposure, these levels may increase significantly. The general population is exposed to nickel *via* the diet and objects containing nickel, such as jewelry and coins.[19] However, the levels of these non-occupational sources of nickel exposure are usually much lower than those encountered in the workplace.[2]

Occupational exposure to nickel and nickel compounds occurs mainly by inhalation of dust particles and fumes or by dermal contact. The most common airborne exposures to nickel in the workplace are to insoluble nickel species such as metallic nickel, nickel sulfide, and nickel oxides from dusts and fumes. Industrial operations with potential exposures to nickel and its compounds include: mining, milling, concentrating, smelting, converting, hydrometallurgical processes, refining, and other operations. Generally, exposures in the production industry are to moderately soluble and insoluble forms of nickel. In the production industry, soluble nickel compounds are more likely to be found in hydrometallurgical operations. Exposures in nickel-use industries vary according to the end product and include both soluble and relatively insoluble forms of nickel.[18,20]

The major routes of nickel and nickel compound exposures that have toxicological relevance in the workplace are inhalation and dermal exposures. Oral exposures can also occur, but the institution of good industrial hygiene practices can greatly minimize such exposures. Workers engaged in nickel production are exposed to a variety of nickel-containing minerals and compounds.[21] Although exposure to specific forms of nickel differs among use and production industries, the main exposure routes are the same in both industries. With the exception of nickel powders, end products of primary nickel production are massive and cannot be inhaled.[21] Exposures to these products will mainly be dermal. In some instances, inhaled particles may be generated as a result of

handling, packaging, shipping, or subsequent treating or processing of these products.

With respect to exposures, two types of exposure data are required in the risk assessment for nickel: those that pertain to the ambient environment and those that pertain to the internal environment (body internal levels of nickel) of the worker. Many factors may affect the internal exposures. These include the aerodynamic size of the particles and whether the particles are inhalable, the concentration of the nickel that is inhaled, the minute ventilation rate of a worker, whether breathing is nasal or oronasal, the use of respiratory protection equipment, indoor air climate conditions of the workplace, personal hygiene practices, age and sex of the worker, and general work patterns.

Occupational Exposure Limits

In the United States, there are three organizations (or government agencies) that develop occupational exposure limits (recommendation or standards). The American Conference of Governmental Industrial Hygienists (ACGIH)[22] is a professional association of industrial hygienists and practitioners of related professions. One of its goals is to advance worker protection by providing timely, objective, scientific information to occupational and environmental health professionals. ACGIH recommends Threshold Limit Values (TLVs) for chemical substances and physical agents and Biological Exposure Indices (BEIs). The TLVs and BEIs are developed as guidelines to assist in the control of occupational hazards. Because ACGIH TLVs and BEIs are based solely on health factors, there is no consideration given to economic or technical feasibility. The National Institute for Occupational Safety and Health (NIOSH)[23] is a United States federal agency created by Congress under the 1920 Occupational Safety and Health Act. Under this act, NIOSH is responsible for conducting research and making recommendations for the prevention of work-related injury and illness. NIOSH is part of the Centers for Disease Control and Prevention (CDC) within the U.S. Department of Health and Human Services. NIOSH was established to help ensure safe and healthful working conditions by providing research, information, education, and training in the field of occupational safety and health. NIOSH conducts risk assessment for occupational exposures and develops Recommended Exposure Limits (RELs) to protect worker health. The Occupational Safety and Health Administration (OSHA) is an agency of the U.S. Department of Labor, and was created by Congress under the 1970 Occupational Safety and Health Act. Its mission is to prevent work-related injuries, illnesses, and deaths by issuing and enforcing rules for workplace safety and health. As a governmental body, OSHA establishes occupational standards, that is, Permissible Exposure Limits (PELs), which are enforceable by law. Therefore, the occupational exposure limits for nickel and nickel compounds in the United States are expressed in three different ways. The threshold limit value–time-weighted average (TLV-TWA) adopted by ACGIH is expressed as the TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. A short-term exposure limit (STEL) is defined as a 15-minute TWA exposure, which should not be exceeded at any time during a workday even if the 8-hour TWA is within the TLV-TWA.[24] NIOSH develops the recommended exposure limit–time-weighted average (REL-TWA) to recommend exposure limit for an 8- or 10-hour TWA exposure and/or ceiling. The permissible exposure limit–time-weighted average (PEL-TWA) established by OSHA means the concentration of a nickel or nickel compound to which workers can be legally exposed averaged over a normal 8-hour workday or a 40-hour workweek.

In Germany, there are technische richtkonzentrationen (TRK, technical exposure limits) and STEL for the permissible exposure limits to nickel and nickel compounds. The United Kingdom has a system based on occupational exposure limit–time-weighted average (OEL-TWA), maximum exposure limit (MEL), and occupational exposure standard (OES).[25] France adopts OEL-TWA and valeur moyenne d'exposition (VME). Most other European Union countries use OEL-TWA, whereas, Japan and Canada adopt OEL and China uses the permissible concentration–time-weighted average (PC-TWA) for the permissible exposure limits for nickel and nickel compounds.

In the production of nickel products, workers are often exposed to nickel and nickel compounds in the form of airborne dust and small particles.[26] The toxic or carcinogenic potency of various nickel compounds varies widely, based on solubility properties and specia-

tion. Current nickel standards generally differentiate only between water-soluble and insoluble nickel compounds and nickel carbonyl. However, health effects associated with nickel exposures may be dependent upon a number of factors, including solubility, chemical form, particle size, surface area, concentration, and route and duration of exposure. Therefore, it is prudent that each worksite be characterized with regard to the individual nickel species present in the air and to the distribution of particle sizes in the aerosols. Currently, differences exist in the classification of nickel species as the various countries/organizations develop OELs for nickel and nickel compounds. In this review, the classification used by the Nickel Institute[27] is recommended, which classifies the nickel and nickel compounds as metallic nickel, insoluble nickel species, soluble nickel species, and nickel carbonyl. Table 2 lists the current occupational exposure limits in various countries around the world for nickel and nickel compounds. Unless otherwise noted, data are adapted from the Nickel Institute.[27]

In addition, it should be kept in mind that although all standards or recommendations for nickel and nickel compounds are based on scientific studies, the decision as to whether a certain level is acceptable might also depend upon economic or technical feasibility.

Toxicokinetics

Absorption

Exposure to nickel can occur through inhalation, ingestion, and dermal contact. The relative amounts of nickel absorbed by the human body are determined not only by the quantities inhaled or ingested, but also by the physical and chemical characteristics of the nickel compounds. Solubility is an important factor in all routes of absorption. Generally, the absorption of nickel compounds follows the following order: nickel carbonyl > soluble nickel compounds > insoluble metallic nickel and its compounds.[7] Nickel carbonyl is the most rapidly and completely absorbed nickel compound in both animals and human beings, although it is insoluble in water. Hence, nickel carbonyl is the most toxic nickel compound encountered in the workplace.[12]

Inhalation of nickel is normally the principal route for its entry into the human body under conditions of occupational exposure. Nickel may be absorbed as the soluble nickel ion, whereas sparingly soluble nickel compounds may be phagocytized. The chemical form and its deposition site in the lungs will affect the extent of absorption.[31] Nickel may be removed from portions of the respiratory tract *via* mucociliary transport, resulting in the chemical entering the gastrointestinal tract. Three processes in the lung influence the respiratory burden of nickel compounds in particulate form: deposition, mucociliary clearance, and alveolar clearance. The deposition pattern of nickel in the respiratory tract is related to particle size, which determines the degree to which particles are affected by inertial impaction, sedimentation, and diffusion at deposition. In humans, about 20–35% of the inhaled less-soluble nickel that is retained in the lungs is absorbed into the blood. The remainder is either cleaned (swallowed or expectorated) or remains in the respiratory tract. Evidence indicates that nickel levels in the nasal mucosa are higher in workers exposed to less-soluble nickel compounds relative to soluble nickel compounds. In workers presumably exposed to insoluble nickel compounds, the biological half-time of nickel that has translocated to the nasal mucosa has been estimated to be several years.[32]

Dermal absorption of nickel is quantitatively minor compared with absorption from inhalation and ingestion, but it may be important in the pathogenesis of contact dermatitis caused by nickel hypersensitivity. Metallic nickel is poorly absorbed through the skin. However, some nickel compounds, such as nickel chloride or nickel sulfate, can penetrate occluded skin, resulting in dermal absorption.[31] Dermal absorption is important toxicologically primarily in the development of contact dermatitis, such as occurs when sweat releases soluble nickel salts from the corrosion of metallic nickel or nickel-bearing alloys.[7,33] Dermal penetration of nickel can be enhanced by many factors including sweat, solvents, or detergents.[27,34]

