DRAFT

For Review Only

Public Health Goal for NICKEL In Drinking Water

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PREFACE

Drinking Water Public Health Goals

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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR NICKEL IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.001 mg/L (1 µg/L or 1 ppb) is proposed for soluble nickel compounds in drinking water. The evaluation is focused on soluble nickel as it is anticipated that the most prevalent exposure through drinking water will be to this form of nickel. The proposed PHG is based on a rat study by Smith et al. (1993) who reported increased frequency of perinatal death in offspring of rats exposed to nickel chloride in drinking water at 10 ppm (1.3 mg Ni/kg_{bw}). An uncertainty factor of 1,000 was used to convert the animal Lowest-Observed-Adverse-Effect-Level (LOAEL) to a human reference level of 1.3 µg Ni/kg_{bw}. It includes a factor of 10 for converting LOAEL to No-Observed-Adverse-Effect-Level (NOAEL), a factor of 10 for inter-species extrapolation, and a factor of 10 for intra-species variability. The PHG was calculated by assuming a relative source contribution of 20 percent, a water consumption rate of 2 L/day, and an adult body weight of 70 kg. In several laboratory and animal studies, nickel compounds have been shown to be genotoxic as well as carcinogenic. For this reason, an additional uncertainty factor of 10 was used in this evaluation to account for the potential carcinogenicity of soluble nickel.

United States Environmental Protection Agency (U.S. EPA) promulgated a Maximum Contaminant Level Goal (MCLG) of 0.1 mg/L and a Maximum Contaminant Level (MCL) of 0.1 mg/L (100 ppb) for nickel (U.S. EPA, 1999). However, the MCL and MCLG for nickel were remanded on February 9, 1995. This means that while U.S. EPA is reconsidering the limit on nickel, there is currently no U.S. EPA limit on the amount of nickel in drinking water (U.S. EPA, 1999).

INTRODUCTION

The purpose of this document is to develop a Public Health Goal (PHG) for soluble nickel in drinking water. Soluble nickel is the focus of this analysis as it is the most important form of nickel in drinking water. Adverse health effects associated with exposure to other forms of nickel are evaluated only if the information is relevant to the development of the PHG.

A Maximum Contaminant Level (MCL) of 0.1 mg/L (100 ppb) was established by the California Department of Health Services (DHS) [California Code of Regulations (CCR) Title 22 for inorganic chemicals Section 64431].

United States Environmental Protection Agency (U.S. EPA) is currently reviewing existing toxicological data and has not released a new risk assessment for soluble nickel salts. U.S. EPA promulgated a Maximum Contaminant Level Goal (MCLG) of 0.1 mg/L and a MCL of 0.1 mg/L (100 ppb) for nickel (U.S. EPA, 1999). However, the federal MCL and MCLG for nickel were remanded on February 9, 1995. This means that while U.S. EPA is reconsidering the limit on nickel, there is currently no U.S. EPA limit on the amount of nickel in drinking water (U.S. EPA, 1999).

In preparing this risk assessment, discussions and information found in many review reports were used. They include: “Toxicological Review of Soluble Nickel Salts” (TERA, 1999);

"Toxicological Profile for Nickel" (ATSDR, 1997); "Proposed Identification of Nickel as a Toxic Air Contaminant, Part B" (CARB, 1991); "Environmental Health Criteria 108, Nickel" (IPCS, 1991); "Draft RoC Background Document for Nickel Compounds" (NTP, 1998); "Health Assessment Document for Nickel and Nickel Compounds" (U.S. EPA, 1986); "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Chromium, Nickel and Welding. Volume 49" (IARC, 1990); and "Nickel in the Human Environment" (IARC, 1984).

CHEMICAL PROFILE

Chemical Identity

Elemental nickel, Ni, is a member of the Group VIII transition metal series. Nickel may exist in a number of oxidation states, and the most important oxidation state under environmental conditions is nickel +2. A large number of nickel compounds have been identified and characterized; many of them, such as nickel sulfate, nickel nitrate, nickel chloride, and nickel acetate are relatively soluble in water. Synonyms, chemical formulae, and identification numbers of nickel and some soluble nickel compounds are listed in Table 1. Other nickel compounds such as nickel hydroxide, nickel oxide, nickel sulfide, and nickel subsulfide are either insoluble or have very low solubility in water.

Physical and Chemical Properties

Important physical and chemical properties of nickel and selected soluble nickel compounds are presented in Table 2.

Production and Uses

Nickel is a natural occurring element; it is neither created nor destroyed by human activities. It is a commercially important metal because of its hardness, strength, and resistance to corrosion. The information on the production of nickel discussed below was mainly obtained from ATSDR (1997) and CARB (1991). Nickel production can be referred to as either primary or secondary depending on the source of the raw material.

Primary nickel is produced by the mining and smelting of nickel ores. Pentlandite $(Ni,Fe)_9S_8$ is an important ore of nickel. It often occurs along with iron mineral pyrrhotite and the copper mineral chalcopyrite. The ore is concentrated by physical means (i.e., flotation and magnetic separation) after crushing. The other ore that is used for nickel production is the lateritic hydrous nickel silicate ores. They are formed by the weathering of rocks rich in iron and magnesium in humid tropical areas. The repeated processes of dissolution and precipitation lead to a uniform dispersal of the nickel that is not amenable for extraction by physical means; therefore, these ores are concentrated by chemical means such as leaching. The nickel content of lateritic ores is similar to that of sulfide ore and typically ranges from 1 percent to 3 percent nickel (ATSDR, 1997).

Table 1. Chemical identity of nickel and soluble nickel compounds (from ATSDR, 1997).

Chemical name	Nickel	Nickel sulfate	Nickel nitrate	Nickel chloride	Nickel acetate
Synonyms	No data	Nickel(II) sulfate; Nickel monosulfate	Nickelous nitrate	Nickel(II) chloride; Nickelous chloride; Nickel dichloride	Nickel(II) acetate; Nickelous acetate; Nickel diacetate
Chemical formula	Ni	$NiSO_4$	$Ni(NO_3)_2$	$NiCl_2$	$Ni(CH_3CO_2)_2$
Identification numbers					
Chemical Abstracts Service Registry number:	7440-02-0	7786-81-4	13138-45-9	7718-54-9	373-02-4
NIOSH Registry of Toxic Effects of Chemical Substances (RTECS)® number:	QR5950000	QR9350000	QR7200000	QR6475000	QR6125000
U.S. EPA Hazardous Waste number:	No data	No data	No data	No data	No data
Oil and Hazardous Materials/Technical Assistance Data System number:	7216810	7216811	No data	7217269	No data
Hazardous Substances Data Bank number:	1096	1114	1829	860	1029

Table 2. Physical and chemical properties of nickel and soluble nickel compounds (from ATSDR, 1997).

Property	Nickel	Nickel sulfate	Nickel nitrate	Nickel chloride	Nickel acetate
Molecular weight	58.69	154.75	182.72	129.6	176.8
Color	Silvery	Greenish-yellow	Green	Golden yellow bronze	Green
Physical state	Solid	Solid	Solid	Solid	Solid
Melting point	1,455°C	840°C	56.7°C	1,001°C	Decomposes
Boiling point	2,730°C	No Data	136.7°C	Sublimes at 973°C	No Data
Density	8.9 g/cm^3	3.68 g/cm^3	2.05 g/cm^3 [a]	3.55 g/cm^3	1.798 g/cm^3
Odor	No Data	Odorless	No Data	None	Acetic odor
Odor threshold: Water Air	 No Data No Data	 No Data No Data	 No Data No Data	 No Data No Data	 No Data No Data
Water solubility	1.1 mg/L at 37°C	293 g/L at 0°C	2,385 g/L at 0°C	642 g/L at 20°C	17 weight % at 68°C
Octanol-water partition coefficients (K_{ow}) Log K_{ow}	 No Data	 No Data	 No Data	 No Data	 No Data
Soil-organic carbon-water partition coefficients (K_{oc}) Log K_{oc}	 No Data	 No Data	 No Data	 No Data	 No Data
Vapor pressure	1 mmHg at 1,810°C	No Data	No Data	1 mmHg at 671°C	No Data No Data
Henry's law constant at 25°C	No Data	No Data	No Data	No Data	No Data

[a] Data is for the hexahydrate

Sulfide ores are processed by a number of pyrometallurgical processes: roasting, smelting, and converting. During these processes, sulfur and iron are removed to yield a sulfur-deficient copper-nickel matte. Especially after roasting and converting, the nickel in the matte may consist primarily of nickel subsulfide. After physical separation of the copper and nickel sulfides, the nickel is refined electrochemically or by the carbonyl process. Alternatively, the sulfide can be roasted to form a nickel oxide sinter that is used directly in steel production.

Lateritic ore is processed by pyrometallurgical or hydrometallurgical methods. In the pyrometallurgical process, sulfur is generally added to the oxide ore during smelting, usually as gypsum or elemental sulfur, and an iron-nickel matte is produced. The smelting process that does not include adding sulfur produces a ferronickel alloy, containing approximately 50 percent nickel, which can be used directly in steel production. Hydrometallurgical techniques involve leaching with ammonia or sulfuric acid, after which the nickel is selectively precipitated.

Secondary nickel is produced by the recovery and refining of nickel-containing scrap metal such as stainless steels, aluminum alloys and copper-based alloys. Production of nickel from scrap is now a major source of nickel for industrial applications.

Annual global production of nickel has averaged over 900 kilotons in recent years (NiDI, 1997 as cited in NTP, 1998). The U.S. imported approximately 3,070 tons of metallurgical grade nickel oxide in 1994, but only 530 tons in 1995. The nickel imported in 1995 was approximately 59 percent of the net nickel consumed. This amount was lower than the amount imported in 1994 because Glenbrook resumed production of ferronickel in 1995 (Kuck, 1997 as cited in NTP, 1998).

More than 80 percent of all nickel is used in its metallic form, principally as nickel-alloys. Nickel is widely used in aircraft and boat manufacturing. Nickel-containing stainless and alloy steels are used in aircraft frames; nickel based superalloys are used for aircraft parts such as jet engines, gas turbines, and turbosuperchargers. In ships and boats, nickel alloys and copper-nickel alloys are used in parts exposed to saltwater such as the hulls, propellers, and pumps (U.S. DOI, 1985).

Nickel alloys are used in pumps and pipes that are exposed to corrosive solution in the chemical and petroleum industries. Nickel is also used in making coins, jewelry, catalysts, magnets, batteries, and color pigments. Large amounts of nickel are used in the construction industry in the form of alloy steels, stainless steels, and cast irons (ATSDR, 1997).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

The primary stationary source categories that emit nickel into ambient air in California are: fuel combustion, nickel alloy manufacturing, cement production, asbestos mining and milling, municipal waste sludge incineration, iron and steel foundries, secondary metal recovery, cooling towers, coal gastification, petroleum processing, and electroplating. In addition, nickel has been detected in the vehicular exhaust of gasoline-powered and diesel-powered vehicles, tobacco smokes, and indoor smokes originated from the combustion of home-heating and cooking fuels (CARB, 1991). U.S. EPA (1986) estimated that particles found in ambient air as a result of oil combustion might contain nickel predominantly in the form of nickel sulfate, with smaller amounts as nickel oxide and complex metal oxides containing nickel.

A majority of the nickel in the atmosphere is believed to be associated with human activities as described above. However, up to a third of the atmospheric nickel could come from natural sources such as nickel containing windblown dusts, forest fires, and volcanic emissions (Nriagu, 1980 as cited in CARB, 1991).

A network of monitoring stations located throughout the state monitors ambient nickel concentrations in California. The average statewide nickel concentrations in air collected over a 24-hour period were 4.2, 4.1, 3.7, and 3.5 ng/m^3 for 1993, 1994, 1995, and 1996, respectively (CARB, 1997).

Soil

Nickel occurs naturally in the earth's crust with an average concentration of 0.008 percent (Duke, 1980 as cited in ATSDR, 1997). The concentration of naturally occurring nickel in soil depends upon the elemental composition of rocks in the upper crust of the earth. According to a U.S. Geological Survey, nickel concentrations in soil throughout the United States ranged from less than 5 to 700 ppm, with a geometric mean of 13±2 ppm (Shacklette and Boerngen,1984 as cited in ATSDR, 1997).

Hutchinson et al. (1981 as cited in U.S. EPA, 1986) estimated that the most important anthropogenic nickel inputs to soil are metals smelting and refining operations and sewage sludge applications. In an agricultural area of Ontario, Canada, the average nickel concentrations in sludge-treated soils and untreated soils were 20 and 16.2 ppm, respectively (Webber and Shamess, 1987 as cited in ATSDR, 1997). Auto emissions can also raise the level of nickel in soil. Lagerwerff and Specht (1970 as cited in U.S. EPA, 1986) studied the contamination of roadside soils near two major highways. Measured nickel concentrations were found to range from 0.9 to 7.4 ppm. The concentrations were lower at greater distances from traffic and at greater soil profile depths.

Water

Nickel enters groundwater and surface water by dissolution of rocks and soils, from atmospheric fallout, from biological decays and from waste disposal. As shown in Table 2, many nickel compounds are relatively soluble in water, especially at pH values less than 6.5, and generally exist as nickel ions in aqueous systems. The nickel concentration of fresh surface water has been reported to average between 15 and 20 µg/L (Grandjean, 1984 as cited in ATSDR, 1997). The nickel content of groundwater is normally below 20 µg/L (U.S. EPA, 1986), and the levels appear to be similar in raw, treated, and distributed municipal water.

Elevated nickel levels may exist in drinking water as a result of the corrosion of nickel-containing alloys used as valves and other components in the water distribution system as well as from nickel-plated faucets. In a Seattle study, mean and maximum nickel levels in standing water were 7.0 and 43 µg/L, respectively, compared with 2.0 and 28 µg/L in running water (Ohanian, 1986 as cited in ATSDR, 1997). In Denmark, nickel in drinking water up to 490 µg/L has been observed (Andersen et al., 1983 as cited in Grandjean, 1984) and a maximum of 957 µg/L has been demonstrated in "first draw" drinking water in the U.S. (Strain et al., 1980 as cited in Grandjean, 1984). Ten used water faucets filled with 15 ml deionized water in an inverted

position and left overnight for 16 hours leached between 18 and 900 µg of nickel (Strain et al., 1980 as cited in Grandjean, 1984).