Poor personal hygiene contributes to gastrointestinal absorption in occupational exposure. Gastrointestinal absorption of nickel is relevant to workplace safety and health in relation to the consumption of food, beverages, and drinking water or the smoking of cigarettes in the workplace without adequate hand washing. Therefore, ingestion of appreciable amounts of nickel or its compounds can occur. In addition, a significant quantity of inhaled material can be swallowed following mucociliary clearance from the

TABLE 2. Occupational Exposure Limits in Various Countries for Nickel and Nickel Compounds

Country/body*	Name of standard	Values of standards (mg Ni/m³)			
		Metallic nickel	Insoluble nickel species	Soluble nickel species	Nickel carbonyl
United States					
ACGIH (22)	TLV-TWA	1.5	0.2	0.1	0.35
NIOSH (23)	REL-TWA	0.015	0.015	0.015	0.007
OSHA (23)	PEL-TWA	1.0	1.0	1.0	0.007
Japan					
The Japan Society for Occupational Health (28)	OEL	1.0	NS	NS	0.007
China					
Ministry of Health of the People's Republic of China (29)	PC-TWA	1.0	1.0	0.5	NS
Korea (30)	TLV-TWA	1.0	0.5	0.1	0.007
United Kingdom	MEL, OEL-TWA, OES	0.5 (MEL)	0.5 (OEL-TWA)	0.1 (MEL)	0.24 (OES)
Sweden	OEL-TWA	0.5	0.1 0.01 (subsulfide)	0.1	0.007
Spain	OEL-TWA	1.0	0.2	0.1	0.12
South Africa	OEL-TWA	0.5	0.5 0.01 (subsulfide)	0.1	0.24 (STEL)
Portugal	OEL-TWA	1.0	NS	0.1	0.12
Norway	OEL-TWA	0.05	0.05	0.05	0.007
New Zealand	OEL-TWA	1.0	1.0 (sulfide roasting fume and dust)	0.1	0.12
Netherlands	OEL-TWA	0.1	NS	0.1	0.35
Italy	OEL-TWA	1.0	1.0	0.1	0.12
Germany	TRK	0.5	0.5	0.05	
	STEL	2.0	2.0	0.2	0.24
France	OEL-TWA	1.0 (VME)	1.0	0.1	0.12
Finland	OEL-TWA	1.0	0.1	0.1	0.007 0.021 (STEL)
Denmark	OEL-TWA	0.05	0.05	0.01	0.007
Chile	OEL-TWA	0.8	0.8	0.08	NA
Canada-Alberta	OEL-TWA	1.0	1.0 (sulfide roasting fume)	0.1	0.12
	STEL	2	3	0.3	0.36
Belgium	OEL-TWA	1.0	1.0	0.1	0.12
Australia	OEL-TWA	1.0	1.0	0.1	0.12
Argentina	OEL-TWA	1.5	0.2 0.1 (sulfidic)	0.1	0.35

*Corresponding reference numbers are given in parentheses.

Note: ACGIH = American Conference of Government Industrial Hygienists; NA = not available; NIOSH = National Institute for Occupational Safety and Health; NS = no standard; OEL = occupational exposure limit; OEL-TWA = occupational exposure limit–time-weighted average; OES = occupational exposure standard; OSHA = Occupational Safety and Health Agency; PC-TWA = permissible concentration–time-weighted average; PEL-TWA = permissible exposure level–time-weighted average; MEL = maximum exposure limit; REL-TWA = recommended exposure limit–time-weighted average; STEL = short term exposure limit; TLV-TWA = threshold limit value–time-weighted average; TRK = technische richtkonzentrationen; VME = valeur moyenne d'expositiòn.

respiratory tract. Following ingestion, the absorption of water-insoluble nickel and its compounds from the gastrointestinal tract is small; however, the absorption of soluble nickel compounds is rapid (1–2 hours) with a bioavailability ranging from 1–5%.[7] The rate of nickel absorption from the gastrointestinal tract is dependent on not only its chemical form but also certain factors, such as composition of the diet, chelating agents, and pH. Soluble nickel compounds are absorbed more readily than relatively insoluble ones after ingestion. Studies with experimental animals and human volunteers have demonstrated a low absorption (less than 1%) from food. However, oral absorption from drinking water is higher, reaching 25%.[35] Therefore, good industrial hygiene practices should include the banning of food consumption and cigarette smoking in areas where nickel and its compounds are used.

Distribution

After absorption, nickel is mainly transported in the blood bound with serum albumin and, to a lesser degree, histidine. The nickel ion may also bind with body proteins to form a nickel-rich metalloprotein.[36] Nickel is readily distributed throughout the body, but may be affected by route of exposure, the chemical form, and time after exposure.[37] The levels of nickel in biological fluids, hair, and some other materials increase remarkably in persons with increased exposure, and decline rapidly when exposure is reduced or stopped. Thus, measurement of nickel levels, particularly in the urine, serum, or hair, may serve as an index of exposure. Although the kidney and lungs are the primary sites of accumulation of nickel, other organs, such as the spleen, liver, heart, and testes, may also accumulate the metal to a much lesser extent. Nickel is known to bind to specific proteins and/or amino acids in blood serum and the placenta. These ligands are instrumental in the transport and distribution of nickel in the body. Nickel distribution may be altered by the formation of lipophilic nickel complexes.[38]

Metabolism

Nickel is not destroyed in the body, but its chemical form may be altered. In human serum, nickel binds to albumin, histidine, nickeloplasmin, and α_2-macroglobulin. Once it has entered into the circulation, 75% of plasma nickel is carried by the circulating proteins, such as albumin and α_2–macroglobulin.[12,39,40] Much of the toxicity of nickel may be associated with its interference with the physiological processes involving manganese, zinc, calcium, and magnesium.[37] The metabolism and distribution of Ni^{2+} in humans have been fitted by a two-compartment toxicokinetic model. Because Ni^{2+} ions have no specific uptake mechanism, they probably enter the cells by way of Ca^{2+}/Mg^{2+} channels. Water-soluble nickel salts are generally thought to be noncarcinogenic, probably because of their low entry into cells and rapid excretion. Water-insoluble nickel compounds may produce their carcinogenic response because they are actively phagocytized into the cells. In the serum, there is also a nonexchangeable pool of nickel tightly bound to nickeloplasm, which is a α-macroglobulin.[36]

Elimination

Nickel is not a cumulative toxicant. The majority of the absorbed amount is excreted rapidly. Urine is the major route for elimination of absorbed nickel. Therefore, urine and plasma nickel concentrations constitute valuable indicators of recent occupational exposure to soluble nickel derivatives.

The elimination routes for nickel and its compounds depend, in part, on the chemical form of the compound and the mode of intake. Generally, urinary excretion is the major route for the elimination of absorbed nickel. Other routes of elimination, comparatively, are of minor importance. Once absorbed into the blood, nickel is predominantly extracted by the kidneys and excreted in urine. Urinary excretion of nickel is thought to follow a first-order kinetic reaction.[25] Excretion *via* other routes is somewhat dependent on the form of the nickel compound absorbed and the route of exposure. Unabsorbed dietary nickel is eliminated in feces. Nickel particles cleared from the lung *via* mucociliary action and deposited in the gastrointestinal tract are also excreted in the feces. All body secretions appear to have the ability to excrete nickel, such as sweat, milk, saliva, and tears. Nickel concentrations in sweat have been reported to be even higher than concentrations in urine.[25,41] Therefore, profuse sweating may also account for an important elimination route for nickel.[36]

Biliary excretion of nickel is minimal in animals,[42] but its importance as an excretory route in humans is unknown.[27] Nickel may also be excreted in human breast milk, leading to dietary exposure of breast-fed infants.[43] Hair is also an excretory tissue of nickel. However, use of hair as an internal exposure index has not gained wide acceptance due to problems associated with external surface contamination and nonstandardized sample cleaning methods.[19]

Biological Monitoring

Biological monitoring is not a substitute for the measurement of nickel in the air of the workplace. Because of the lack of standardized human data and well-defined toxic endpoints, biological monitoring supplements, rather than replaces, the environmental monitoring of nickel.[7]

Urine and serum are the fluids commonly analyzed for the biological monitoring of nickel exposure. Nickel concentrations in urine specimens from unexposed populations usually exceed the current analytical detection limits. In addition, urine collection is painless, noninvasive, and convenient. The advantages of serum for biological monitoring of nickel exposure include controlled sample collection, low matrix variation, and little diurnal fluctuation, but a disadvantage is that nickel concentrations in serum specimens from nonoccupational exposure individuals often are below the analytic detection limit.[36] For these reasons, urine is more practical than serum for the biological monitoring of nickel-exposed workers.[44]

For some metals, such as lead and manganese, biological monitoring of urine, serum, and other tissues or fluids may provide a reasonable estimate of exposure that is predictive of health risks.[45,46] However, this is not always the case for nickel and its compounds.[36,44] Soluble nickel compounds are rapidly excreted from the body. The biological half-time of soluble nickel in urine following inhalation has been reported to vary from 17 to 39 hours in humans.[46] Reported urinary excretion of soluble nickel (nickel sulfate) following oral exposures is also quite rapid. The elimination half-time averaged about 28 (±9) hours.[47] The half-time of nickel in serum is similar to that in urine. Values ranging from 20–34 hours have been reported for workers exposed to soluble nickel compounds *via* inhalation.[46] In another study, a half-time of 11 hours in serum was observed in human volunteers orally dosed with soluble nickel sulfate hexahydrate.[25] Because of such rapid clearance of soluble nickel from the body regardless of route of exposure, nickel levels in urine and serum are indicative only of relatively recent exposures.

Urinary and serum nickel levels provide an integrative measure of the nickel that has been absorbed in the body from all routes of exposure including inhalation, dermal, and oral. Although they provide a reasonable estimate of recent exposure to soluble nickel compounds and nickel metal powder, they do not provide a reliable measure of exposure to other less-soluble forms of nickel. Furthermore, no consistent correlation has been found between nickel concentrations in biological media and increased health risks following exposure to either soluble or insoluble nickel compounds with the exception of nickel carbonyl.[36] Moreover, assessments of workplace exposure to inhalable aerosols are likely to better reflect health risks than consideration of nickel levels in urine or serum.[48] Due to a paucity of quantitative information on dose-response relationships between nickel levels in urine and/or serum and nickel toxicity, acceptable health-based limits of permissible nickel concentrations in urine or serum of workers exposed to nickel are still lacking.[7] Biological indicators of nickel exposure are currently under study by several nongovernmental bodies, including the ACGIH and the World Health Organization (WHO).[18] Despite the generally recognized poor correlation between exposure and nickel concentrations in serum and urine, one study suggested action levels for exposure to soluble nickel compounds at 5–8 μg Ni/L serum and 30–50 μg Ni/L urine.[7,49] The latter concentration of nickel in the urine corresponds to about 0.5 mg Ni/m^3 in ambient air.[50]

Electrothermal atomic absorption spectrometry with the Zeeman background correction is currently the method of choice for the analysis of nickel in biological materials.[19,44,51] It is important that the analyses of nickel be reported in appropriate units; in the case of urine, typically as mg Ni/gm creatinine or μmol Ni/mol creatinine. In the case of blood, analysis is commonly reported as mg Ni/100 mL (whole blood or serum) or μmol Ni/100 mL (whole blood or serum). Urine samples for nickel analysis can be collected by spot sampling or by 24-hour sampling. Because collection of a 24-hour urine sample may be impractical in an occupational setting, post-

shift or end-of-week spot sampling is the preferred method when 24-hour sampling cannot be carried out. Urinary nickel levels can vary considerably, even in nonoccupationally exposed individuals. Because of this, they are most useful when interpreted on a group basis. Reported urinary nickel concentration in non-exposed individuals ranges from approximately 0.2–10 μg Ni/L urine, depending upon the method of analysis.[47] In blood sample analysis, pre-shift or post-shift sampling is typically performed,[36] although in some instances both morning and after-work samples have been taken in the same workers.[52] Serum and plasma concentrations of nickel tend to be similar, whereas whole blood concentrations have been found to be approximately twice that of serum or plasma.[53] Nickel concentrations in the serum and plasma of healthy non-exposed individuals range from 0.05–1.1 μg Ni/L serum.[36]

Acute Toxicity

There is little evidence that nickel compounds accumulate in the food chain. Nickel is not a cumulative toxin in animals or in humans.[7] Overexposure to nickel and its compounds may produce both local and systemic symptomatology. The most common local manifestations are various forms of rhinitis, including those with ulceration, and signs of irritation of the respiratory pathways after exposures to dust containing metallic nickel, nickel sulfide, or nickel oxide.[12,54,55] In terms of human health, acute toxic effects are mainly reported after inhalation of nickel and its compounds. Via this route, nickel carbonyl is the most acutely toxic nickel compound. Nickel carbonyl is a toxic, colorless, highly volatile, and flammable liquid that is formed when carbon monoxide comes into contact with active nickel. Nickel carbonyl is used in the extraction of nickel, gas plating, and as a catalyst and reactant in chemical synthesis. It is usually encountered as a vapor that is rapidly absorbed after inhalation. The initial effects involve irritation of the respiratory tract and nonspecific symptoms. Patients with severe poisoning develop intense pulmonary and gastrointestinal toxicity.[7] The effects of acute nickel carbonyl poisoning include: frontal headache, vertigo, nausea, vomiting, insomnia, and irritability, followed by pulmonary symptoms similar to those of a viral pneumonia. Pathological pulmonary lesions include: hemorrhage, edema, and cellular derangement. The liver, kidneys, adrenal glands, spleen, and brain can also be affected.[56,57] Diffuse interstitial pneumonitis and cerebral edema are the main causes of death. The clinical course of nickel carbonyl poisoning involves two stages. The initial stages are characterized by headache, chest pain, weakness, dizziness, nausea, irritability, and a metallic taste in the mouth.[58,59] There is then generally a remission lasting 8–24 hours followed by a second phase characterized by a chemical pneumonitis. Common clinical signs in severe cases include: tachypnea, cyanosis, tachycardia, and hyperemia of the throat. Hematological results include leukocytosis. Chest X rays in some severe cases are consistent with pulmonary edema or pneumonitis.[57] The second stage reaches its greatest severity in several days. In ten patients with nickel carbonyl poisoning, there were initial changes in pulmonary function tests consistent with acute interstitial lung disease. However, these results returned to normal after several months.[27,59] Sodium diethyldithiocarbamate is an investigational drug used to chelate nickel following exposure to nickel carbonyl.[7] Despite its extreme acute toxicity in the occupational setting, nickel carbonyl does not seem to represent any actual threat from the standpoint of an environmental pollution, because of its relatively short (about 30 min) half-life.[12]

Acute inhalation toxicity of nickel fumes in humans was reported in a male worker who sprayed nickel with a metal arc process without wearing personal protective equipment. The death occurred 13 days after the 1-hour exposure to an estimated concentration of 382 mg Ni/m^3 of principally metallic nickel fumes with the size of the majority of particles being <1.4 μm. The total amount of nickel inhaled by the worker was estimated to be nearly 1 g. Histological examination of the lungs revealed alveolar wall damage and edema in alveolar spaces, and marked tubular necrosis was noted in the kidneys.[60]

Other reports on the acute oral toxicity of nickel in humans come from accidental exposures or studies of nickel-sensitized individuals. Gastrointestinal upset (vomiting, abdominal discomfort, cramps, diarrhea) and neurological symptoms (giddiness, headache, weariness) were observed in workers accidentally ingesting water containing approximately 7.1–35.7 mg Ni/kg as nickel sulfate and nickel chloride.[61] Allergic dermatitis was observed in previously nickel-sensitized individuals ingesting a single challenge dose of greater than 0.01 mg Ni/kg as nickel sulfate.[62]

Chronic Toxicity (Excluding Cancer)

In most work environments, the potential chronic toxicity of various species is likely to be more of concern than acute effects, with the exception of nickel carbonyl. Both noncancerous and cancerous respiratory effects have been observed in humans exposed to airborne nickel compounds. Noncancerous chronic effects, such as rhinitis, sinusitis, nasal septal perforations, and asthma, have been reported in nickel refinery and nickel-plating workers.[19] Accumulation of nickel in the body through chronic exposure may lead to lung fibrosis.[63,64] Early studies show that workers overexposed to nickel ore dust may develop signs of pneumoconiosis,[12,65] but co-exposure of some other dust components, such as silica, cannot be excluded in these cases. A recent case-control study indicates that pulmonary ventilatory function was significantly impaired in 34 retired miners exposed to nickel dust compared to control groups.[66] An association between the presence of irregular opacities in chest X rays and cumulative exposures to soluble nickel, sulfide nickel, and possibly metallic nickel was reported. This evidence suggests that soluble nickel and sulfide nickel act to induce pulmonary fibrosis.[27] In 2003, radiographs of 1046 workers in a nickel refinery in Norway were read blindly and independently by three NIOSH certified B-readers, according to the International Labor Organization (ILO) standards. Results of this study indicate that in addition to age and smoking, exposure to soluble and sulfidic nickel compounds was a risk factor of pulmonary fibrosis in humans.[64] With respect to noncancerous respiratory effects, a number of animal studies have reported on the inflammatory effect of nickel compounds on the lung.[67–71] These effects include increased enzymes in bronchoalveolar lavage fluid, chronic inflammation, focal alveolar epithelial hyperplasia, macrophage hyperplasia, and fibrosis. However, studies examining the risk of death from noncancerous respiratory disease among nickel workers have not found significant increases.[6,72,73]