Nickel has been detected in California drinking water sources. According to the monitoring data collected by California Department of Health Services (DHS) between 1984 and 1997, the highest, the average, and the median concentrations of nickel in water were 540 µg/L, 26.1 µg/L, and 17.9 µg/L, respectively (DHS, 1998). The detection limit for the purposes of reporting to DHS for nickel is 10 µg/L (10 ppb).

Food

Terrestrial plants take up nickel from soil primarily via the roots. The amount of nickel uptake from soil depends on the concentration of nickel in soil, soil pH, organic matter content of the soil, and the plant. The nickel concentrations in most natural vegetation ranged from 0.05 to 5 mg/kg dry weight (NRC, 1975). Some food sources such as chocolate, nuts, beans, peas, and grains are relatively rich in nickel (Table 3).

Calamarie et al. (1982 as cited in IPCS, 1991) showed that nickel is not likely to accumulate in fish. They exposed *Salmo gairdneri* (rainbow trout) to a nickel contaminated water at 1 mg/L for 180 days and found 2.9 mg/kg wet weight in liver, 4.0 mg/kg in kidneys, and 0.8 mg/kg in muscle. Nickel levels at the start of the study were 1.5, 1.5, and 0.5 mg/kg in liver, kidneys, and muscle, respectively. Hutchinson et al. (1975 as cited in IPCS, 1991) reported that accumulation factors of nickel in zooplankton, crayfish, clams, and the predatory yellow pickerell were 643, 929, 262, and 229, respectively. As nickel in aquatic ecosystems decreases in concentration with increasing levels of the food chain, Hutchinson et al. (1975 as cited in IPCS, 1991) suggested that biomagnification of nickel is not likely to occur.

Myron et al. (1978) studied nickel levels in meals sampled from a study center of the University of North Dakota and from a rehabilitation hospital. The average nickel concentration of the student meals (breakfast, lunch, and dinner) ranged from 0.19 to 0.29 µg/g (dry weight). For the hospital meals, the nickel concentration ranged from 0.21 µg/g (dry weight) in the puree meals to 0.41 µg/g (dry weight) in the low-calorie meal. Based on the nine diets examined, the authors estimated that the average daily dietary intake was 168±11 µg. This value is comparable with those estimated by other researchers. Nielsen and Flyvholm (1984) estimated a daily intake of 150 µg in the average Danish diet; however, if the average diet was combined with certain food items that had high nickel content, a daily intake as high as 900 µg might be reached. Knutti and Zimmerli (1985 as cited in IARC, 1990) found daily dietary intakes in Switzerland of 73±9 µg in a restaurant and 142±20 µg in a military canteen. The mean nickel intake in the United Kingdom in 1981-84 was 140-150 µg/day (Smart and Sherlock, 1987).

Stainless-steel kitchen utensils have been shown to release nickel into acid solutions, especially during boiling (Christensen and Möller, 1978 as cited in IARC, 1990). The amount of nickel released depends on the composition of the utensil, the pH of the food, and the duration of contact. It has been estimated that the contribution of kitchen utensils to the oral intake of nickel can be as much as 1 mg/day (Grandjean et al., 1989 as cited in IARC, 1990).

Table 3. Nickel content of food items (from Nielsen and Flyvholm, 1984).

Food	Sample size	Interval (µg/g)	Mean (µg/g)
Oatmeal	10	0.80 – 2.3	1.2
Rice	3	0.28 – 0.41	0.33
Beans	10	0.20 – 0.55	0.33
Peas	10	0.13 – 0.56	0.37
Spinach	6	0.02 – 0.12	0.06
Dried legumes	9	0.57 – 3.3	1.7
Soya beans	3	4.7 – 5.9	5.2
Soya products	5	1.08 – 7.8	6.0
Hazel nuts	7	0.66 – 2.3	1.9
Cocoa	6	8.2 – 12	9.8
Milk chocolate	6	0.46 – 0.80	0.57
Dark chocolate	6	1.3 – 2.7	1.8

Low concentrations of nickel have been detected in human milk. Casey and Neville (1987) monitored nickel levels in milk of 13 women between delivery and 38 days postpartum. They reported that nickel concentrations in human milk did not change over that period of time; the overall average in the 46 milk samples analyzed was 1.2±0.4 µg/L. Rica and Kirkbright (1982 as cited in Casey and Neville, 1987) analyzed 179 milk samples from several different countries and found a range of 3-50 µg/L.

METABOLISM AND PHARMACOKINETICS

U.S. EPA (1986), IPCS (1991), and (ATSDR, 1997) have reviewed the absorption, distribution, and excretion of nickel compounds. Most of the information provided below was obtained from these three reports.

Absorption

Oral route

Ishimatsu et al. (1995) demonstrated that the absorption fraction of orally administered nickel compounds was closely related to the water solubility of the compounds. They administered eight kinds of nickel compounds to male rats by gavage at 10 mg of nickel and determined the total amount of nickel absorbed by summing the nickel content of the organs, blood, and urine collected in 24 hours. They found that the absorbed fraction in the rats given insoluble nickel metal and nickel oxides ranged from 0.01-0.09 percent. The absorbed fraction was 0.5-2.1 percent for the slightly soluble compounds, nickel subsulfide and nickel sulfide, and 10-34 percent for the soluble nickel compounds (Table 4).

Table 4. Solubility and oral absorption of eight nickel and nickel compounds in rats (from Ishimatsu et al., 1995).

Nickel compounds	Solubility in saline solution, µg/ml *	Absorption fraction via gavage administration in rats, % **
Nickel oxide (green)	1.34±0.08	0.01
Nickel metal	3.57±0.22	0.09
Nickel oxide (black)	4.49±0.20	0.04
Nickel subsulfide	572±23	0.47
Nickel sulfide	2,176±91	2.12
Nickel sulfate	>300,000	11.12
Nickel chloride	>300,000	9.8
Nickel nitrate	>300,000	33.8

*The suspension was shaken for 1 week at 37°C. There were 5 trials for each compound.

** There were eight rats in each group.

Ho and Furst (1973) reported that intubation of rats with ^{63}Ni (as the chloride) in 0.1 N hydrochloric acid led to 3-6 percent absorption of the labeled nickel, regardless of the administered dose (4, 16, and 64 mg Ni/kg_{bw}). Nielsen et al. (1993) administered γ-emitting isotope ^{57}Ni as nickel chloride at 3-300 µg Ni/kg_{bw} to male mice by gastric intubation, and estimated that intestinal absorption ranged from 1.7 to 7.5 percent of the administered dose.

It has been demonstrated that nickel, either as free ion or in complexes, is absorbed by humans through the gastrointestinal tract. U.S. EPA (1986) reviewed the data published on the oral bioavailability of nickel and reported that between 1 to 10 percent of dietary nickel is absorbed; the absorption efficiency appears to be dependent on the fasting conditions of the subjects. Cronin et al. (1980) reported that ingestion of a soluble nickel compound during fasting by a group of female subjects resulted in urinary elimination rates of 4-20 percent of the dose. Based on a review paper published by Diamond et al. (1998), it can be estimated that the gastrointestinal absorption efficiency of nickel in humans ranged from 1 to 3 percent (Table 5).

Oral bioavailability of soluble nickel compounds in humans appears to be dependent on dietary composition. Sunderman et al. (1989) found that approximately 40 times more nickel was absorbed from the gastrointestinal tract when nickel sulfate was given to human volunteers in the drinking water (27±17 percent) than when it was given in food (0.7±0.4 percent). In the same paper, Sunderman et al. (1989) reported that the oral absorption rate constant for nickel in humans was not significantly different at dosages of 12, 18, or 50 µg Ni/kg_{bw}. By modeling the absorption, distribution, and elimination of nickel, they showed that the rate constants for absorption of nickel from water and food did not differ significantly. This led them to believe that the availability of nickel for alimentary absorption was substantially diminished when nickel sulfate was added to food, owing to chelation or reduction of Ni^{2+} by dietary constituents.

Solomons et al. (1982) and Nielsen et al. (1999) reported similar results. They found that plasma nickel levels in five fasted human subjects were significantly elevated when they were given nickel sulfate (equivalent to 5 mg nickel) in drinking water (peak concentration was approximately 80 µg Ni/L at 3 hours after the oral administration). When they added 5 mg of nickel (in the form of nickel sulfate) to five beverages, whole cow-milk, coffee, tea, orange juice,

and Coca Cola®, the rise in plasma nickel was significantly suppressed with all but Coca Cola®. Solomons et al. (1982) also showed that the plasma nickel levels of subjects who consumed a typical Guatemalan meal with 5 mg of nickel or a North American breakfast with 5 mg of nickel were only about 5 to 20 percent of that which resulted from the consumption of 5 mg nickel in water. Nielsen et al. (1999) administered nickel in drinking water (12 µg Ni/kg_{bw}) to eight volunteers fasted overnight and at different time intervals, via standardized portions of scrambled eggs. They found that the highest fraction of nickel dose (25.8 percent) excreted in urine was observed when the scrambled eggs were taken 4 hours prior to nickel in drinking water. A much lower fraction of nickel dose (2.5 percent) was observed when the nickel was mixed into the eggs or when the drinking water was taken together with the eggs (3.4 percent).

Table 5. Absorption of ingested nickel in humans as estimated from bioavailability studies using urinary nickel as a biomarker (from Diamond et al., 1998).

Study	Number of subjects	Vehicle or exposure media	Duration	Fasting status	Absorption (% of dose)
Sunderman et al. (1989)	8	water	acute	fasted	29.3
Sunderman et al. (1989)	8	food	acute	fasted	1.8
Cronin et al. (1980)	5	capsule plus 100 mL of water	acute	fasted	12 - 32
Christensen and Lagassoni (1981)	8	capsule	acute	with meal	5.7
Gawkrodger et al. (1986)	3	capsule	acute	with meal	2.7, 2.8
Menne et al. (1978)	6	capsule	acute	not fasted	2.2 (women)
Menne et al. (1978)	7	capsule	acute	not fasted	1.7 (men)
Horak and Sunderman (1973)	10 - 50	food	chronic	not fasted	1.0
McNeeley et al. (1972)	19	food and water	chronic	not fasted	1.6
McNeeley et al. (1972)	20	food	chronic	not fasted	1.2

Inhalation route

Animal models have been used to estimate the inhalation absorption of water-soluble and water-insoluble nickel compounds. English et al. (1981 as cited in NTP, 1996a) administered nickel chloride and nickel oxide intratracheally to rats and reported greater than 50 percent of the soluble nickel chloride was cleared from the lungs within 3 days. Most of the nickel excreted was in the urine. In contrast, the water-insoluble nickel oxide persisted in the lung for more than 90 days, and the nickel excreted was equally divided between feces and urine.

Valentine and Fisher (1984 as cited in NTP, 1996a) administered the slightly soluble nickel subsulfide intratracheally to mice and found the pulmonary clearance has two distinct components with initial and final biological half-lives corresponding to 1.2 and 12.4 days, respectively. The excretion of the chemical (measured as ^{63}Ni) was 60 percent in the urine and

40 percent in the feces. These data showed that only a fraction of the instilled nickel was removed by mucocilliary clearance and excreted in the feces. A larger fraction of the instilled nickel subsulfide was absorbed, distributed systemically, and excreted in the urine. Similar findings were reported by Finch et al. (1987 as cited in NTP, 1996a). They found that the pulmonary clearance of intratracheally administered nickel subsulfide in mice was biphasic with a clearance half-life of 2 hours for the first phase and 119 hours (5 days) for the second phase. These data show that even for the relatively insoluble nickel compounds such as nickel oxide and nickel subsulfide, a portion of the inhaled material was dissolved and distributed systemically in the exposed animals.

Distribution

The information published on the distribution of nickel in humans after oral exposure is limited. Solomons et al. (1982), Christensen and Lagesson, (1981 as cited in ATSDR, 1997) and Sunderman et al. (1989) reported that serum nickel levels peaked 2.5-3 hours after ingestion of soluble nickel compounds. There is much more extensive information on the distribution of nickel in animals. Studies showed that Ni^{2+} administered to rodents via the oral route was mainly concentrated in the kidneys, liver, and lungs, and the absorbed nickel was excreted primarily in the urine (Borg and Tjalve, 1988; Jasim and Tjalve 1984, 1986a and b; Dieter et al., 1988, as cited in ATSDR, 1997).

Nielsen et al. (1993) showed that the retention and distribution of nickel in mice was dependent on the route of administration. As shown in Table 6, Nielsen et al. (1993) showed that 20 hours after nickel administration, percentages of the total body burden in the kidneys and carcass resulted from intraperitoneal injection was much higher than those observed after gavage administration.

Table 6. Median nickel body burden and contents of major organs in mice given as percentage of administered dose (from Nielsen et al., 1993).

	Gastric intubation[a]	Intraperitoneal injection[b]
Liver	0.0439 (0.046)	0.255 (0.044)
Kidneys	0.029 (0.030)	1.772 (0.306)
Lungs	<0.010 (0.010)	0.114 (0.020)
Carcass	0.106 (0.111)	3.164 (0.546)
Stomach	0.014 (0.015)	<0.010 (0.002)
Intestine	0.762 (0.799)	0.490 (0.084)
Total body burden	0.954 (1)	5.794 (1)

[a]Measurements were made 20 hours after oral administration of 10 µmol Ni/kg_{bw}. Value in parenthesis is the ratio of the relative organ burden over the total body burden.

[b]Measurements were made 20 hours after intraperitoneal injection of 1 µmol Ni/kg_{bw}. Value in parenthesis is the ratio of the relative organ burden over the total body burden.

In humans and in animals, it has been shown that the absorbed nickel is not likely to exist in free ionic form as Ni^{2+}, but occurred in the form of nickel complexes. Sunderman and Oskarsson (1991 as cited in ATSDR, 1997) noted that in humans most of the absorbed nickel is transported

by binding to a metalloprotein (nickeloplasmin), albumin, and ultrafiltrable ligands, such as small polypeptides and L-histidine. Van Soestbergen and Sunderman (1972 as cited in IPCS, 1991) administered nickel chloride (^{63}Ni) to rabbits by intravenous injection at 0.24 mg Ni/kg$_{bw}$ and found that, between 2-24 hours after the injection, approximately 90 percent of serum ^{63}Ni was bound to proteins (e.g., albumin) with molecular weights greater than 10,000 and the remaining bound to small organic molecules such as short peptides and amino acids. They reported that three of the five ultrafiltrable nickel complexes detected in serum were also found in urine.