Renal effects, such as renal edema with hyperemia and parenchymal degeneration, have been reported in cases of accidental industrial exposure to nickel carbonyl.[19] Information on the chronic renal toxicity of nickel in humans comes from a report of 14 male and 12 female workers highly exposed to soluble nickel compounds. A significant increase in urinary β_2-microglobulin levels was observed in a group of workers with urinary nickel levels exceeding 100 μg/L. Urinary β_2-microglobulin levels were not significantly altered in workers with urine nickel levels of less than 100 μg/L. Urinary levels of total proteins, β_2-microglobulin, retinol binding protein, and N-acetyl-β-D-glucosaminidase (NAG) were increased in 12 women, and urinary lysozyme and NAG were increased in 14 men occupationally exposed to soluble nickel (sulfate, chloride) compounds at an average concentration of 0.75 mg Ni/m^3. No effects on markers of glomerular function, urinary albumin levels, or transferrin levels were noted.[74] These biochemical markers of kidney damage reflect tubular dysfunction.

Nickel and nickel compounds have a strong sensitizing potential on the skin, which is manifested by irritation, eczema, and allergic contact dermatitis. Oral intake of low doses of nickel may provoke allergic dermatitis in sensitized individuals.[35] Nickel contact hypersensitivity has been documented in workers exposed to soluble nickel compounds.[19,56] To examine whether nickel exposure plays a role in occupational contact dermatitis (OCD), data on occupational skin disease collected by two occupational disease surveillance schemes in the United Kingdom were studied. Results indicated that 1190 cases of occupational contact dermatitis, thought to have relevant nickel exposure, were derived from reports by dermatologists (12% of total estimated OCD).[75]

Immunological toxicity of nickel in humans was reported in 38 production workers exposed to nickel (compound not specified). Significant increases in levels of immunoglobulin G (IgG), IgA, and IgM and a significant decrease in IgE levels were observed.[76,77] Significant increases in other serum proteins, which may be involved in cell-mediated immunity (including α_1-antitrypsin, α_2-macroglobulin, and ceruloplasmin), were also observed. The increase in immunoglobulins and serum proteins suggests that the immune system was stimulated by nickel exposure.

No studies were found regarding gastrointestinal, cardiovascular, hematological, musculoskeletal, endocrine, or hepatic effects in humans after inhalation exposure to nickel or its compounds.[6]

Genotoxicity

A number of studies have examined the genotoxicity of nickel compounds by using different toxicological

test systems. The results are summarized in Table 3. As listed in Table 3, toxicological test systems used frequently in the *in vivo* studies of genotoxicity of nickel compounds include: human lymphocytes and bacterial systems, rat or mouse bone marrow cells, and *Drosophila melanogaster*. Toxicological test systems or end points used mainly in the *in vitro* studies include: micronucleus test, Ames test, mammalian cell (including human, rat, and mouse) gene mutation, sister chromatid exchange, DNA-protein cross-links, DNA single-strand breaks, chromosomal alterations, and cell transformation. These genotoxic results provide useful data not only for carcinogenicity evaluation of different nickel compounds but also for their hazard identification.

Table 3 shows that nickel chloride ($NiCl_2$), nickel sulfate ($NiSO_4$), nickel oxide (NiO), nickel (III) oxide (Ni_2O_3), nickel subsulfide (Ni_3S_2), and nickel sulfide (NiS) are the most frequently examined nickel compounds in the genotoxic studies in the past 30 years. The genotoxicity of metallic nickel has not been tested yet, except for a few studies conducted on nickel stainless steel (contain 3.5% nickel).[78] The micronucleus test is used in toxicological screening for potential genotoxic compounds. The assay is now recognized as one of the most successful and reliable assays for identification of genotoxic carcinogens. There are two major versions of this test, one *in vivo* and the other *in vitro*. The *in vivo* tests normally analyze animal bone marrow or peripheral blood. Based on Table 3, most *in vivo* micronucleus tests of nickel compounds show negative results. However, Arrouijal et al.[79] reported that administration of 250 mg/kg of Ni_3S_2 in mice revealed a clear increase of micronuclei frequency in polychromatic erythrocytes after 24, 48, and 72 hours of treatment. The Ames test is a frequently used biological assay to assess the mutagenic potential of chemical compounds. A positive test indicates that the chemical might act as a carcinogen, because cancer is often linked to DNA damage. Zeiger et al.[80] tested Bis (1, 5-cyclooctadiene) nickel in an Ames test using bacterial strains TA100, TA1535, TA97, and TA98. In their publication, responses in strains TA1535 and TA98 were uniformly negative. "Weak positive" results were obtained in some experiments with strain TA97. Only strain TA100 gave results considered "positive". However, as shown in Table 3, not all research agrees with these Ames test results. Based on Table 3, we conclude that nickel and its compounds are not mutagenic in Ames tests or genotoxic using *in vivo* micronucleus tests. However, based on the information of *in vitro* studies, there is sufficient evidence to conclude that both soluble nickel compounds [nickel chloride ($NiCl_2$) and nickel sulfate ($NiSO_4$)] and insoluble nickel compounds [nickel oxide (NiO), nickel subsulfide (Ni_3S_2), and nickel sulfide (NiS)] are genotoxic. The most frequently used end points *in vitro* tests for the genotoxicity of nickel and its compounds are mammalian cell transformation and DNA damage.

Reproductive Toxicity

It has not yet been established whether human exposure to nickel and its compounds causes reproductive toxicity. With respect to animal studies, a variety of developmental, reproductive, and teratogenic effects have been reported in animals exposed mainly to soluble nickel *via* oral and parenteral administration.[134] There is some evidence in humans to indicate that absorbed nickel may be able to move across the placenta into fetal tissue.[135–137] Workers at a Russian nickel hydrometallurgy refining plant, when compared to a reference group, showed a marked increase in frequency of spontaneous and threatening abortions and in structural malformations of the heart and musculoskeletal system in live-born infants of nickel-exposed mothers.[138] However, the investigators noted that the nickel-exposed women manually lifted heavy nickel anodes and they may have experienced heat stress. In recent years, several studies were set to investigate whether women employed under conditions of nickel exposure were at elevated risks of spontaneous abortion (SA), delivering a newborn with a small-for-gestational-age (SGA),[62] a genital malformation, or a malformation or deformation of the musculoskeletal system. Multiple logistic regression analysis was used to analyze the association of the outcome with the assigned exposure-rating category. Results indicated that there was no statistical association between maternal occupational exposure to water-soluble nickel in early pregnancy and risk of self-reported SA.[139] There was no adverse effect of maternal occupational exposure to water-soluble nickel in the first part of pregnancy on the risk of delivering an SGA newborn.[140] In addition, no negative effect of maternal exposure to water-soluble nickel on the risk of delivering a newborn with malformations