It has been demonstrated that chelation of Ni^{2+} by organic compounds has a significant effect on the cellular uptake, absorption, and distribution of Ni^{2+} (Sarkar, 1984; Nieborer et al., 1984; Borg and Tjälve, 1988; Hopfer et al., 1987). Nieborer et al. (1984) studied cellular uptake of Ni^{2+} in human B-lymphoblasts, human erythrocytes, and rabbit alveolar macrophages. They observed that addition of L-histidine or human serum albumin at physiological concentrations to the cell cultures reduced Ni^{2+} uptake by 70-90 percent. The concentration of nickel used in the study was $7x10^{-8}$ M (or 4.1 µg/L); it was comparable to serum nickel levels observed in workers occupationally exposed to nickel.

Borg and Tjälve (1988) demonstrated the importance of the formation of nickel complexes in the absorption and tissue distribution of soluble nickel compounds. They showed that gavage administration of dimethyldithiocarbamate pesticides (ferbam, ziram) or thiram together with Ni^{2+} resulted in increased levels of nickel in several tissues of rats, in comparison with animals given only Ni^{2+} (Table 7).

Table 7. Effects of thiram, ferbam, and ziram on tissue distribution of $^{63}Ni^{2+}$ in rats (from Borg and Tjälve, 1988).

	Tissue concentration of $^{63}Ni^{2+}$ (pmol/100 mg of wet tissue)[a]			
	Control (n=20)	**Thiram (n=6)**	**Ferbam (n=6)**	**Ziram (n=5)**
Liver	41±3	853±142*	362±35*	146±37*
Kidney	833±85	1823±191*	906±86	881±72
Lung	181±13	629±116*	358±30*	198±16
Brain	15±6	772±67*	555±58*	40±1*
Spinal cord	33±4	698±64*	435±38*	81±10*
Heart	25±2	120±14*	50±5*	33±2
Pancreas	21±2	134±11*	75±8*	49±11*
Plasma[b]	37±4	176±22*	83±18*	67±10*

[a]Mean ± S.E. Mice were given $^{63}Ni^{2+}$ (10 µmol/kg$_{bw}$) orally by gastric intubation, either alone (control), or immediately followed by of thiram, ferbam, or ziram (1 mmol/kg$_{bw}$) also by gastric intubation. All mice were killed after 24 hours.
[b]The values are given in pmol/100 µl.
*Significantly different from controls (P<0.05).

Another chemical that is known to affect the absorption and tissue distribution of nickel is disulfiram. Disulfiram is used for alcohol aversion therapy; it is metabolized into two molecules of diethyldithiocarbamate in vivo. Following oral exposure of mice to ^{57}Ni (3 µg/kg$_{bw}$), the residual body burdens of nickel after 22 hours and 48 hours were increased several folds in

groups receiving clinically effective doses of diethyldithiocarbamate, either orally or intraperitoneally, compared with controls. The distribution pattern of nickel among various organs was also changed after exposure to disulfiram. Higher levels of nickel were found in the brain, kidneys, liver, and lungs of individuals exposed to both nickel and disulfiram than those exposed to nickel alone (Nielsen et al., 1987 as cited in IPCS, 1991). Similar effects had been observed in humans. Hopfer et al. (1987) reported that average nickel concentrations in the serum of 61 patients with chronic alcoholism increased from 0.3 to 5.4 µg/L after 4-36 months treatment of a daily dose of 250 mg disulfiram.

Nickel has been shown to cross the human placenta; it has been found in both the fetal tissue (Schroeder et al., 1962 as cited in IPCS, 1991) and the umbilical cord serum (McNeely et al., 1971 as cited in IPCS, 1991). Similar findings have been reported in animal studies. Szakmary et al. (1995 as cited in ATSDR, 1997) administered a single gavage dose of 5.4, 11.3, or 22.6 mg Ni/kg_{bw} as nickel chloride to pregnant rats. Twenty-four hours after the exposure, nickel levels in fetal blood were raised from 10.6 to 14.5, 65.5, and 70.5 µg/L for the low-, medium-, and high-dose groups, respectively. Jacobsen et al. (1978 as cited in IPCS, 1991) showed that when pregnant mice were given a single intraperitoneal injection of ^{63}Ni chloride (0.14 mg/kg_{bw}) on day 18 of gestation, passage of ^{63}Ni from mother to fetus was rapid and concentrations in fetal tissues were generally higher than those in the dam.

Excretion

Nickel burden in humans does not increase with age (Schneider et al., 1980 as cited in Anke et al., 1984). A majority of nickel absorbed from environmental media and diet is rapidly removed through urinary excretion. Solomons et al. (1982) found that nickel in water was quickly absorbed and excreted by humans; they estimated a biological half-life of about 8 hours in humans. Hogetveit et al. (1978 as cited in IPCS, 1991) reported that elevated levels of nickel were detected in urine samples collected from workers exposed to soluble or insoluble nickel through inhalation.

The kinetics of nickel elimination in humans and animals appear to be similar. Onkelinx et al. (1973 as cited in IARC, 1990) intravenously injected labeled nickel chloride to rats and rabbits and followed the nickel level in plasma over time. Elimination profiles were similar for both species. They followed a two-compartment model, with first-order kinetics of nickel elimination from plasma with half-times of 6 and 50 hours for rats and 8 and 83 hours for rabbit, respectively.

Sweat and milk are also possible excretion routes for absorbed nickel in humans. Hohnadel et al. (1973 as cited in IPCS, 1991) found that, in sauna bathers, the mean concentrations of nickel in the sweat from healthy men and women were significantly higher than the mean concentrations in the urine. Several studies demonstrated that excretion of nickel in human milk is quite low and should be considered a minor route of excretion in lactating women (Feeley et al., 1983; Mingorance and Lachica, 1985 as cited in U.S. EPA, 1986).

However, Dostal et al. (1989 as cited in ATSDR, 1997) showed that milk is an excretion pathway of nickel in rodents. They showed that daily subcutaneous injections of lactating rats with 3 or 6 mg Ni/kg_{bw} for four days raised nickel levels in milk from <2 µg/L to 513 and 1,030 µg/L, respectively. They also showed that nickel treatment significantly changed the composition of milk by increasing the milk solids (42 percent) and lipids (110 percent) and decreasing milk protein (29 percent) and lactose (61 percent).

TOXICOLOGY

Some adverse health effects of nickel compound are dependent on the route of exposure and the water solubility of the compound. As the purpose of this analysis is to develop a PHG for soluble nickel in drinking water, discussions in the following sections are mainly focused on the health effects associated with exposure to soluble nickel compounds by the oral route.

Toxicological Effects in Animals

Acute and Sub-chronic Toxicity

It has been shown that water-soluble nickel compounds are more acutely toxic than the less soluble ones. The single dose oral LD_{50}s in rats for the less-soluble nickel oxide and subsulfide were >3,600 mg Ni/kg_{bw}, while the oral LD_{50}s for the more soluble nickel sulfate and nickel acetate ranged from 39 to 141 mg Ni/kg_{bw} in rats and mice (Mastromatteo, 1986 as cited in ATSDR, 1997; Haro et al., 1968 as cited in NRC, 1975).

Soluble nickel compounds appear to be more toxic by intraperitoneal injection than by intramuscular or subcutaneous injections. Sunderman and his associates reported that acute LD_{50} values for nickel chloride in rats were 5 mg Ni/kg_{bw} by intraperitoneal injection, 23 mg Ni/kg_{bw} by intramuscular injection, and 25 mg Ni/kg_{bw} by subcutaneous injection (Knight et al., 1991).

At sublethal doses, injection of soluble nickel compounds has been shown to impair kidney functions and decrease body temperature. Sanford et al (1988 as cited in IPCS, 1991) reported that an intraperitoneal injection of 3 mg Ni/kg_{bw} in rats was toxic to the kidney, induced a decrease in Bowman's space, dilated tubules, loss of brush border, flattened epithelia, and some regenerative activity. Hopfer and Sunderman (1988 as cited in IPCS, 1991) demonstrated that 1.5 hour after intraperitoneal injection of nickel chloride at 1.5 mg Ni/kg_{bw} to rats, the core body temperature averaged 3.0±0.5 °C below the simultaneous value in control rats. The effect was temporary as the body temperature of the treated rats returned normal after 4 hours.

To investigate the sub-chronic toxicity of nickel, RTI (1988a and b as cited in ATSDR, 1997) administered nickel chloride in drinking water to male and female rats for 21-30 weeks. At 20 mg Ni/kg_{bw}/day, they observed histiocytic cellular infiltration of the lung and increased pituitary weight in males. At approximately 50 mg Ni/kg_{bw}/day, they found increased lung and kidney weights in females.

Nickel compounds administered sub-chronically through gavage seem to be more toxic than those administered through the drinking water. American Biogenics Corporation (1988 as cited in ATSDR, 1997) administered 1.2 and 8.6 mg Ni/kg_{bw}/day nickel chloride hexahydrate to Sprague-Dawley rats by gavage for 91 days and found 2/60 and 6/52 died at the end of the study, respectively. Vyskocil et al. (1994) administered drinking water containing 100 mg Ni/L to 20 male and 20 female Wistar rats and did not observe any mortality after 3 months. Based on the amount of drinking water consumed, the authors estimated that the average intake rates of nickel for male and female rats were 7.6 and 8.4 mg Ni/kg_{bw}/24 hr, respectively. In terms of body weight gains, they did not observe any differences between the control and exposed rats.

Developmental and Reproductive Toxicity

Administration of soluble nickel compounds via the oral route has been associated with developmental toxicity in rodents (Ambrose et al., 1976; Schroeder and Mitchener, 1971; RTI, 1987 as cited in U.S. EPA, 1998; and Smith et al., 1993). These studies are discussed in detail below.

Ambrose et al. (1976) examined the effects of dietary administration of nickel sulfate hexahydrate in a three-generation reproduction study in rats. Male and female rats of the parent generation were exposed to levels of 0, 250, 500, and 1,000 ppm nickel, starting at 28 days of age. Mating was initiated after 11 weeks of feeding. Rats in the first, second, and third generations were also placed on the same diet as the parent generation. At each mating, 20 females from each diet were transferred to individual breeding cages and each was mated with a male of the same dietary level of nickel. Ambrose et al. (1976) did not observe any adverse effect on fertility, pregnancy maintenance, or postnatal survival of the offspring throughout the three generations. A higher incidence of stillborn was observed in the first generation at all levels of nickel, but the adverse health effect was not observed in the two subsequent generations. They also reported that the number of siblings weaned per litter were progressively fewer with increasing nickel dose, averaging 8.1, 7.2, 6.8, and 6.4 for 0, 250, 500, and 1,000 ppm diets, respectively. On average weaning body weight, a clear-cut adverse effect was only apparent in weanlings of rats on 1,000 ppm diet, averaging 73 percent of the controls. U.S. EPA (1998) reviewed this study and noted it suffered from some statistical design limitations including small sample size and use of pups rather than litters as the unit for comparison.

Schroeder and Mitchener (1971) conducted a three-generation reproduction study in which rats of the Long-Evans BLU:(LE) strain were administered drinking water with 5 mg Ni/L (estimated as 0.43 mg Ni/kg_{bw}/day by U.S. EPA, 1998). Five pairs of rats were randomly selected at the time of weaning, placed in separate cages and given the nickel in drinking water continuously. Rats were allowed to breed as often as they would up to 9 months of age or longer. At weaning time, pairs were randomly selected from the first, second, or the third litter (F_1) and allowed to breed and to produce the F_2 generation. Pairs were likewise selected at random from the F_2 litters to breed the F_3 generation. They observed that all exposed animals in the three generations gave birth to litters that exhibited a significantly increased perinatal mortality, and there was a significantly increased number of “runts” in the first and third generations (Table 8). U.S. EPA (1998) criticized this study for its small sample size, for the fact that matings were not randomized and the males were not rotated, and for the possibility of interaction between nickel and other trace metals (e.g., chromium content in the diet was estimated to be inadequate).

Berman and Rehnberg (1983 as cited in ATSDR, 1997) treated mice on gestation days 2-17 with nickel chloride in drinking water at 80 and 160 mg Ni/kg_{bw}/day. An increase in the number of spontaneous abortions was observed in mice of the high-dose group, but no increase was observed in mice of the low-dose group.

Table 8. Reproductive outcome of rats exposed to 5 ppm nickel in drinking water (from Schroeder and Mitchener, 1971).

	Control rats	Rats exposed to nickel
F_1 generation		
Maternal deaths	0	1
Number of litters	10	11
Average litter size	11.4	11
Young deaths	0	11*
Runts	0	37*
Number of rats	114	121
F_2 generation		
Maternal deaths	0	0
Number of litters	10	15
Average litter size	11.3	10.5
Young deaths	0	16*
Runts	1	8
Number of rats	113	157
F_3 generation		
Maternal deaths	0	0
Number of litters	11	10
Average litter size	11	8.1
Young deaths	1	17*
Runts	0	5*
Number of rats	121	81

* Statistically significant, $p<0.025$.

In a two-generation study (RTI, 1987 as cited in U.S. EPA, 1998), nickel chloride was administered in drinking water to male and female rats (30/sex/dose) at dose levels of 0, 50, 250, or 500 ppm for 90 days before breeding. A significant decrease in the P_0 maternal body weight was observed at the highest dose level. A significant decrease in live pups/litter and average pup body weight in comparison with controls was observed at the 500 ppm dose level in the F_1a generation. Similar effects were seen with F_1b litters of P_0 dams exposed to 500 ppm dose level. Increased pup mortality and decreased live litter size was also observed in the 50 and 250 ppm dose groups in the F_1b litters. However, U.S. EPA (1998) noted that the validity of these effects is questionable since the temperature and humidity experienced by F_1b litters were different from the normal at certain times and that might have caused the observed adverse effect. As discussed in a paper by Edwards (1986), body temperatures that are 1.5-5 °C above normal during fetal development can cause adverse developmental effects in many mammalian species. Therefore, U.S. EPA (1998) did not consider the results seen at 50 and 250 ppm as genuine adverse effects.

F_1b males and females of the RTI (1987 as cited in U.S. EPA, 1998) study were randomly mated on postnatal day 70 and their offspring were evaluated through postnatal day 21. The authors found that the 500 ppm dose caused significant body weight depression of both mothers and pups, and increased neonatal mortality during the postnatal developmental period. The 250 ppm dose produced transient depression of maternal weight gain and water intake during gestation of the

F_2b litters. A significant increase in short ribs was observed in the 50 ppm dose group, but since this adverse effect was not seen in the two higher dose groups, U.S. EPA (1998) did not considered it to be biologically significant.

Smith et al. (1993) administered nickel chloride in drinking water at 0, 10, 50, or 250 ppm nickel (0, 1.3, 6.8, or 31.6 mg Ni/kg_{bw}/day) to female Long-Evans rats for 11 weeks prior to mating and then during two sequential gestation (G1, G2) and lactation (L1, L2) periods. Dams were rested for 2 weeks after weaning of the first litters before initiating the second breeding. During this time, nickel exposure was continuous. Breeder males were unexposed. The average-daily-nickel-intake dose for female rats drinking nickel chloride solutions is presented in Table 9. Throughout the study, there were no overt clinical signs of toxicity in any of the groups. Reproductive performance was unaltered by nickel exposure though maternal weight gain was reduced during G1 in the high- and middle-dose groups.

Table 9. Estimated average daily nickel intake dose for female rats drinking nickel chloride solution (from Smith et al., 1993).

Dose (ppm Ni)	Estimated average daily nickel intake dose[a] (mg/kg)					
	Prebreeding	**First gestation period, G1**	**First lactation period, L1[b]**	**Second gestation period, G2**	**Second lactation period, L2[b]**	**Overall average[c] (mg/kg)**
0	-	-	-	-	-	-
10	1.05	1.09	2.11	0.92	1.89	1.33
50	5.35	5.48	10.68	4.57	9.91	6.80
250	24.44	24.3	52.35	22.04	48.76	31.63

[a] Milligrams nickel per kilogram mean body weight for that experimental segment.
[b] Measured until Day 16 of lactation when pup activity begins to affect apparent maternal intake values.
[c] Based on values for dams with litters in G1 and G2 (n=78) and including all rest periods. Calculated as total cumulative water consumption divided by study average body weight.

The most significant toxicological finding was the increased frequency of perinatal death. Smith et al. (1993) reported that the proportion of dead pups per litter was significantly increased at the highest dose in the first breeding (Table 10) and at 10 and 250 ppm in the second breeding. In the second breeding the proportion of dead pups per litter at 50 ppm was marginally significant (P=0.076) (Table 11). The authors noted that if only one additional female drinking 50 ppm with no dead pups had lost one pup at birth, the probability level for the analysis at this dose would change from 0.076 to 0.04.

Table 10. Reproductive outcome of first breeding of female rats drinking nickel chloride solutions (from Smith et al., 1993).

Conc. of nickel in water (ppm Ni)	Sperm positive females	No. viable litters	Average no. of pups per litter (live and dead)	No. litters with dead pups at birth	Total dead pups on postnatal day 1 (% dead pups per litter)
0 (34[a])	29	25	12.9	5[b]	5 (1.7)
10 (34)	30	25	12.2	5	9 (3.1)
50 (34)	30	24	11.7	0	0 (0)
250 (34)	32	27	13.2	11†	35*** (13.2)**

[a]Number of females entering study.
[b]Number of litters with at least one dead pup.
†Significant levels, pairwise comparison to the control.
0.05<P≤0.10, **0.01<P≤0.03, ***0.001<P≤0.01.

Table 11. Reproductive outcome of second breeding of female rats drinking nickel chloride solutions (from Smith et al., 1993).

Conc. of nickel in water (ppm Ni)	Sperm positive females	No. viable litters	Average no. of pups per litter (live and dead)	No. litters with dead pups at birth	Total dead pups on postnatal day 1 (% dead pups per litter)
0 (29[a])	28	23	10.6	2[b]	2 (1.0)
10 (29)	28	22	12.5	7†	11** (4.3)**
50 (30)	29	24	13.3	6	16* (4.6) †
250 (31)	31	25	11.3	10**	22*** (8.8)***

[a]Number of females bred for second time.
[b]Number of litters with at least one dead pup.
†Significant levels, pairwise comparison to the control.
0.05<P≤0.10, *0.03<P≤0.05, **0.01<P≤0.03, ***0.001<P≤0.01.

The apparent discrepancy between the outcomes of the two sequential breedings may be explained by the fact that the female rats had been exposed to nickel chloride for a longer period of time before the second gestation. Another plausible explanation is that the nickel doses administered before the second breeding were significantly higher than those administered before the first breeding. As shown in Table 9, female rats consumed almost twice as much water and nickel chloride during L1 than in the prebreeding period. However, the authors did not provide drinking water consumption data during the two-weeks resting period; as a result, the nickel dose administered just before the second gestation was not presented in the paper. Smith et al. (1993) did not suggest mechanism(s) that could account for the apparent increased prenatal mortality at the lower doses in the second breeding. Based on the result of their study, Smith et al. (1993) concluded that 10 ppm nickel in drinking water (1.3 mg Ni/kg_{bw}/day) represents the LOAEL in rats.

Nadeenko et al. (1979 as cited in IARC, 1990; in Russian) administered nickel chloride in drinking water to female rats at 0.1 or 0.01 mg Ni/L (0.1 or 0.01 ppm) for seven months and then during pregnancy. They reported that embryonic mortality was 57 percent among nine rats

exposed to the higher concentration, compared to 34 percent among eight controls. No such difference was observed at the lower concentration.

Diwan et al. (1992) showed that intraperitoneal injection of nickel acetate to pregnant F344/NCr rats caused early mortality in the offspring. They administered four intraperitoneal injections of nickel acetate (2.6 mg Ni/kg_{bw}) on days 12, 14, 16 and 18 of gestation and reported that all offspring died within 72 hours after birth. Furthermore, they demonstrated that when the injection doses to pregnant rats were reduced (once for 5.3 mg Ni/kg_{bw} or twice for 2.6 mg Ni/kg_{bw} each) around day 17 of gestation and the offspring were given drinking water containing 500 ppm sodium barbital, there were significant increases of renal cortical tumors and renal pelvic tumors in male offspring. Pituitary tumor incidences were also increased in male rats given nickel acetate prenatally, with or without postnatal sodium barbital. A more detailed discussion of the results of this study is presented in the section on animal carcinogenicity.

Sunderman et al. (1978 as cited in IARC, 1990) administered nickel chloride (16 mg Ni/kg_{bw}) to Fischer rats by intramuscular injection on day 8 of gestation. The body weights of fetuses on day 20 of gestation and of weanlings four to eight weeks after birth were reduced. No congenital anomaly was found in fetuses from nickel-treated dams, or in rats that received ten intramuscular injections of 2 mg Ni/kg_{bw} as nickel chloride twice daily from day 6 to day 10 of gestation.

A number of animal studies have shown soluble nickel compounds can negatively impact the male reproductive system. Sobti and Gill (1989) administered soluble nickel compounds (23-43 mg Ni/kg_{bw}) in water to mice by the oral route and took smears of spermatozoa from the epididymis after five weeks of the last exposure. The number of animals in the control and exposed groups was not reported. The authors showed that administration of nickel induced a statistically significant increase in the incidence of micronuclei and abnormalities in the head of the spermatozoa. The different types of the abnormal spermatozoa were of Daphnia, polyp, amorphous, giant amorphous and anvil-shape.

Hoey (1966 as cited in IPCS, 1991) administered nickel sulfate at 2.3 µg Ni/kg_{bw} to male Fischer rats by intracutaneous injection. The author found shrinkage of epididymis tubules and complete degeneration of the spermatozoa 18 hours after exposure. Mathur et al. (1977) exposed male rats to nickel sulfate at daily levels of 40, 60, or 100 mg Ni/kg_{bw} through the dermal route. They also observed tubular damage and spermatozoal degeneration in the testis following exposure to 60 and 100 mg Ni/kg_{bw} for 30 days. There were no effects on the testis following exposure to 40 mg/kg_{bw} for 30 days or at any dose level after 15 days of exposure. Waltschewa et al. (1972 as cited in IPCS, 1991) reported infertility in rats after 120 days of daily ingestion of 25 mg nickel sulfate/kg (9 mg Ni/kg_{bw}).

Immunotoxicity

NTP (1996c) and IPCS (1991) recently summarized the immunologic effects of nickel compounds and the results are reproduced in Table 12.

Smialowicz et al. (1984, 1985 as cited in IPCS, 1991) injected nickel chloride intramuscularly to mice and found a significant reduction in a variety of T-lymphocytes and natural killer cell-mediated immune functions. They also demonstrated that suppression of natural killer cell activity could be detected in vitro and in vivo assays and that reduction of natural killer cell activity was not associated with either a reduction in spleen cellularity or the production of suppressor cells. Their findings confirmed those reported by other investigators on the immuno-suppressive effects of nickel compounds on circulatory antibody titres to T_1 phage in rats (Figoni

and Treagan, 1975 as cited in IPCS, 1991), on antibody response to sheep erythrocytes (Graham et al., 1975 as cited in IPCS, 1991), on interferon production in vivo in mice (Grainer, 1977 as cited in IPCS, 1991), and on susceptibility to induced pulmonary infection in mice following inhalation of nickel chloride (Adkins et al., 1979 as cited in IPCS, 1991).

The effects of nickel compounds on natural killer cells are of particular interest because of the suspected function of these cells in nonspecific defense against certain types of infections and tumors (ICPS, 1991).

Table 12. Studies on the immunologic effects of nickel compounds in rodents (from NTP, 1996a).

Nickel Compound	Species/Route	Chemical treatment	Response	Reference
Cell-Mediated Immunity				
Nickel chloride	CBA/J mice/ intramuscular	Single injection, 18 mg/kg_{bw}	Reduced T-lymphocyte proliferation	Smialowicz et al. (1984)
Nickel sulfate	B6C3F_1 mice (female)/oral	Up to 4,000 mg/kg_{bw}/day for 23 weeks	Depressed spleen lymphoproliferative response to LPS (no effect on NK activity; PFC assay; mitogen response in spleen cells; resistance to *Listeria* challenge)	Dieter et al. (1988)
Humoral Immunity				
Nickel chloride	CBA/J mice /intramuscular	Single injection, 18 mg/kg_{bw}	Reduced antibody response to T-cell dependent sheep red blood cells	Smialowicz et al. (1984)
	Swiss albino mice/ intramuscular	3-12 μg Ni/kg_{bw} followed by immunization with sheep red blood cells	Depressed antibody formation	Graham et al. (1975a)
	Swiss mice/inhalation	2-hour inhalation exposure at 250 μg/m^3	Depressed antibody response to sheep red blood cells	Graham et al. (1978)
Nickel acetate	Sprague-Dawley rats/intraperitoneal	11 mg/kg_{bw} immunized with E. coli bacteriophage	Depressed circulating antibody response	Figoni and Treagan (1975)

Table 12 (continued). Studies on the immunologic effects of nickel compounds in rodents (from NTP, 1996a).

Nickel Compound	Species/Route	Treatment	Response	Reference
Macrophage Function				
Nickel chloride	CBA/J mice /intramuscular	Single injection, 18 mg/kg_{bw}	No effect on phagocytic capacity of peritoneal macrophages	Smialowicz *et al.* (1984)
Natural Killer Cell Activity				
Nickel chloride	CBA/J and C57BL/6J mice/intramuscular	Single injection, 18 mg/kg_{bw}	Depressed NK activity (against Yac-1 murine lymphoma cells)	Smialowicz *et al.* (1984, 1985, 1986)
Host Resistance				
Nickel chloride and nickel oxide	CD mice and Sprague-Dawley rats/inhalation	0.5 mg/m^3 for 2 hours	Enhanced respiratory infection to Streptococcus	Adkins *et al.* (1979)

Endocrine effects

Endocrine effects of soluble nickel on test animals have been recently reviewed by IPCS (1991). Ashraf and Sybers (1974) found lysis of pancreatic exocrine cells in rats fed 0.1-1.0 percent nickel acetate in diet. Bertrand and Macheboeuf (1926 as cited in IPCS, 1991) reported that parenteral administration of nickel chloride or nickel sulfate to rabbits or dogs antagonized the hyperglycaemic action of insulin. Several researchers also showed that injection of nickel into rabbits, rats, or chickens caused a rapid increase in plasma glucose concentrations, which returned to normal within four hours (Kadota and Kurita, 1955; Gordynia, 1969; Clary and Vignati, 1973; Freeman and Langslow, 1973; Horak and Sunderman, 1975 as cited in IPCS, 1991).

Lestrovoi et al. (1974 as cited in IPCS, 1991) showed that nickel chloride given orally to rats (0.5-5.0 mg/kg_{bw}/day) significantly decreased iodine uptake by the thyroid gland. Dormer et al. (1973 as cited in IPCS, 1991) showed that nickel ion is a potent inhibitor of secretion in vitro in the parotid gland (amylase), the islets of Langerhans (insulin), and the pituitary gland (growth hormone).

La Bella et al. (1973 as cited in IPCS, 1991) reported that administration of nickel to rats raised the concentration of the metal within the pituitary and the hypothalamus and inhibited prolactin secretion. Clemons and Garcia (1981 as cited in IPCS, 1991) demonstrated that subcutaneous injection of 10 or 20 mg nickel chloride/kg_{bw} in rats initially produced a drop in serum prolactin, but resulted in a sustained elevation of the hormone after one day, which lasted up to four days. Smith et al. (1993) administered nickel chloride in drinking water at 0, 10, 50 or 250 ppm nickel to female rats and observed a statistically significant decrease of prolactin levels in the females exposed to 250 ppm nickel compared with those in the controls.