TABLE 3. Genotoxicity of Nickel Compounds *In vivo* and *In vitro

Compound	*In vivo* test system		*In vitro* test system	
	Positive*	Negative	Positive	Negative
Nickel chloride ($NiCl_2$)	Mouse bone marrow cells: chromosome aberrations (ip) (81); *Drosophila melanogaster*: weakly positive of gene mutation (wing spot test) of (82)	*Drosophila melanogaster*: gene mutation (83); Mouse bone marrow cells: micronucleus test (ip) (84, 85)	Human lymphocytes: sister chromatid exchange (86), DNA single-strand breakage (comet assays) (87), DNA-protein cross-links (88); *Corynebacterium* sp.: gene mutation (89); Human HeLa cells and *Escherichia coli*: DNA replication rate (90); Virus-infected mouse sarcoma cells: induction of revertant foci (91, 92); Mouse lymphoma cells: forward mutation (93, 94); Chinese hamster ovary cells: gene mutation at gpt locus (95), DNA protein cross-links/single-strand breaks (96, 97), DNA strand breaks (98); Chinese hamster embryo cells: chromosomal alterations, cell transformation (99); Syrian hamster embryo cells: cell transformation (100); Mouse BALB/c-3T3 fibroblasts: cell transformation (101)	Ames test: gene mutation; *Escherichia coli* WP2: gene mutation (102-104); Human diploid fibroblasts: DNA single-strand breaks (105); Mouse embryo fibroblast cells: cell transformation (106)
Nickel sulfate ($NiSO_4$)	*Drosophila melanogaster*: Recessive lethal mutation (107)	Rat bone marrow and spermatogonial cells: chromosome aberrations (108); Mouse bone marrow cells: Micronucleus test (ip) (84)	Primary human kidney: cell transformation and chromosome aberrations (109, 110); Human foreskin fibroblasts: cell transformation (111); V79 Chinese hamster cells: cell transformation and chromosomal aberrations (112); Human peripheral lymphocytes: DNA single-strand breaks (113); Mouse lymphoma cells: forward mutation (93, 94) Chinese hamster ovary cells: gene mutation at gpt locus (95); Human bronchial epithelial cells: chromosome aberrations (114); Syrian hamster embryo cells: cell transformation (115)	Ames test: gene mutation (102, 103, 116); *Saccharomyces*: reverse mutation (117); Mouse embryo fibroblast cells: cell transformation (106)
Nickel sulfate hexahydrate ($NiSO_4 \cdot 6H_2O$)		Rat bone marrow cells: Micronucleus test (118)	Human peripheral lymphocytes: DNA single-strand breaks (113)	
Nickel oxide (NiO)	Human lymphocytes from workers in a nickel refinery: chromosome gaps (119)	Mouse bone marrow cells: Micronucleus test (ip) (84); Human lymphocytes from workers in a nickel refinery: sister chromatid exchange (119)	Human lymphocytes sister chromatid exchange, and DNA single-strand breaks (86, 113); Baby hamster kidney (BHK-21) fibroblasts: cell transformation (120); Mouse embryo fibroblast cells: cell transformation (106)	*Bacillus subtilis*: DNA damage (121)
Nickel (III) oxide (Ni_2O_3)				*Bacillus subtilis*: DNA damage (121)
Nickel nitrate ($Ni(NO_3)_2$)		*Drosophila melanogaster*: gene mutation (83); mouse bone marrow cells: micronucleus test (ip) (85)		Ames test: gene mutation (102, 103, 116)

continued

TABLE 3. (Continued)

Nickel acetate ($Ni(CH_3COO)_2$)		Mouse: dominant lethal (ip) (85)	Chinese hamster ovary AS52 cells: gene mutation at gpt locus (95); Baby hamster kidney (BHK-21) fibroblasts: cell transformation (120); Human foreskin fibroblasts: cell transformation (111)	
Nickel subsulfide (Ni_3S_2)	Human lymphocytes from workers in a nickel refinery: chromosome gaps (119); Mouse bone marrow cells: micronucleus test (79)	Human lymphocytes from workers in a nickel refinery: sister chromatid exchange (119)	Human lymphocytes: sister chromatid exchange, chromosomal aberrations and DNA single-strand breaks (79, 86, 113); Chinese hamster ovary cells: gene mutation at gpt locus (95); CD 2F1 mouse lung and nasal mucosa cells: DNA fragmentation (122); Human lymphocytes: sister chromatid exchange (123, 124); Human lymphocytes: micronucleus formation and metaphase analysis (124); Syrian hamster embryo cells: cell transformation (125); Baby hamster kidney (BHK-21) fibroblasts: cell transformation (120); Mouse embryo fibroblast cells: sister chromatid exchange and cell transformation (106, 123); Rat liver T51B cells: cell transformation (126); Human foreskin fibroblasts: cell transformation (111)	Ames test: gene mutation (79)
Nickel (II) carbonate hydroxide tetrahydrate ($2NiCO_3 \cdot 3Ni(OH)_2 \cdot 4H_2O$)			Human peripheral lymphocytes: DNA single-strand breaks (113)	
Nickel sulfide (NiS)			Chinese hamster ovary cells: DNA protein cross-links/ single-strand breaks (96, 97), DNA strand breaks (98); Chinese hamster embryo cells: chromosomal alterations, cell transformation (99, 127); Syrian hamster embryo cells: cell transformation (100, 128, 129); Mouse embryo fibroblast cells: cell transformation (106); Human bronchial epithelial: cell transformation (101, 130, 131)	
Nickel stainless steel (0.07% carbon, 1.0% manganese, 1.0% silicon, 15.5–17.5% chromium, 3–5% nickel, 3–5% copper, 0.15–0.45% niobium + tantalum) (78)	Human buccal cell: micronucleus test (30 days after the placement of orthodontic appliances) (78)	Human buccal cell: comet assays (30 days after the placement of orthodontic appliances) (78)		Ames test, mouse fibroblasts and human MG63 osteoblasts: sister-chromatid exchanges and chromosomal aberrations (132)
Bis (1,5-cyclooctadiene) nickel ($C_{16}H_{24}Ni$)			Ames test: strain TA100 (80)	Ames test (133)
Bis(triphenylphosphine) dicarbonylnickel ($Ni(PPh_3)_2(CO)_2$)				Ames test (133)

*Corresponding reference numbers are given in parentheses.

Note: ip = intraperitoneal.

of the genital organs was found.[141] The incidence of defects in the musculoskeletal system at birth was high, especially for feet deformities, but no effect of maternal exposure to water-soluble nickel on the risk of delivering a newborn with musculoskeletal deformities and malformations was found.[142]

It should be noted that it is not possible to find women whose occupational nickel exposure persisted throughout their pregnancies until birth. Generally, fetal protection policies require removal of pregnant women from jobs with exposures to possible reproductive toxicants. Therefore, it cannot be concluded that occupational exposure to nickel and its compounds during pregnancy presents no risk.[27]

Carcinogenicity

Nickel compounds are known to be human carcinogens based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information, which indicates a causal relationship between exposure to nickel compounds and human cancer.[143] The findings of an increased risk of cancer in exposed workers are supported by evidence from experimental animals that shows exposure to nickel compounds by multiple routes causes malignant tumors to form at various sites.[9] Metallic nickel can also be anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals. A variety of carcinogenicity studies in rodents indicate that metallic nickel powder can produce tumors when given by intratracheal instillation or subcutaneous, intramuscular, or intraperitoneal injection. Intratracheal instillation of metallic nickel powder primarily induces adenocarcinoma, whereas injection most frequently induces sarcoma, demonstrating that metallic nickel can induce both epithelial and connective-tissue tumors.[8] However, the available data from human studies of metallic nickel exposures are less informative. The available epidemiological studies of workers are limited by inadequate exposure information, low exposures, short follow-up periods, and the small number of cases.[9]

Epidemiological studies have demonstrated a strong association between lung and nasal cancers and exposure by inhalation to nickel compounds in nickel refineries, primarily in the early stages of nickel refining.[8,26] Very high risks of lung and nasal cancer have been reported in nickel refinery workers employed in the high-temperature roasting of sulfide ores, involving substantial exposure to nickel subsulfide and oxide. Similar risks have been reported in workers exposed to soluble nickel, but often combined with some nickel oxide exposure. The cancer risk to miners and other refinery workers has been reported to be much lower.[19]

Although the evidence is sufficient to consider less-soluble nickel compounds as carcinogens following inhalation exposure, how environmental exposure to nickel affects cancer risk is not clear. Nickel levels in the environment are much lower than those that were associated with cancer in workers. In addition, in the environment, nickel is also more likely to be in the form of a mineral lattice rather than the more active nickel refinery dust that contains nickel subsulfide, the form of nickel most consistently associated with cancer.[6] Recently, a case-control study was conducted by Kou et al. to verify the role of heavy metals in the development of lung cancer. They found that Ni and Cr contents in lung tumors of lung cancer patients were significantly higher than those in normal lung tissue of noncancer controls. They suggest that accumulation of metallic nickel in lung tumors may play a role, at least in part, in the development of lung cancer.[144]

Although IARC, as well as many other agencies, have classified nickel compounds as carcinogenic to humans, it is still not known with certainty which forms of nickel pose the most risk. In a case-control study of Norwegian nickel-refinery workers, the authors examined dose-related associations between lung cancer and cumulative exposure to four forms of nickel: water-soluble, sulfidic, oxidic, and metallic. A clear dose-related effect was seen for water-soluble nickel. A general rise in risk from the other types of nickel could not be excluded, but no dose-dependent increase was seen.[145,146] This study suggests an important role of the water-soluble nickel species in nickel-related cancer. It appears that the traditional emphasized higher carcinogenic risk of the less-soluble compounds might be somewhat overstated. Further experimental studies are necessary to elucidate the difference in carcinogenicity between water-soluble and insoluble nickel compounds. Currently, there are little epidemiological data to indicate that exposure to the carcinogenic forms of nickel causes cancer outside the lung and the nasal cavity.[7]

Molecular Mechanisms of Carcinogenesis

Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, damage genetic materials. DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair have been observed in *in vitro* studies.[9] However, the exact mechanisms of nickel-induced carcinogenesis are still not clear. Recent evidence indicates that ROS formation and alterations in normal signal transduction induced by nickel and its compounds may play an important role in the etiology of their carcinogenesis.[147] Therefore, this review summarizes the generation of ROS and alterations of signaling components due to different nickel compounds.

Induction of ROS

ROS are well known to be cytotoxic and have been implicated in the etiology of a wide array of human diseases, including cancer. Various carcinogens may also partly exert their effect by generating ROS during their metabolism. Oxidative damage to cellular DNA can lead to mutations and may, therefore, play an important role in the initiation and progression of multistage carcinogenesis. The changes in DNA—such as base modification, rearrangement of DNA sequence, miscoding of DNA lesions, gene duplication, and the activation of oncogenes— may be involved in the initiation of various cancers. Elevated levels of ROS and downregulation of ROS scavengers and antioxidant enzymes are associated with various cancers.[148] ROS form as natural byproducts of the normal metabolism of oxygen and have important roles in cell signaling. However, during times of environmental stress, such as ultraviolet (UV) exposure, ROS can increase dramatically. The ROS consist of a group of partially reduced forms of molecular oxygen, such as hydroxyl radical (•OH), superoxide anion ($O_2^{-\bullet}$), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), lipid peroxides, and hypochlorous acid (HClO).[149] Accumulation of ROS may be accompanied by the production of reactive nitrogen species,[150] such as the highly reactive peroxynitrite anion, a strong oxidant formed by the reaction of $O_2^{-\bullet}$ and nitric oxide (NO). Under physiological conditions, cells defend themselves against ROS damage through antioxidants that remove free-radical intermediates and inhibit oxidation. An imbalance between endogenous oxidants and antioxidants results in oxidative stress.[151,152] The cumulative production of ROS through either endogenous or exogenous insults is termed oxidative stress.

Nickel and other heavy metals can generate ROS directly from molecular oxygen in a two-step process to produce superoxide anion.[153] In the continued presence of heavy metals, the superoxide anions formed can then combine with protons in the dismutation reaction, generating hydrogen peroxide in the process. Oxidative stress induces a cellular redox imbalance, which has been found to be present in various cancer cells compared with normal cells. The redox imbalance, thus, may be related to oncogenic stimulation. The ROS could nonselectively induce DNA damage, possibly resulting in genetic changes in active genes. Nickel may bind to DNA-repair enzymes and generate oxygen-free radicals to cause protein degradation *in situ*. This irreversible damage to the proteins involved in DNA repair, replication, recombination, and transcription could be important for the toxic effects of nickel.[154,155]

Experimental data suggest that oxidative stress may be important in nickel-induced carcinogenesis; however, a direct correlation between the ability of nickel to produce oxidative stress and carcinogenicity is not yet fully understood. The possible involvement of ROS in nickel carcinogenesis was reviewed previously.[1,156–158] Nickel produces rather low but measurable levels of free radicals in cells.[159–161] A summary of ROS or oxidative stress generated by different nickel compounds is shown in Table 4.

Table 4 shows that nickel chloride ($NiCl_2$), nickel sulfate ($NiSO_4$), nickel subsulfide (Ni_3S_2), and nickel oxide (NiO) are the most frequently examined nickel compounds in the ROS generation studies. Only a few studies were conducted on nickel acetate [$Ni(CH_3COO)_2$] and nickel sulfide (NiS). Research evidence seems to be sufficient to conclude that both soluble nickel compounds [nickel chloride ($NiCl_2$) and insoluble nickel compounds [nickel subsulfide (Ni_3S_2)] generate ROS demonstrated by both *in vivo* and *in vitro* studies. The most frequently used end points in nickel-induced oxidative stress include DCF oxidation, formation of DNA damage such as 8-OH-dG, and levels of LPO, GSH, and GSSG in cells or in tissues. However, all these end points

TABLE 4. ROS or Oxidative Stress Generated by Different Nickel Compound

Compound	Test system	Treatment	Result	Ref no.
Nickel chloride ($NiCl_2$)	CHO cells	0-5 mM, 3 h	DCF oxidation ↑	(162)
		5 mM, 3 h	LPO ↔; DCF oxidation ↑	(163)
		2 mM, 18 h	DCF oxidation ↑	(159)
	BALB-3T3 and B200 cells	05–1 mM, 6 h	GSH ↓	(160)
	Human A549 cells	0.25–1 mM, 45 min	DCF oxidation	(161)
	Rat tissues	0.12–0.75 mM/kg, sc injection, 48 h	Liver, kidney and lung: MAD and LPO↑; brain, heart, spleen and testis MAD and LPO ↔	(42)
	Rat cortical slice	0–2 mM, 4 h	LPO↑; LDH release↑	(164)
	Human leukemia cells	0.5–1 mM, 0–96 h	LPO (MDA)↑	(165)
	Rat serum	20 mg/kg, 24 h	LPO (MDA)↑	(165)
	Human lymphocytes	0–10 mM, 1 h	DCF oxidation↑; LPO↑;	(166)
	BALB-3T3 cells	2 mM, 20 h	Cytoskeletal protein sulfhydryls and cellular GSH↓	(167)
	Human hepatoma cells (Hep3B)	0–1 mM, 8 h	DCF oxidation↑	(168)
	Mouse embryo fibroblast PW cells	1 mM, 1 h	LPO (MDA)↑	(169)
	Human T cells (Jurkat)	0–80 μg/mL, 6 h	GSH ↓; GSSG↑	(170)
	Mice	12.5–50 μM/kg, 3 days	Whole homogenates, mitochondrial fraction, microsomal fractions of testis, and epididymal sperm: LPO↑; Cytolic fraction of testis: GPx, GST, and CAT↑	(171)
	Mice liver	8–16 mg/kg, oral, 30 days	LPO↑; GSH, total-SH groups, total ascorbic, SOD and CAT↓	(172)
	Calf thymus DNA dG (0.75 mM)	10 mM, 37°C for 5 and 9 days	8-OH-dG ↔	(173)
	Alcaligenes latus	0–250 nM, grown in air at 25°C with shaking	Hydrogenase↑	(174)
	Rat, mouse, hamster and guinea pig renal tissue	0.25 mM/kg, sc injection, for 17 h	Renal heme oxygenase ↑	(175)
	SD rat serum	0.1–0.75 mM/kg , ip injection, 24 h	•OH↑	(176)
Nickel chloride hexahydrate ($NiCl_2 \cdot 6H_2O$)	Wistar rat tissues	150 μM/kg, ip, 16 h	Liver LPO↑; kidney LPO ↔; liver and kidney NOS↑	(177)
Nickel sulfate ($NiSO_4$)	Wheat leaves	0.1 mM for 3, 6, and 9 days	$O2^{-\bullet}$, H_2O_2, APX and POD↑;	(178)
	Human leukemic cells (Jurkat)	0.17 μM, 4 h	SOD and CAT ↓; LPO ↔ DCF oxidation↑	(179)
	HeLa cells	10 μg/mL, 24 h	8-OH-dG ↔	(180)
	Wistar rat lung	1 mg/rat, intratracheal, 48 h	8-OH-dG ↑	(180)
	Human PMNs	1 μM/2.5x10^5 PMNs, 30 min	H_2O_2 ↔	(181)
Nickel sulfate hexahydrate ($NiSO_4 \cdot 7H_2O$)	HeLa cells	10 μg/mL, 24 h	8-OH-dG ↔	(182)
	Wistar rat lung	0.5–1 mg/rat, intratracheal, for 48 h	8-OH-dG ↑	(182)
	FSDC	100 μg/mL, 24 h	iNOS ↑	(183)
Nickel acetate ($Ni(CH_3COO)_2$)	Mice	170 mM/kg, 3–38 h	Renal GSH ↓; LPO↑	(184)
	F344/NCr rat	90–180 μM/kg, ip, for 24 or 48 h	DNA base damage of 5-hydroxy-5-methylhydantoin, 5-hydroxyhydantoin, 5-(hydroxymethyl)uracil, cytosine glycol, thymine glycol, 5,6-dihydroxycystosine, 4,6-diamino-5-formamidopyrimidine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine, 8-hydroxyadenine, 2-hydroxyadenine, and 8-hydroxyguanine (8-OH-Gua) ↑	(185)

continued

TABLE 4. (Continued)