Chronic Toxicity

The kidney is the main target organ following chronic exposure to nickel via the oral route. Vyskocil et al. (1994) administered nickel sulfate in drinking water to 20 male and 20 female Wistar rats at 100 ppm Ni^{2+}. Equal numbers of males and females were used as controls. After six months of exposure, they observed that the average level of albumin excreted in the urine of treated females was significantly higher than that of the controls. Urinary excretion of albumin was also higher in the treated male than the controls, but the difference was not significant. Vyskocil et al. (1994) suggested that chronic exposure to nickel in drinking water either induced changes of glomerular permeability in rats or enhanced the normal age-related glomerular nephritis lesions of aging rats. They estimated the average daily intake dose received by the female rats was 6.8 mg/kg_{bw}/day.

Discolored gastrointestinal contents, ulcerative gastritis, and enteritis were observed in rats exposed to nickel chloride hexahydrate by gavage at 1.2-25 mg Ni/kg_{bw}/day for up to 91 days (American Biogenics Corporation, 1988 as cited in ATSDR, 1997). However, gastrointestinal effects were not observed in rats treated with nickel sulfate in the diet at 187 mg Ni/kg_{bw}/day for two years (Ambrose et al., 1976). Different administration method may explain the different results, as the gavage treatment is likely to produce a much higher concentration of nickel in the gastrointestinal tract than the dietary treatment.

Decreased liver weight was observed in rats and mice chronically exposed to $\geq$1.5 mg Ni/kg_{bw}/day (Ambrose et al., 1976; Dieter et al., 1988; Weischer et al., 1980; American Biogenics Corporation, 1988 as cited in ATSDR, 1997). Because histological changes in the liver were not observed in these studies, the significance of the liver weight changes is unclear.

Additional chronic animal studies are discussed in the sections on developmental and reproductive toxicity, and carcinogenicity of nickel.

Essentiality in Animals

Nickel is an essential nutrient in 17 animal species, including chicken, cow, goat, mini-pig, pig, rat, and sheep (IPCS, 1991). It has been suggested that nickel is also essential to humans, at very low levels (Anke et al., 1984).

Schnegg and Kirchgessner (1975, 1976 as cited in IPCS, 1991) showed that nickel deficiency in rats led to a reduced iron content in organs, reduced hemoglobin and hematocrit values, and anemia. Nielsen et al. (1979 as cited in IPCS, 1991) reported that iron supplementation did not cure this anemia; they also found that nickel deficiency markedly impaired iron absorption. Anke et al. (1980 as cited in IPCS, 1991) found that nickel-deficient goats eliminated 33 percent more iron via the feces than the controls. There are several studies reporting nickel-deficient mini-pigs and rats have less calcium in their skeletons than those found in animals on a nickel-rich diet.

Many animal studies have shown nickel deficiency depresses enzyme activities. Schnegg and Kirchgessner (1975, 1977 as cited in IPCS, 1991) found that the activities of some dehydrogenases and transaminases were decreased by 40-75 percent in rats that are deficient in nickel. Kirchgessner and Schnegg (1979 and 1980 as cited in IPCS, 1991) observed a 50 percent reduction in the activity of alpha-amylase in the liver and pancreas of rats that are deficient in

nickel. King et al (1985 as cited in IPCS, 1991) suggested that nickel might serve as a co-factor for the activation of calcineurin, a calmodulin-dependent phosphoprotein phosphatase.

It has also been shown that nickel deficiency can cause growth retardation in goats, pigs, and rats (Anke et al., 1980, 1986; Spears, 1984; Spears et al., 1984; Nielsen et al., 1975; Schnegg and Kirchgessner, 1980 as cited in IPCS, 1991). Various studies found that nickel-deficiency in rats and pigs was associated with small litter sizes (Anke et al., 1974; Nielsen et al., 1975; Schnegg and Kirchgessner, 1975 as cited in IPCS, 1991).

Genetic Toxicity

ADSTR (1997), NTP (1998), Snow (1992), Kasprzak (1991), IPCS (1991), Costa (1991), IARC (1990), CARB (1991), and Sunderman (1989) have recently reviewed the genotoxicity data and mode of action of nickel and nickel compounds. Most of the information summarized in this section was obtained from these reviews. Table 13 summarizes the in vitro and in vivo genotoxicity data of nickel compounds.

In vitro studies

Examination of the genotoxicity database for soluble nickel compounds indicated that they generally did not cause mutation in bacterial test systems. Positive results have been observed (1) in tests for single and double DNA strand breaks and/or crosslinks in both human and animal cells, (2) in tests for cell transformation, (3) in tests for sister chromatid exchanges and chromosomal aberrations in hamster and human cells, and (4) in tests for mutation at the HGPRT locus in animal cells (IARC, 1990). For a more detailed discussion of the genotoxicity data of nickel and nickel compounds, the reader is recommended to consult CARB (1991), IPCS (1991), and ADSTR (1997).

Several studies reported that nickel compounds have the ability to enhance the cytotoxicity and mutagenicity of other DNA damaging agents such as ultra-violet light, benzo(a)pyrene, cis-platinum, and mitomycin C (Hartwig and Beyersmann, 1989; Christie, 1989; Rivedal and Sanner, 1980 as cited in Hartwig et al., 1994). Hartwig et al. (1994) showed that Ni^{2+} inhibited the removal of pyrimidine-dimer and repair of DNA strand break in HeLa cells after exposure to ultra-violet light or X-rays. Hartmann and Hartwig (1998) demonstrated that the inhibition of DNA repair was effective at relatively low concentration, 50 µM Ni^{2+}, and partly reversible by the addition of Mg^{2+}. Based on these observations, they suggested that Ni^{2+} disturbed DNA-protein interactions essential for the DNA repair process by the displacement of essential metal ions.

Studies have demonstrated that soluble nickel compounds can inhibit the normal DNA synthesis, impair or reduce the fidelity of DNA repair, and transform initiated cells in vitro. Basrur and Gilman (1967 as cited in IARC, 1990) and Swierenga and McLean (1985 as cited in IARC, 1990) showed that nickel chloride inhibited DNA synthesis in primary rat embryo cells and in rat liver epithelial cells. Costa et al. (1982 as cited in IARC, 1990) found that nickel chloride at 40-120 µM selectively blocked cell cycle progression in the S phase in Chinese hamster ovary cells.

Nieborer et al. (1984) demonstrated that chelation of Ni^{2+} by amino acids and proteins has a significant effect on the cellular uptake of Ni^{2+} in human B-lymphoblasts, human erythrocytes, and rabbit alveolar macrophages. They observed that addition of L-histidine or human serum albumin at physiological concentrations to the cell cultures reduced Ni^{2+} uptake by 70-90 percent.

Table 13. Genotoxicity of nickel in vitro (from ATSDR, 1997).

Compound	Species (test system)	End point	Result	Reference
Nickel chloride, nickel nitrate, nickel sulfate	Prokaryotic organisms: *Salmonella typhimurium*	Gene mutation	-	Arlauskas et al. 1985; Biggart and Costa 1986; Marzin and Phi 1985; Wong 1988
Nickel chloride	*Escherichia coli*	Gene mutation	-	Green et al. 1976
Nickel chloride	*Escherichia coli*	DNA replication	+	Chin et al. 1994
Nickel chloride	*Cornebacterium sp.*	Gene mutation	+	Pikalek and Necasek 1983
Nickel oxide and trioxide	*Bacillus subtilis*	DNA damage	-	Kanematsu et al. 1980
Nickel sulfate	Eukaryotic organisms: Fungi: *Saccharomyces cerevisia*	Gene mutation	-	Singh 1984
	Mammalian cells			
Nickel chloride	CHO cells	Gene mutation	+	Hsie et al. 1979
Nickel chloride	Virus-infected mouse cells	Gene mutation	+	Biggart and Murphy 1988; Biggart et al. 1987
Nickel chloride, nickel sulfate	Mouse lymphoma cells	Gene mutation	+	Amacher and Paillet 1980; McGregor et al. 1988
Nickel chloride	Chinese hamster V79 cells	Gene mutation	+	Hartwig and Beyersmann 1989; Miyaki et al. 1979
Cystalline NiS, nickel chloride	CHO cells	DNA damage	+	Hamilton-Koch et al. 1986; Patierno and Costa 1985
Nickel chloride	Human diploid fibroblasts	DNA damage	-	Hamilton-Koch et al. 1986
Nickel sulfate	Human gastric mucosal cells	DNA damage	-[b]	Pool-Zobel et al. 1994

Table 13 (continued). Genotoxicity of nickel in vitro (from ATSDR, 1997).

Compound	Species (test system)	End point	Result	Reference
Nickel oxide (black and green); amorphous nickel sulfide; nickel subsulfide; nickel chloride; nickel sulfate; nickel acetate	CHO AS52 cells	Gene mutation	+	Fletcher et al. 1994
Nickel chloride	Human HeLa cells	DNA replication	+	Chin et al. 1994
Nickel sulfate, nickel chloride; crystalline NiS	Hamster cells	Sister chromatid exchange	+	Andersen 1983; Larremendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981
Nickel sulfate, nickel sulfide	Human lymphocytes	Sister chromatid exchange	+	Andersen 1983; Larremendy et al. 1981; Saxholm et al. 1981; Wulf 1980
Nickel sulfate, nickel chloride, nickel monosulfide	Hamster cells	Chromosome aberration	+	Conway and Costa 1989; Larremendy et al. 1981; Sen and Costa 1986b; Sen et al. 1987
Nickel sulfate	Human lymphocytes	Chromosome aberration	+	Larremendy et al. 1981
Nickel subsulfide	Human lymphocytes	Sister chromatid exchange Metaphase analysis Micronucleus	+	Arrouijal et al. 1982
Nickel sulfate	Human bronchial epithelial cells	Chromosome aberration	+	Lechner et al. 1984

Table 13 (continued). Genotoxicity of nickel in vitro (from ATSDR, 1997).

Compound	Species (test system)	End point	Result	Reference
Nickel monosulfide, nickel subsulfide, nickel chloride, nickel oxide or trioxide	Hamster cell and C3H/10T1/2 cells	Cell transformation	+	Conway and Costa 1989; Costa and Heck 1982; Costa and Mollenhauer 1980; Costa et al. 1982; DiPaolo and Castro 1979; Hansen and Stern 1984; Saxholm et al. 1981
Nickel sulfate, nickel chloride	Mouse embryo fibroblasts	Cell transformation	-	Miura et al. 1989
Nickel subsulfide, nickel monosulfide, nickel oxide	Mouse embryo fibroblasts	Cell transformation	+	Miura et al. 1989
Nickel subsulfide, nickel oxide, nickel sulfate, nickel acetate	Human foreskin cells	Cell transformation	+	Bidermann and Landolph 1987

[a]metabolic activation is not an issue for nickel compounds.
[b]Nickel was genotoxic and cytotoxic at the same concentration (9.5 μmol/mL), so it was not a selective genotoxicant.
- = negative result; + = positive result; ++ = highly positive; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NiS = nickel sulfide

Table 13 (continued). Genotoxicity of nickel in vivo (from ATSDR, 1997).

Compound	Species (test system)	End point	Result	Reference
Nickel nitrate or chloride	*Drosophila melanogaster*	Gene mutation	-	Rasmuson 1985
Nickel sulfate	D. *melanogaster*	Recessive lethal	+	Rodriquez-Arnaiz and Ramos 1986
Nickel chloride	*D. melanogaster*	Gene mutation (wing spot test)	±	Ogawa et al. 1994
	Mammalian cells:			
Nickel oxide, nickel subsulfide	Human lymphocytes	Chromosome aberrations (gaps)	+	Waksvik and Boysen 1982
Nickel oxide, nickel subsulfide	Human lymphocytes	Sister chromatid exchange	-	Waksvik and Boysen 1982
Nickel sulfate	Rat bone marrow and spermatogonia cells	Chromosome aberrations	-	Mathur et al. 1978
Nickel chloride, nickel sulfate, nickel nitrate	Mouse bone marrow cells	Micronucleus test (oral)	+	Sobti and Gill 1989
Nickel chloride	Mouse bone marrow cells	Chromosome aberrations (ip)	+	Dhir et al. 1991
Nickel chloride	Mouse bone marrow cells	Micronucleus test (ip)	-	Deknudt and Leonard 1982
Nickel acetate	Mouse	Dominant lethal (ip)	-	Deknudt and Leonard 1982

- = negative result; + = weakly positive; (ip) = intraperitoneal

The concentration of nickel used in the study was $7x10^{-8}$ M (or 4.1 µg/L); it was comparable to serum nickel levels observed in workers occupationally exposed to nickel.

Consistent with the findings of Nieborer et al. (1984), Abbracchio et al. (1982) demonstrated that Chinese hamster ovary cells maintained in a minimal salts/glucose medium accumulated 10-fold more ^{63}Ni than did cells maintained in a minimal salts/glucose medium with 5 mM cysteine. The results were obtained after the removal of surface-associated radioactivity by treating the cells with trypsin. They also showed that supplementation of the salts/glucose medium with fetal bovine serum decreased in a concentration dependent fashion both the Ni^{2+} uptake and cytotoxicity. Findings of Nieborer et al. (1984) and Abbracchio et al. (1982) indicate the important role of specific amino acids and proteins in regulating the uptake and cytotoxicity of Ni^{2+}. For this reason, when in vitro genotoxicity test results are compared, it is important to standardize the concentration of these chelating agents.

In vivo studies

The clastogenic potential of soluble nickel compounds has been shown in many in vivo studies. Sobti and Gill (1989) reported that oral administration of nickel sulfate (28 mg Ni/kg_{bw}), nickel nitrate (23 mg Ni/kg_{bw}), or nickel chloride (43 mg Ni/kg_{bw}) to mice increased the frequency of micronuclei in the bone marrow at 6 and 30 hours after treatment. Details of the study were not reported and it was not clear how many animals were used in each experiment.

Mohanty (1987 as cited in IARC, 1990) reported that intraperitoneal injections of nickel chloride at 6, 12, or 24 mg/kg_{bw} increased the frequency of chromosomal aberrations in bone-marrow cells of Chinese hamsters. However, Mathur et al. (1978 as cited in U.S. EPA, 1986) observed that intraperitoneal injections of nickel sulfate at 3 and 6 mg/kg_{bw} did not induce chromosomal aberrations in bone-marrow cells and spermatogonia of male albino rats. Saplakoglu et al. (1997) administered 44.4 mg nickel $chloride/kg_{bw}$ to rats via subcutaneous injections and did not observe increased levels of single-strand breaks in cultured lung, liver, or kidney cells. Similarly, Deknudt and Leonard (1982) administered 25 mg/kg_{bw} nickel chloride (about 50 percent of the LD_{50}) and 56 mg/kg nickel nitrate (about 50 percent of the LD_{50}) to mice by intraperitoneal injection and did not detect a significant increase of micronuclei in the bone marrow of the animals after 30 hours.

Inhibition of DNA synthesis has been observed in vivo. Amlacher and Rudolph (1981 as cited in IARC, 1990) observed that intraperitoneal injections of nickel sulfate at 15-30 percent of the LD_{50} to CBA mice suppressed DNA synthesis in hepatic epithelial cells and in the kidney. Hui and Sunderman (1980 as cited in IARC, 1990) also reported that intramuscular injections of nickel chloride to rats at 20 mg Ni/kg_{bw} inhibited DNA synthesis in the kidney.

Mode of action

A number of hypotheses have been proposed about the mechanisms that can explain the observed genotoxicity and transformation potential of soluble nickel compounds. Costa et al. (1982) and Sahu et al. (1995) showed that soluble nickel compounds affected cell growth by selectively blocking the S-phase of the cell cycle. Kasprzak (1991) and Sunderman (1989) suggested that most of the genotoxic characteristics of Ni^{2+} including DNA strand breaks, DNA-protein cross-links, and chromosomal damage could be explained by the ability of Ni^{2+} to generate oxygen free radicals. While Ni^{2+} in the presence of inorganic ligands is resistant to oxidation, Ni^{2+} chelated with peptides has been shown to be able to catalyze reduction-oxidation reactions.

Martin (1988 as cited in Sunderman, 1993) and Andrews et al. (1988 as cited in Sunderman, 1993) observed that certain peptides and proteins (especially those containing a histidine residue) form coordination complexes with Ni^{2+}. Many of these complexes have been shown to react with $O_2^{\bullet-}$ and/or H_2O_2 and generate oxygen free radicals (such as •OH) in vitro (Bossu et al., 1978;

Inoue and Kawanishi, 1989; Torreilles and Guerin, 1990; Nieboer et al., 1984 and 1989 as cited in Kasprzak, 1991). It is important to note that the major substrates for nickel mediated oxygen activation, $O_2^{\bullet-}$ and H_2O_2, are found in mammalian cells, including the nucleus (Peskin and Shlyahova, 1986 as cited in Kasprzak, 1991).

Tkeshelashvili et al. (1993) showed that mutagenesis of Ni^{2+}in a bacterial test system could not only be enhanced by the addition of both hydrogen peroxide and a tripeptide glycyl- glycyl-L-histidine but also could be reduced by the addition of oxygen radical scavengers. Huang et al. (1993) treated Chinese hamster ovary cells with 0-5 mM of nickel chloride and the precursor of fluorescence dye, 2,7-dichlorofluorescin diacetate, and observed a significant increase of fluorescence in intact cells around the nuclear membranes. The effect was related to the concentration of the nickel chloride concentration and detectable at or below 1 mM. Since only strong oxidants, such as hydrogen peroxide and other organic hydroperoxides, can oxidize the nonfluorescence precursor to a fluorescent product, Huang et al. (1993) suggested that Ni^{2+} increased the level of such oxidants in intact cells.

Evidence of oxidative damage to cellular and genetic materials as a result of nickel administration has also been obtained from a number of in vivo studies. There are data indicating lipid peroxidation participates in the pathogenesis of acute nickel poisoning (Sunderman et al., 1985; Donskoy et al., 1986; Knight et al., 1986; Kasprzak et al., 1986 and Sunderman, 1987 as cited in Sunderman, 1989). Stinson et al. (1992) subcutaneously dosed rats with nickel chloride and observed increased DNA strand breaks and lipid peroxidation in the liver 4-13 hours after the treatment. Kasprzak et al. (1992) administered nickel acetate (5.3 mg Ni/kg_{bw}) to pregnant rats by a single or two interperitoneal injections and identified eleven oxidized purine and pyrimidine bases from the maternal and fetal liver and kidney tissues. Most of the products identified were typical hydroxyl radical-produced derivatives of DNA bases, suggesting a role for hydroxyl radical in the induction of their formation by Ni^{2+}. In two other animal studies, Kasprzak et al. (1990 and 1992) also observed elevated levels of 8-hydroxy-2'-deoxyguanosine (8-OH-dG) in the kidneys of rodents administered with a single interperitoneal injection of nickel acetate. Formation of 8-OH-dG is often recognized as one of the many characteristics of •OH attack on DNA.

Besides generating oxygen free radicals, Ni^{2+} can also weaken cellular defense against oxidative stresses. Donskoy et al. (1986 as cited in Sunderman, 1989) demonstrated that administration of soluble nickel compounds depleted free-radical scavengers (e.g., gluthathione) or catalase, superoxide dismutase, glutathione peroxidase, or other enzymes that protect against free-radical injury in the treated animals.

Insoluble crystalline nickel compounds are generally found to be more potent in genetic toxicity assays than the soluble or amorphous forms of nickel. To find out the reason for this phenomenon, Harnett et al. (1982) compared the binding of ^{63}Ni to DNA, RNA, and protein isolated from cultured Chinese hamster ovary cells treated with either crystalline nickel sulfide (^{63}NiS) or a soluble nickel compound, $^{63}NiCl_2$ (both at 10 µg/ml). They reported that in the case of $^{63}NiCl_2$ treatment, cellular proteins contained about 100 times more bound ^{63}Ni than the respective RNA or DNA fractions; whereas in cells treated with crystalline ^{63}NiS, equivalent levels of nickel were associated with RNA, DNA, and protein. In absolute terms, RNA or DNA had 300 to 2,000 times more bound nickel following crystalline ^{63}NiS treatment compared to cells treated with $^{63}NiCl_2$. Fletcher et al. (1994) reported similar findings. Chinese hamster ovary cells were exposed to either water-soluble or slightly water-soluble salts. They observed relatively high nickel concentrations in the cytosol and very low concentrations in the nuclei of the cells exposed to the water-soluble salts. In contrast, they found relatively high concentrations of nickel in both the cytosol and the nuclei of the cells exposed to the slightly water-soluble salts.

Sen and Costa (1986) and Costa et al. (1994) theorized that this is because NiS and $NiCl_2$ are taken up by cells through different mechanisms. Ni^{2+} has a high affinity for protein relative to DNA, treatment of cells with soluble nickel compounds resulted in substantial binding of the metal ion to cytoplasmic proteins, with a small portion of the metal ion eventually reaching the nucleus. When cells are treated with crystalline nickel sulfide, the nickel containing particles were phagocytized and delivered to sites near the nucleus. This mode of intracellular transport reduces the interaction of Ni^{2+} with cytoplasmic proteins and peptides (Figure 1).

To support their theory, Sen and Costa (1986) exposed Chinese hamster ovary cells to nickel chloride alone, nickel chloride-albumin complexes, nickel chloride-liposomes, and nickel chloride-albumin complexes encapsulated in liposomes. They found that at a given concentration (between 100 and 1,000 μM), cellular uptakes of nickel were 2-4 fold higher when the ovary cells were exposed to nickel chloride-liposomes or nickel chloride-albumin complexes encapsulated in liposomes than to nickel chloride alone or nickel chloride-albumin complexes. Even at comparable levels of cellular nickel (approximately 300 pmole $Ni/10^6$ cells), fragmentation of the heterochromatic long arm of the X chromosome was only observed in cells treated with nickel encapsulated in liposomes and not in those exposed to nickel or nickel-albumin. Based on these data, they suggested that the higher genotoxic potency of crystalline nickel sulfide and nickel encapsulated in liposomes was not primarily due to the higher cellular nickel concentration, but rather to the way nickel ion was delivered into cells.

IARC (1980) suggested that cellular binding and uptake of nickel depend on the hydro- and lipophilic properties of the nickel complexes to which the cells are exposed. Nickel-complexing ligands, L-histidine, human serum albumin, D-penicillamine, and ethylenediaminetetraacetic acid, which form hydrophilic nickel complexes, inhibited the uptake of nickel by rabbit alveolar macrophages, human B-lymphoblasts, and human erythrocytes. Diethyldithiocarbamate and sodium pyridinethione, however, which form lipophilic nickel complexes, enhanced the cellular uptake of nickel.

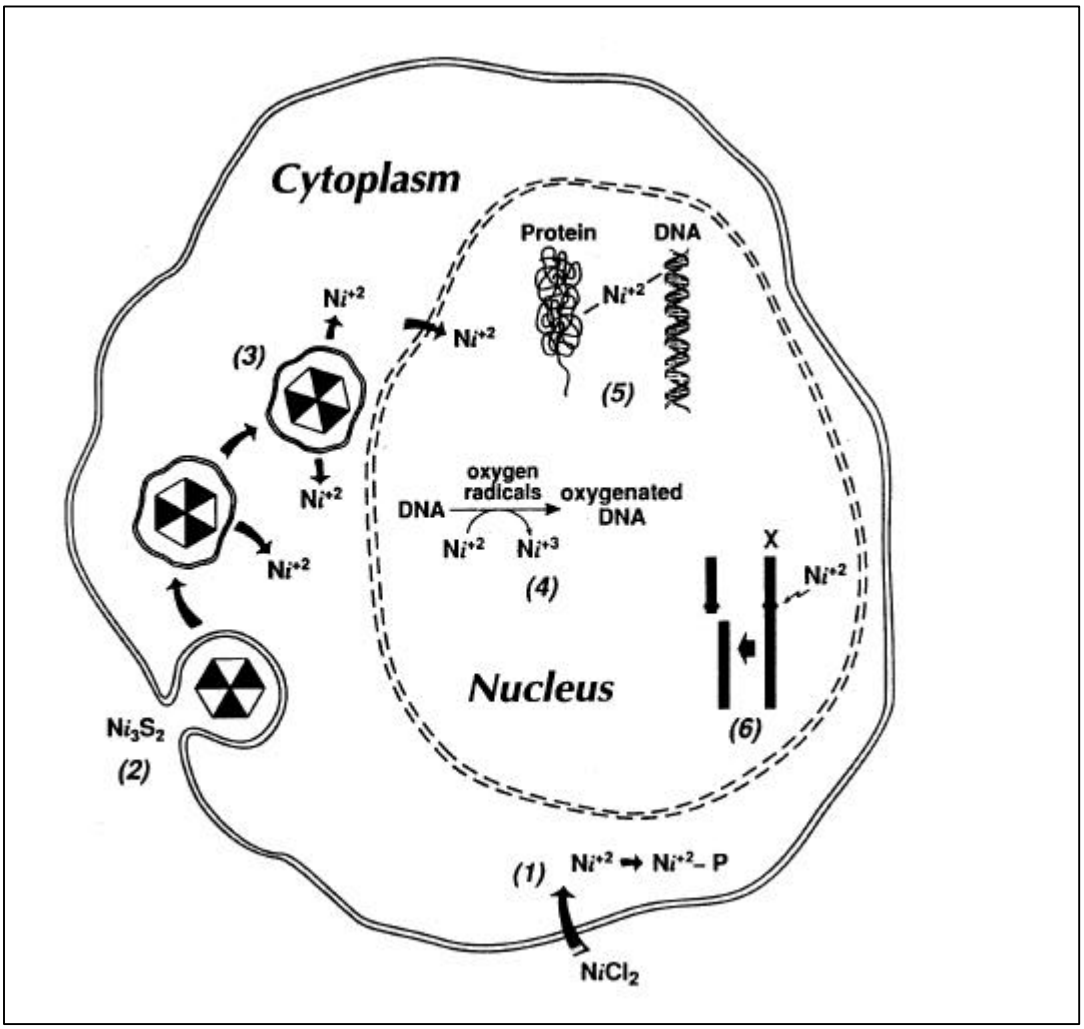

Figure 1. Possible mechanisms of nickel-induced genotoxicity (from NTP, 1996a).

1) Soluble nickel compounds such as nickel chloride diffuse into the cell; Ni^{2+} ions are rapidly bound to cytoplasmic proteins (P) (Lee et al., 1993). 2) Insoluble nickel compounds such as nickel subsulfide are phagocytized into the cell and move toward the nucleus (Costa et al., 1982). 3) Lysosomal breakdown of insoluble nickel compounds releases large quantities of Ni^{2+} ions that concentrate adjacent to the nuclear membrane (Costa and Heck, 1983). 4) Oxidative damage is induced in DNA by nickel ions bound to nuclear proteins ($Ni^{2+} \rightarrow Ni^{3+}$), releasing active oxygen species (Tkeshelashvili et al., 1993; Sugiyama, 1994). 5) DNA-protein crosslinks are produced by Ni^{2+} ions binding to heterochromatin (Lee et al., 1982; Patierno and Costa, 1985; Sen and Costa, 1986). 6) Binding of nickel ions to the heterochromatic regions of the long arm of the X chromosome, which may contain a senescence gene and a tumor suppressor gene, can cause deletion of all or part of this region, leading to an immortalization of the cell and clonal expansion (Conway and Costa, 1989; Klein et al., 1991).

Carcinogenicity

Several scientific and regulatory bodies have recently reviewed the carcinogenicity data of soluble and insoluble nickel compounds:

- In the overall evaluation, IARC (1990) identified nickel compounds as Group 1 carcinogens. IARC (1990) found that there is sufficient evidence in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry. IARC (1990) found that there is inadequate evidence in humans for the carcinogenicity of metallic nickel and nickel alloys. There is sufficient evidence in experimental animals for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides and crystalline nickel sulfides. IARC (1990) also found there is limited evidence in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides and nickel telluride.
- In a draft report to the Carcinogens Subcommittee of the NTP Board of Scientific Counselors, NTP (1998) made the recommendation of upgrading nickel compounds to a known human carcinogen. They suggested 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.
- IPCS (1991) concluded that there is evidence of a carcinogenic risk through the inhalation of nickel metal dusts and some nickel compounds. IPCS (1991) determined that there is a lack of evidence of a carcinogenic risk from oral exposure to nickel, but suggested that there is a possibility that it may act as a promoter.
- The U.S. EPA has not evaluated carcinogenicity of soluble salts of nickel (U.S. EPA, 1998).
- CARB (1991) determined that the evidence for carcinogenicity in humans from inhaled nickel is strong.