Nickel subsulfide (Ni_3S_2)	CHO cells	0–20 μg/cm², 5 h	DCF oxidation ↑	(162)
		10 μg/cm², 5 h	DCF oxidation↑; LPO↑	(163)
		20 μg/cm², 18 h	DCF oxidation ↑	(159)
	Rat kidney tissue	0.36 mM/kg intrarenal administration 1–20 days	Kidney MAD ↔	(42)
	Mouse embryo fibroblast PW cells	2 μg/cm², 1h	•OH↑	(169)
	Rat lymphocytes	0–2 mM, 2 h	DCF oxidation ↑	(186)
	HeLa cells	10 μg/mL, 24 h	8-OH-dG ↑	(180)
	Wistar rat lung	1 mg/rat, intratracheal, 48 h	8-OH-dG ↑	(180)
	Human PMNs	1 μM/2.5x 10^5 PMNs, 30 min	H_2O_2↑	(181)
	Calf thymus DNA dG (0.75 mM)	5 mg/mL, 37°C for 5 and 9 days	8-OH-dG ↑	(173)
	HeLa cells	10 μg/mL, 24 h	8-OH-dG ↑	(182)
	Wistar rat lung	0.5–1 mg/rat, intratracheal, 48 h	8-OH-dG ↑	(182)
	RAW 264.7 cells	10–30 μg/mL, 48 h	NO_2^-↑;	(182)
	HL-60	10 μg/mL, 4–12 h	$O_2^{-\bullet}$↑	(182)
	Rat renal tissue	10 mg/rat, intrarenal injection, 1 week (but not 2, 3, or 4 weeks)	Renal heme oxygenase ↑	(175)
	Human bronchial epithelial cells	2.34 μg/cm², 24 h	DCF oxidation ↑	(187)
Nickel sulfide (NiS)	CHO cells	5–20 mg/cm², 5 h	LPO↑	(163)
	Human PMNs	1 μM/2.5x 10^5 PMNs, 30 min	H_2O_2 ↑	(181)
Nickel oxide (NiO)	CHO cells	5–20 mg/cm², 5 h	DCF oxidation ↑; LPO↑	(167)
	HeLa cells	10 μg/mL, 24 h	8-OH-dG ↔	(180)
	Wistar rat lung	1 mg/rat, intratracheal, 48 h	8-OH-dG ↑	(180)
	HeLa cells	10 μg/mL, 24 h	8-OH-dG ↔	(182)
	Wistar rat lung	0.5–1 mg/rat, intratracheal, 48 h	8-OH-dG ↑	(182)
	RAW 264.7 cells	10–100 μg/mL, 48 h	NO_2^-↑	(182)

Note: ↑ = increase; ↔= no change; ↓ = decrease; 8-OH-dG = 8-hydroxydeoxyguanosine; APX = ascorbate peroxidase; CAT catalase; CHO cells = Chinese hamster ovary cells; DCF = dichlorofluorescein diacetate; dG = 2'-deoxyguanosine; FSDC = fetal skin-derived dendritic cells; GPx = glutathione peroxidase; GSH = glutathione; GSH-Px = glutathione peroxidase; GST = glutathione-S-transferase; iNOS = isoform of nitric oxide synthase; ip = intraperitoneal; LDH = lactate dehydrogenase; LPO = lipid peroxidation; MDA = malondialdehyde; NOS = nitric oxide synthase; PMNs = polymorphonuclear leukocytes; POD = guaiacol peroxidase; sc = subcutaneous; SD = Sprague-Dawley; SOD = superoxide dismutase.

reflect indirect indices of ROS generation. Only a few studies measured the generation of ROS, such as H_2O_2, •OH, or $O_2^{-\bullet}$, directly.[169,176,178] However, no study evaluated the ROS generation induced by metallic nickel.

Alterations in Signal Transduction

As stated above, numerous studies have examined the effects of nickel compound–induced ROS and DNA damage formation. Although these effects are relevant to carcinogenesis, recent data indicate that nickel-induced alterations in signal transduction may also play a role in the etiology of cancer either independently, or in concert with DNA damage.[188–191] Metal exposure has been shown to activate or inactivate cancer-related genes and their protein products. These include the MAPKs and nuclear transcription factors, such as NFκB, AP-1, HIF-1, NFAT, and p53.[147,160,190–196] These effects may be direct and through the interaction of nickel with proteins, or indirect and through the formation of nickel-induced ROS. The effects of nickel and its compounds on signaling pathways may mimic extracellular ligands, such as physical hypoxia, *via* mechanisms that are poorly understood. Alterations in signal transduction events as a result of exposure to different nickel compounds are summarized in Table 5.

Table 5 demonstrates that nickel chloride ($NiCl_2$), nickel sulfate ($NiSO_4$), and nickel subsulfide (Ni_3S_2) are the most frequently examined nickel compounds in the studies of signaling components affected by nickel compounds. Few studies were conducted on

TABLE 5. Alterations of Signaling Components Produced by Different Nickel Compounds

Compound	Test system	Treatment	Signaling component						Ref
			NFκB	AP-1	HIF-1	NFAT	p53	Others	no.
Nickel chloride ($NiCl_2$)	Mouse fibroblast 3T3 cells	1 μM, 48 h	↑	↔					(197)
	Human bronchial epithelial cells	1 μM, 36 h	↑	↔					(197)
	HUVEC	1.5 mM, 1 h	↑						(198)
	Mouse epidermal cells	0.5-1 mM, 0–24 h			↑			PI-3K ↑, p-AKT↑	(199)
	Mouse embryonic fibroblasts	1 mM, 20 h			↑				(200)
	Human MoDC	0.1–1 mM, 0–1 h	↑					p-p38↑, p-ERK↑	(201)
	Mouse embryo fibroblasts	1 mM, 24 h		↔		↑	↔		(169)
	HUVEC	0–2 mM, 0–24 h	↑					p-p38↑, MCP-1↑	(202)
	Human A549 lung cells	1 mM, 16 h			↑				(161)
	HOS and SA-8 cells	1 mM, 16 h			↑		↑		(203)
	Mouse fibroblast 3T3 cells	1 mM, 24 h						ATF-1 ↑	(204)
	HUVEC	1 mM	↑	↑					(205)
	HUVEC	1 mM	↑	↑					(206)
	Human bronchial epithelial cells	0.5 mM , 0.5 h	↑						(207)
	Human bronchial epithelial cells	0.125–0.5 mM, 48 h						COX-2 ↑	(207)
	C57 B mouse cells	0.5 mM, 24 h						AhR ↓	(208)
	C57 B mouse cells	0.5 mM, 20 h			↑				(209)
	Mouse fibroblast cells	1 mM, 20 h			↑		↑		(210)
	Human bronchial epithelial cells, Murine embryonic fibroblasts	0–0.5 mM, 0–48 h		↑				COX-2 ↑	(211)
	Human A549 lung cells	0–1 mM, 12–24 h	↑		↑			TNF-α ↑	(212)
	Human epidermal keratinocytes	11 μM, 0.5–6 h	↓	↑					(213)
	Murine epidermal and keratinocyte cells	0.1–10 μM, 1–4 h						TNF-α ↑	(214)
	Human bronchial epithelial cells	0–0.5 mM, 12–48 h	↑	↑		↑		TNF-α ↑	(215)
Nickel chloride hexahydrate ($NiCl_2 \cdot 6H_2O$)	HUVEC	1.5 μM, 16 or 5 h	↑		↑				(216)
	Human monocytic cells	0–30 μM, 6–72 h	↔					Nrf2 ↑	(217)
	Human THP1 monocytic cells	0–90 μM, 72 h	↑						(218)
Nickel sulfate ($NiSO_4$)	FSDC	100 μg/mL, 0.5–2 h	↑	↑					(183)
	Human dendritic cells	500 μM, 8 h	↑					p-p38↑	(219)
	HepG2 Human hepatoma cells	100 μM, 1 h						p-AKT↑	(220)
	CD34+-progenitor-derived DCs	60 μM, 0.5–24 h	↑					COX-2 ↑	(221)
	Murine epidermal and keratinocyte cells	0.1–10 μM, 1–4 h						TNF-α ↑	(214)
	Human bronchial epithelial or human keratinocyte HaCaT cells	0–1 mM, 0–24 h						c-Myc ↑, p-ERK↑	(222)
Nickel sulfate hexahydrate ($NiSO_4 \cdot 6H_2O$)	Human airway epithelial cells transformed with simian vacuolating virus 40	0.5 mM, 0–16 h			↑			CAIX ↑	(223)
	Human bronchial epithelial cells	90 μM, 24 h			↑			IL-8 ↑	(224)
Nickel acetate ($Ni(CH_3COO)_2$)	Normal rat kidney cells	480 μM, 6–48 h					↔		(225)
	Chinese hamster ovary cells	0–640 μM, 6–72 h					↔		(226)
	Normal rat kidney cells	160–240 μM, 2 mo						FHIT	(227)

continued

nickel acetate [$Ni(CH_3COO)_2$], and nickel sulfide (NiS). No studies were found in nickel oxide (NiO) and metallic nickel. This research evidence seems to be sufficient to conclude that both soluble and insoluble nickel compounds induce NFκB and HIF-1 upregulation in different cell lines *in vitro*. Controversy