Oral studies

There are four negative oral cancer bioassays reported in the literature. In three separate oral studies, Schroeder and his co-workers (Schroeder et al., 1964 and 1974; Schroeder and Mitchener, 1975) administered 5 ppm nickel in drinking water to groups of 33-52 mice and rats of each sex and did not observe any increase in cancer risks. The usefulness of these study results in cancer evaluation is limited, as the nickel doses used in the studies were much lower than the corresponding maximum tolerated doses and not all the animals and all tissues were examined for tumors.

In another oral study, Ambrose et al. (1976) fed nickel sulfate hexahydrate to groups of 25 male and 25 female albino (Wistar derived) rats at 0, 100, 1,000 or 2,500 ppm nickel in diet for two years. U.S. EPA estimated that the dietary doses received by the rats were 0, 5, 50, and 125 mg Ni/kg_{bw}/day, respectively. Males at 2,500 ppm dose group and females at the 1,000 and 2,500 ppm dose groups exhibited reduced weight gain, which indicated that the maximally tolerated dose might have been reached. Histopathological examination of 19 organs or organ systems for a variety of tumors revealed no tumors in rats that could be attributed to the ingestion of nickel sulfate. Since two-year survival was especially poor in controls of both sexes and high dose males, the early mortality observed was not thought to be induced by nickel.

Injection studies

Insoluble nickel compounds (such as nickel monoxide and nickel subsulfide) and metallic nickel powder had been shown in many animal bioassays to induce local tumors through various implantations or injections (IARC, 1990).

Both positive and negative injection studies have been reported on soluble nickel compounds in test animals (Table 14). Pott et al. (1989, 1990) showed that intraperitoneal injection of nickel acetate, nickel sulfate, or nickel chloride increased the incidence of abdominal tumors in rats, compared with the controls. Stoner et al. (1976) and Poirier et al. (1984) demonstrated that intraperitoneal injection of nickel acetate induced lung tumors in a strain of mice that are highly susceptible to lung cancer (Strain A mice).

Other researchers administered soluble nickel compounds to rats by intramuscular injection and did not observe a statistically significant increase of cancer (Payne, 1964; Gilman, 1962 and 1966 as cited in IARC, 1990; Knight et al., 1991; Kasprzak et al., 1983). The fact that local tumors were induced following multiple intraperitoneal injections of soluble nickel compounds but not after single or multiple intramuscular injections may be related to the repeated exposure of potential target cells in multiple intraperitoneal injections but not in multiple intramuscular injections (IARC, 1990).

It should be noted that the injection doses used in all the positive studies (Stoner et al., 1976; Poirier et al., 1984; Pott et al., 1990) described above were close to the maximum tolerated dose determined in the corresponding studies. Poirier et al. (1984) stated that the maximum tolerated dose of nickel acetate was 2.3 mg Ni/kg_{bw}/injection and that was the dose used in their cancer study. Stoner et al. (1976) stated that the maximum tolerated dose was used as the highest dose in the Strain A mouse study. The other two dose levels used were 1:2 and 1:5 dilution of the maximum tolerated dose. Pott et al. (1990) noted that when the intraperitoneal injection dose of the three soluble nickel compounds used in their study was doubled to 2 mg nickel, mortality was raised to between 10 and 40 percent.

It is also important to note that all tumors induced by injection are at the site of contact. The only exceptions were the lung tumors of the Strain A mice. However, the extrapolation of these results to human exposure to soluble nickel in drinking water is complicated by the fact that this strain of mice is highly susceptible to lung tumors and it has been shown that the effect of nickel treatment could be completely abolished by the co-administration of either calcium acetate or magnesium acetate (Poirier et al., 1984).

Recently, two additional injection studies have been reported. Kasprzak and his coworkers showed that rats exposed to nickel acetate by intraperitoneal injection plus sodium barbital via drinking water developed tumors in the kidney (Kasprzak et al., 1990). They also showed that rats exposed to nickel acetate prenatally plus sodium barbital via drinking water developed tumors in the kidney, renal pelvis, and pituitary gland (Diwan et al., 1992).

Kasprzak et al. (1990) intraperitoneally injected a single dose of nickel acetate tetrahydrate at 5.3 mg Ni/kg_{bw} to 47 male F344/NCr rats (Groups 3 and 4). Forty-eight rats were used as controls and were injected with normal saline (Groups 1 and 2). Two weeks after the injection, approximately half of the exposed and control rats (Groups 2 and 4) were provided with drinking water containing 500 ppm of sodium barbital, a known renal tumor promoter. All animals were weighed weekly, and all survivors were killed at 101 weeks of age. Tumor incidence data of this study are shown in Table 15. Kasprzak et al. (1990) reported that renal cortical epithelial tumors (adenomas and carcinomas combined) were significantly increased in the rats exposed to both nickel and sodium barbital (Group 4), compared to the controls (Groups 1 and 2). In addition, four renal cortical carcinomas were found in Group 4; no carcinomas were found in any other groups. Based on these results, Kasprzak et al. (1990) suggested nickel acetate was an initiator of kidney tumors in rats.

Table 14. A summary of tumor induction by soluble nickel compounds via either intraperitoneal or intramuscular injections (modified from IARC, 1990).

Compound	Route	Species	Tumor incidence (dose)	Duration of study	Reference
Nickel acetate	Intraperitoneal (a total of 24 injections)	Mouse, Strain A	6/19 (untreated controls) 7/19 (vehicle controls) 8/18 lung tumors (24x0.59 mg Ni/kg_{bw}) 7/14 lung tumors (24x1.8 mg Ni/kg_{bw}) 12/19 lung tumors[a] (24x3.5 mg Ni/kg_{bw})	30 weeks	Stoner et al. (1976)
Nickel acetate	Intraperitoneal (a total of 24 injections)	Mouse, Strain A	1.5 lung tumors/mouse[a]* (24x2.3 mg Ni/kg_{bw}) 0.32 lung tumors/mouse (controls)	24/30 treated animals survived 30 weeks	Poirier et al. (1984)
Nickel acetate tetrahydrate	Intraperitoneal injections (25x1 mg Ni or 50x1 mg Ni)	Rat	1/33 and 0/34 in two control groups 3/35 abdominal tumors (25 mg Ni/rat or 25x5 mg Ni/kg_{bw}) 5/31 abdominal tumors[b] (50 mg Ni/rat or 50x5 mg Ni/kg_{bw})[c]	120 weeks	Pott et al. (1989, 1990)
Nickel chloride tetrahydrate	Intraperitoneal injections (50x1 mg Ni)	Rat	1/33 and 0/34 in two control groups 4/32 abdominal tumor* (50 mg Ni/rat or, 50x5 mg Ni/kg_{bw})[c]	120 weeks	Pott et al. (1989, 1990)
Nickel sulfate heptahydrate	Intraperitoneal injections (50x1 mg Ni)	Rat	1/33 and 0/34 in two control groups 6/30 abdominal tumors* (50 mg Ni/rat or 50x5 mg Ni/kg_{bw})[c]	120 weeks	Pott et al. (1989, 1990)
Nickel acetate	Three intramuscular implants	Rat	1/35 local tumor (7 mg Ni compound/rat or 3x3.5 mg Ni/kg_{bw})[c]	72 weeks	Payne (1964)
Nickel ammonium sulfate	Three intramuscular implants	Rat	0/35 local tumor (7 mg Ni compound /rat or 3x2.3 mg Ni/kg_{bw})[c]	72 weeks	Payne (1964)
Nickel chloride	Three intramuscular implants	Rat	0/35 local tumor (7 mg Ni compound /rat or 3x5.3 mg Ni/kg_{bw})[c]	72 weeks	Payne (1964)

Table 14 (continued). A summary of tumor induction by soluble nickel compounds via either intraperitoneal or intramuscular injections (modified from IARC, 1990).

Compound	Route	Species	Tumor incidence (dose)	Duration of study	Reference
Nickel sulfate	Three intramuscular implants	Rat	1/35 local tumor (7 mg Ni compound/rat or 3x4.7 mg Ni/kg_{bw})[c]	72 weeks	Payne (1964)
Nickel sulfate	Intramuscular	Rat	0/20 local tumor, dose unspecified	Not specified	Gilman (1966)
Nickel sulfate	15 intramuscular injections over one month	Rat	0/20 controls 0/20 local tumor (15x1.2 mg Ni/kg_{bw})[c]	104 weeks	Kasprzak et al. (1983)
Nickel sulfate hexahydrate	Single intramuscular injection	Rat	0/32 local tumor (19 mg Ni/kg_{bw})	13 rats survived 86 weeks	Gilman (1962)
Nickel sulfate	Fourteen intramuscular injections	Rat	0/10 local tumor (vehicle controls) 0/7 local tumor (14x3.7 mg Ni/kg_{bw}) 0/9 local tumor (14x4.9 mg Ni/kg_{bw})	104 weeks	Knight et al. (1991)

[a] Maximum tolerated dose.
[b] Statistically significant for trend, $p<0.05$.
* Statistically significant compared with controls, $p<0.05$.
[c] Young rats are assumed to have a body weight of 200 g.

Consistent with the notion that sodium barbital is a known renal tumor promoter, Kasprzak et al. (1990) found increased incidences of hyperplasia of tubular epithelium in rats given sodium barbital alone (Group 2) or sodium barbital following nickel treatment (Group 4). These lesion data were not included in Table 15. In contrast, lower incidences of hyperplasia were seen in rats exposed to nickel alone (Group 3) and none were found in the untreated rats (Group 1).

In the same study, Kasprzak et al. (1990) observed evidence showing that the combination of nickel injection and oral exposure to sodium barbital was toxic to the treated rats, especially to the kidneys. They noted that the mean body weight of Group 4 was significantly lower and the mean kidney weight was significantly higher than those of the untreated controls (Group 1). Mortality was significantly increased in Group 4 than in any other groups. By 85 weeks, approximately 40 percent of rats in this group were dead and only 8 percent were alive when the study was terminated at 101 weeks. Kasprzak et al. (1990) suggested that high mortality of Group 4 rats was related to severe nephrotoxicity and large, multiple kidney lesions.

This finding described above is consistent with the nickel toxicity study reported by Gitlitz et al. (1975). They showed that a single intraperitoneal injection of nickel chloride at doses between 2 and 5 mg Ni/kg_{bw} to female Fischer rats caused nephrotoxicity. They observed a positive correlation between the amount of proteins and amino acids excreted in the urine and the dose of nickel. At doses of 4 and 5 mg Ni/kg_{bw}, the injections caused significantly increased excretion of protein (three to five fold) and most of the alpha-amino acids (2 to 24 fold).

Table 15. Tumor incidence data on male rats injected intraperitoneally with nickel acetate (from Kasprzak et al., 1990).

Treatment	Tumor incidence
Single intraperitoneal injection (with or without 500 ppm sodium barbital in drinking water)	Renal cortical epithelial adenomas and carcinomas Group 1: 0/24 (vehicle controls + water); Group 2: 6/24 (vehicle controls + sodium barbital controls); Group 3: 1/23 (5.3 mg Ni/kg_{bw} + water); Group 4: 16/24[a] (5.3 mg Ni/kg_{bw} + sodium barbital). Renal pelvic papillomas and carcinoma Group 1: 0/24 (vehicle controls + water); Group 2: 13/24 [b] (vehicle controls + sodium barbital controls); Group 3: 0/23 (5.3 mg Ni/kg_{bw}+ water); Group 4: 8/24 [c] (5.3 mg Ni/kg_{bw}+ sodium barbital).

[a]Incidence of tumors statistically significant ($p<0.005$) compared with Group 1 or Group 2. Four renal carcinomas were observed in Group 4; all tumors observed in other groups were adenomas.

[b]One pelvic carcinoma was found in Group 2; no carcinomas were found in any other groups.

[c]Incidence of tumors statistically significant ($p<0.005$) compared with Group 1. All tumors in Group 4 were papillomas.

Diwan et al. (1992) reported that nickel acetate when injected intraperitoneally was a complete transplacental carcinogen in rats. They injected pregnant F344/NCr rats either once a day on day 17 (5.3 mg Ni/kg_{bw}; Group 1) or twice on days 16 and 18 of gestation (2.6 mg Ni/kg_{bw}); Group 2). Offspring of these rats were subdivided into groups 1A and 1B and 2A and 2B, respectively. Groups 1A and 2A received ordinary tap water while groups 1B and 2B received drinking water containing 500 ppm sodium barbital during weeks 4-85 of age. Renal cortical epithelial and renal pelvic transitional epithelial tumors were observed in male offspring exposed to both chemicals (Group 1B), but not in male offspring of any other groups (Table 16). No renal tumors were observed in female offspring. Diwan et al. (1992) also observed significantly increased pituitary tumor incidences in the male and female offspring given nickel acetate prenatally, without postnatal sodium barbital (Table 16). They also reported that pituitary tumors appeared much earlier in rats given nickel acetate prenatally, with or without postnatal sodium barbital, compared with the controls.

It is important to note that the nickel doses used by Diwan et al. (1992) were at or close to the dose that was lethal to rat fetuses. When Diwan et al. (1992) increased the total nickel dose administered to Group 3 pregnant rats to 10.6 mg Ni/kg (four intraperitoneal injections of nickel acetate at 2.6 mg Ni/kg_{bw} on days 12, 14, 16, and 18 of gestation), they found that all offspring died within 72 hours after birth. Therefore, all Group 3 rats were excluded from the study.

Signs of toxicity were also observed in other treated groups. The first eight rats found dead or in poor condition during the 60 weeks observation period were all in groups 1A, 2A, 1B, and 2B. In contrast, no deaths occurred in rats of groups 4A and 4B until week 71 and very few rats died before the end of the study in these two groups. While body weights were not significantly different between the treated and untreated female offspring, mean body weights were consistently lower in male rats exposed prenatally to nickel acetate (groups 1A, 1B, 2A, and 2B) than in control groups 4A and 4B.