TABLE 5. (Continued)

Nickel subsulfide (Ni_3S_2)	Mouse fibroblast 3T3 cells	1μg/cm², 48 h	↑	↔					(197)
	Human bronchial epithelial cells	1 μM, 36 h	↑	↔					(197)
	Mouse epidermal cells	0.5–1μg/cm², 0-24 h			↑			PI-3K↑, p-AKT↑	(199)
	Mouse embryo fibroblasts	2 μg/cm² , 24 h	↔			↑	↔		(169)
	Human bronchial epithelial cells	12.34 μg/cm², 24–48 h			↑			IL-8 ↑	(224)
	Human bronchial epithelial cells	2.34 μg/cm², 2–48 h		↑				PAI-1 ↑	(228)
	Human bronchial epithelial cells	0.58–2.34 μg/cm², 24 h		↑	↑			PAI-1 ↑	(187)
	Mouse fibroblast cells	0.3 μg/sm², 20 h			↑		↑		(210)
	C57BL/6 mouse tumor cells	5 mg/mice, 8 months						p-MAPK ↑, p16-hyper-methylation↑	(229)
	Human bronchial epithelial cells, Murine embryonic fibroblasts	0–2 μg/cm², 6–48 h		↑				COX-2 ↑	(211)
Nickel sulfide (NiS)	Human bronchial epithelial cells	2 μg/cm² , 1 h	↑						(207)
	Human bronchial epithelial cells	1–2 μg/cm² , 48 h						COX-2 ↑	(207)
	Human A549 lung cells	0–2 μg/cm² , 12–24 h	↑		↑			TNF-α ↑	(212)
	Human bronchial epithelial cells	0–2 μg/cm², 12–48 h	↑	↑		↑		TNF-α ↑	(215)

Note: ↑ = activation; ↔ = no change; ↓ = inhibition; Ap-1 = activator protein-1; ATF-1 = activating transcription factor-1; CAIX = carbonic anhydrase IX; COX-2 = cyclooxgenase-2; DCs = dendritic cells; ERK = extracellular signal-regulated kinase; FHIT = Fragile histidine triad gene; FSDC = fetal skin-derived dendritic cells; HIF-1 = hypoxia inducible factor 1; HOS cells = Human osteosarcoma cells; human MoDC = human monocyte-derived dendritic cells; HUVEC = human umbilical vein epithelial cell; IL-8 = interleukin-8; MAPK = mitogen-activated protein kinase; MCP-1 = monocyte chemoattractant protein-1; NFAT = nuclear factor of activated T cells; p16 = cyclin-dependent kinase inhibitor; p-AKT = phosphor-AKT; p-ERK = phosphor-extracellular signal-regulated kinases; p-MAPK = phospho-mitogen activated protein kinase; PAI-1 = plasminogen activator inhibitor-1; PI-3K = phosphatidylinositol 3-kinase; SA-8 cells = a Ni-transformed derivative.

exists in AP-1 regulation reported by different studies. Only one *in vivo* study revealed that nickel subsulfide produced upregulation of p-MAPK.

Gaps in Knowledge

Although nickel and its compounds have been studied extensively, there is still much remaining to be elucidated concerning their possible health effects. First, although certain forms of nickel or its compounds tend to predominate in certain industrial settings, workers are not exposed purely to one form of nickel species in any known industry. Consequently, it is difficult to identify the health effects of an individual nickel species using human data alone. Animal and *in vitro* experiments using a single nickel species are needed when determining species-specific occupational exposure limits.[18] Conversely, more *in vitro* and *in vivo* studies are necessary to mimic occupational exposure to mixtures of various nickel species.

Second, occupational exposure to metallic nickel can occur through a variety of sources. However, in nearly all cases, metallic nickel exposures include concomitant exposures to other nickel compounds and can also be confounded with exposure to toxic non-nickel substances. Because of this, carcinogenesis of metallic nickel has not been elucidated yet. Therefore, further experimental studies are necessary to elucidate the toxicity and carcinogenicity of metallic

nickel. These results will be useful as an important reference when comparing the toxicities of different nickel compounds.

Third, at present, little is known about the potential human adverse effects of nickel nanoparticles. Further studies should be centered on the difference of toxicity and carcinogenicity between nickel fine particles and nanoparticles. Studies on the effects of ultrafine metallic nickel powder showed significant inflammation, cytotoxicity, and/or increased epithelial permeability of lung tissue.[230,231] Preliminary studies in our laboratory indicate that metallic nickel nanoparticles elicit higher cytotoxicity and apoptosis induction than fine particles.[232] To clarify the influence of particle size, inhalation animal studies that address the influence of particle size on cell transformation, clearance, and inflammatory/proliferative responses would be useful.

Fourth, the majority of the absorbed nickel is excreted rapidly because nickel is not a cumulative toxicant. Therefore, biomarkers of nickel exposure have not been found yet and should be a subject of detailed investigation in future studies.

Recent epidemiological evidence suggests an important role of water-soluble nickel species in nickel-related cancer. Furthermore, the majority of research evidence shows that both water-soluble and insoluble nickel species produce similar effects in ROS generation and signal alteration *in vitro*, which strongly suggests that a similarity in carcinogenesis between these two different nickel species exists. Therefore, further *in vivo* and *in vitro* studies are necessary to compare the difference in carcinogenicity between water-soluble and insoluble nickel compounds.

In addition, there are a number of nickel alloys for which there is not enough information available to reliably predict their human hazards. Further studies are necessary to elucidate their potential carcinogenesis.

Finally, the molecular mechanisms by which nickel and its compounds cause cancer are far from understood. Therefore, intense investigation is still needed to elucidate the molecular mechanisms of carcinogenicity of nickel and its compounds.

Summary

Nickel and nickel compounds belong to the classic noxious agents encountered in the workplace, but are also known to affect nonoccupationally exposed individuals. The chemical and physical properties of nickel and nickel compounds strongly influence their bioavailability and toxicity. Nickel can enter the body through the lungs, gastrointestinal tract, or skin. Inhalation of nickel is normally the principal route for its entry into the human body under conditions of occupational exposure. The lung and the skin are the principal target organs upon occupational exposure. The most important occupational health problems due to exposure to nickel and nickel compounds are allergic dermatitis and increased incidence of lung and nasal cancers. Nickel carbonyl is the most acutely toxic nickel compound encountered in the occupational settings. Acute adverse effects include dermal and lung toxicity. Whether human exposure to nickel and its compounds may cause reproductive toxicity remains unclear. No studies were found regarding gastrointestinal, cardiovascular, hematological, musculoskeletal, endocrine, or hepatic effects in humans after inhalation exposure to nickel and its compounds. Nickel and its compounds are not mutagenic in Ames tests or genotoxic using *in vivo* micronucleus tests. However, both soluble and insoluble nickel compounds are genotoxic in *in vitro* studies. Nickel is not a cumulative toxicant because the majority of the absorbed amount is excreted rapidly. Urine is the major route for elimination of absorbed nickel. Therefore, urine and plasma nickel concentrations constitute valuable indicators of recent exposure to soluble nickel derivatives. A systematic medical surveillance of workers with known long-term exposure to nickel is essential. Nickel-induced generation of ROS and alterations in normal signal transduction pathways are currently considered to play an important role in the etiology of carcinogenesis of nickel and its compounds.

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Disclaimer

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