Furthermore, the intraperitoneal injection method used in the study might have increased the nickel dose delivered to the rat fetuses. As shown in Table 6, intraperitoneal injection of soluble nickel to mice resulted in a much higher (approximately 6 fold) total body burden than that via oral intubation. The route of administration also affected the distribution of nickel in major organs. For mice exposed via oral intubation, the intestine (0.8 percent of the administered dose) had the highest nickel content; whereas for mice exposed through intraperitoneal injection, the carcass and the kidneys (3.2 percent and 1.8 percent of the administered dose, respectively) had the highest nickel content (Table 6).

Inhalation studies

In a series of two-year inhalation carcinogenicity studies, NTP (1996a, b, c) exposed mice and rats of both sexes to nickel oxide, nickel subsulfide, or nickel sulfate. NTP (1996a, b) reported that nickel oxide and nickel subsulfide were carcinogenic in male and female rats resulting in alveolar/bronchiolar adenomas and carcinomas, and benign and malignant pheochromocytomas of the adrenal medulla. The series of inhalation studies did not show that nickel oxide and nickel subsulfide were carcinogenic in mice of either sex. The study results also did not show nickel sulfate was carcinogenic in either rats or mice of both sexes (NTP, 1996c).

Table 16. Incidences of renal cortical epithelial, renal pelvis transitional epithelial, and pituitary tumors in male and female rat offspring after prenatal exposure to nickel acetate (from Diwan et al., 1992).

Intraperitoneal injections, either once at 0.09 mmol/kg_{bw} or twice at 0.045 mmol/kg_{bw} to pregnant rats (with or without 500 ppm sodium barbital in drinking water for the offspring)	<u>Renal cortical epithelial adenomas and carcinomas</u> Group 1A: 0/17 (male, 5.3 mg Ni/kg_{bw} + water); 0/16 (female, 5.3 mg Ni/kg_{bw} + water); Group 1B: 6/15 (male, 5.3 mg Ni/kg_{bw} + sodium barbital)*[a]; 0/15 (female, 5.3 mg Ni/kg_{bw} + sodium barbital); Group 2A: 0/15 (male, 2x2.6 mg Ni/kg_{bw} + water); 0/16 (female, 2x2.6 mg Ni/kg_{bw} + water); Group 2B: 5/15 (male, 2x2.6 mg Ni/kg_{bw} + sodium barbital); 0/15 (female, 2x2.6 mg Ni/kg_{bw} + sodium barbital); Group 4A: 0/15 (male, sodium acetate + water); 0/16 (female, sodium acetate + water); Group 4B: 1/15 (male, sodium acetate + sodium barbital); 0/14 (female, sodium acetate + sodium barbital). <u>Renal pelvis transitional epithelial papillomas and carcinomas</u> Group 1A: 0/17 (male, 5.3 mg Ni/kg_{bw} + water); 0/16 (female, 5.3 mg Ni/kg_{bw} + water); Group 1B: 8/15 (male, 5.3 mg Ni/kg_{bw} + sodium barbital)*[b]; 0/15 (female, 5.3 mg Ni/kg_{bw} + sodium barbital); Group 2A: 0/15 (male, 2x2.6 mg Ni/kg_{bw} + water); 0/16 (female, 2x2.6 mg Ni/kg_{bw} + water); Group 2B: 7/15 (male, 2x2.6 mg Ni/kg_{bw} + sodium barbital)*; 0/15 (female, 2x2.6 mg Ni/kg_{bw} + sodium barbital); Group 4A: 0/15 (male, sodium acetate + water); 0/16 (female, sodium acetate + water); Group 4B: 1/15 (male, sodium acetate + sodium barbital); 0/14 (female, sodium acetate + sodium barbital). <u>Pituitary adenomas and carcinomas</u> Group 1A: 9/17 (male, 5.3 mg Ni/kg_{bw} + water)**; 5/16 (female, 5.3 mg Ni/kg_{bw} + water)[c]; Group 1B: 6/15 (male, 5.3 mg Ni/kg_{bw} + sodium barbital); 5/15 (female, 5.3 mg Ni/kg_{bw} + sodium barbital); Group 2A: 6/15 (male, 2x2.6 mg Ni/kg_{bw} + water)**; 8/16 (female, 2x2.6 mg Ni/kg_{bw} + water); Group 2B: 7/15 (male, 2x2.6 mg Ni/kg_{bw} + sodium barbital); 6/15 (female, 2x2.6 mg Ni/kg_{bw} + sodium barbital); Group 4A: 1/15 (male, sodium acetate + water); 3/16 (female, sodium acetate + water); Group 4B: 2/15 (male, sodium acetate + sodium barbital); 4/14 (female, sodium acetate + sodium barbital).

[a]One carcinoma was observed in this group, all other renal cortex tumors in this study were adenomas.

[b]One carcinoma was observed in this group, all other renal pelvis tumors in this study were papillomas.

[c]Pituitary carcinomas, but not adenomas, were significantly increased; $p<0.05$.

*Statistically significantly different from Group 4B, male; $p<0.05$.

**Statistically significantly different from Group 4A, male; $p<0.05$.

A summary of the tumor incidence data and the exposure concentrations used in the rat inhalation studies is shown in Table 17. It is intriguing to note that inhalation exposure of rats to two relatively insoluble nickel compounds, nickel oxide and nickel subsulfide, induced a significant increase in the incidences of pheochromocytomas in adrenal medulla, an organ some distance from the lung. Yet, exposure of rats to a soluble nickel compound, nickel sulfate, did not significantly increase the incidence of pheochromocytomas. One possible explanation is that the highest concentration of nickel sulfate used was about 7-18 times lower than the highest concentrations of nickel subsulfide and nickel oxide used in the inhalation studies. However, even at the same nickel concentration, 0.11 mg Ni/m^3, the pheochromocytoma rate in male rats exposed to nickel subsulfide (30/53) was still significantly higher ($p<0.001$) than that in male rats exposed to nickel sulfate (12/55) (Table 17). Another possible contributing factor is that the background rate of pheochromocytomas in male rats is highly variable. The background rate of pheochromocytomas in the controls of the nickel oxide study (27/54) was almost twice as high as those observed in the controls of the other two studies (16/54 and 14/53).

Toxicological Effects in Humans

Acute Toxicity

A 2-year-old child died after accidentally ingesting an oral dose of approximately 570 mg/kg_{bw} nickel sulfate (Daldrup et al., 1983 as cited in ATSDR, 1997). Cardiac arrest occurred four hours after the ingestion, and the child died eight hours after the accident.

Webster et al. (1980 as cited in Norseth, 1984) reported nickel intoxication in a group of 23 dialyzed patients. The source of nickel was nickel plated stainless steel in a water heater tank. The concentration of nickel was approximately 250 g/L in the dialysate. This level was much higher than the levels found in the other five dialysis units (average of 3.6 g/L and a range of 2.5 – 4.5 g/L). The symptoms recorded in the patients were nausea, weakness, vomiting, headache and palpitations. Remission was rapid and spontaneous, generally from three to 13 hours after cessation of dialysis.

Sunderman (1983 as cited in Grandjean, 1984) has suggested a maximal permissible amount of 35 µg in intravenous fluids per day for a 70-kg adult individual. This limit was based on a finding that ten-fold higher doses cause cardiotoxicity in dogs.

Sunderman et al. (1988 as cited in ATSDR, 1997) reported an accident in which workers drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid. Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The symptoms included nausea, abdominal cramps, diarrhea, and vomiting. The dose to which the workers with symptoms were exposed was estimated to be 7.1 - 35.7 mg Ni/kg_{bw}. The investigators suggested that the observed effects were not likely to be caused by the intake of 20-200 mg boric acid as adverse effects of boric acid are generally observed only following ingestion of $\geq$4 g by adults.

Table 17. Carcinogenicity data of male and female rats exposed to nickel sulfate hexahydrate, nickel oxide, or nickel subsulfide via inhalation (from ATSDR, 1997).

	No. of animals with neoplasms/number of animals examined										
	Exposure to nickel sulfate hexahydrate (mg Ni/m^3)				Exposure to nickel subsulfide (mg Ni/m^3)			Exposure to nickel oxide (mg Ni/m^3)			
Effect	**0**	**0.03**	**0.06**	**0.11**	**0**	**0.11**	**0.73**	**0**	**0.5**	**1**	**2**
Male rats											
Alveolar/bronchiolar adenoma/carcinoma	2/54	0/53	1/53	3/53	0/53	6/53[a]	11/53[b]	1/54	1/53	6/53[c]	4/52[c]
Adrenal medulla benign or malignant pheochromocytoma	16/54	19/55	13/55	12/55	14/53	30/53[b]	42/53[b]	27/54	24/53	27/53	35/54
Female rats											
Alveolar/bronchiolar adenoma/carcinoma	0/52	0/53	0/53	1/54	2/53	6/53[c]	9/53[a]	1/53	1/53	6/53[c]	5/54[c]
Adrenal medulla benign or malignant pheochromocytoma	2/52	4/53	2/53	3/54	3/53	7/53	36/53[b]	4/53	7/53	6/53	18/54[b]

[a] $p \leq 0.05$
[b] $p \leq 0.01$
[c] $p \leq 0.05$ versus historical data (1.4 percent, 3/210 males; 1.4 percent, 4/208 females)

In a nickel kinetic study, Sunderman et al. (1989) reported that seven hours after ingesting nickel sulfate in drinking water at 50 µg Ni/kg_{bw}, a human subject developed left homonymous hemianopsia, which lasted 2 hours. This condition of blindness in the corresponding vision field of each eye (i.e., the left field is affected in the left eye) was believed to be related to the administration of nickel as it occurred shortly after the peak serum concentration of nickel. The nickel dosages for subsequent volunteers were reduced to 18 or 12 µg Ni/kg_{bw}, and no adverse symptoms or signs were noted in any of these subjects. Based on the effects observed in these acute exposures, a NOAEL of 18 µg Ni/kg_{bw} was identified. However, it is important to note that in this experiment all the nickel was administered as one bolus dose and the serum nickel levels achieved between 3-10 hours after administration were above 30 µg Ni/L (Sunderman et al., 1989).

Effect of some illnesses on serum concentration of nickel in humans

In a National Research Council (NRC, 1975) report on nickel, it was noted that serum concentration of nickel in humans could be affected by several common illnesses. D'Alonzo et al. (1963 as cited in NRC, 1975) found that nickel levels in serum were significantly increased in 19 of their 20 patients 24 hours after acute myocardial infarction. Several investigators (McNeely et al., 1971 as cited in IPCS, 1991; Sunderman et al., 1971 and 1972 as cited in NRC, 1975; Leach et al., 1985; Leach and Sunderman, 1987) reported that increased concentrations of serum nickel were usually observed during the period from 12 to 72 hr after onset of acute myocardial infarction, stroke, and burns. The frequent occurrence of hypernickelaemia after acute myocardial infarction has been confirmed by studies in Europe (Vollkopf et al., 1981; Howard, 1980; Nozdryukhina, 1978, all cited in IPCS, 1991) and in USA (Leach et al., 1985).

Developmental and Reproductive Toxicity

Chashschin et al. (1994 as cited in ATSDR, 1997) reported that an increase in spontaneous abortions was observed among 356 women (15.9 percent) who worked in a nickel hydrometallurgy refining plant in Russia, compared with controls (8.5 percent). The workers were exposed to primarily nickel sulfate at 0.08-0.20 mg Ni/m^3. In the same study, the researchers also noted that there was a statistically significant increase in structural malformations among babies born to the workers (16.9 percent) compared with those born to the controls (5.8 percent). They reported that relative risks were 2.9 for all kinds of defects, 6.1 for cardiovascular system defects, and 1.9 for musculoskeletal defects. Chashschin et al. (1994 as cited in ATSDR, 1997) noted that heavy manual activities and heat stress were potential confounders.

Immunotoxicity

Dermal exposure to nickel and nickel alloys has long been known to cause dermatitis in both nickel workers and the general population. A number of studies indicated that oral exposure of nickel could aggravate nickel dermatitis in people who are sensitive to nickel. Christensen and Möller (1975 as cited in U.S. EPA, 1986) found that oral administration of nickel (approximately 5 mg) in diet worsen hand eczema in nickel-allergic patients. In a clinical trial, Kaaber et al. (1978) reduced the nickel dose to 2.5 mg and observed flaring of hand dermatitis in 13 of the 28 patients with chronic nickel dermatitis. A similar finding was reported by Veien et al. (1983); they observed that 26 patients had flare-ups following oral challenge with nickel compounds

(2.5 mg nickel in a capsule). The conditions of some of the patients improved when they were placed on a low-metal allergen diet for four to six weeks (Kaaber et al., 1978; Veien et al., 1983).

Cronin et al. (1980) gave groups of five fasting female patients that had hand eczema a gelatine-lactose capsule containing nickel, together with 100 ml of water. Three doses were used, 2.5 mg, 1.25 mg, and 0.6 mg nickel as nickel sulfate. After administration of nickel, the fast was continued for a further hour, at which time the patient was given a cup of coffee; thereafter, normal meals were taken. Clinical response was observed over the next 24 hours and the results are presented in Table 18. Assuming a body weight of 70 kg and the lowest dose that aggravated nickel dermatitis was 0.6 mg, a LOAEL of 8.6 µg Ni/kg_{bw} was estimated.

Table 18. Flare-ups of hand eczema in nickel-sensitive patients and level of nickel taken orally (from Cronin et al., 1980).

Dose of nickel (mg)	Erythema	Worsening of hand eczema (number of patients)	Flare of patch test site
2.5	4/5	5/5	3/4 *
1.25	4/5	3/5	3/5
0.6	1/5	2/5	3/5

*One patient of the group of five was not examined.

Nielsen et al. (1999) studied the aggravation of nickel dermatitis in people by giving them an oral dose of soluble nickel. Twenty nickel-sensitized women and 20 age-matched controls, both groups having vesicular hand eczema of the pompholyx type, were given a single dose of nickel in drinking water (3 µg/ml or 12 µg Ni/kg_{bw}). All patients fasted overnight and fasting was maintained for another 4 hours after the nickel administration. Nielsen et al. (1999) reported that nine of 20 nickel allergic eczema patients experienced aggravation of hand eczema after nickel administration, and three also developed a maculopapular exanthema. No exacerbation was seen in the control group. From the results of this study, a LOAEL of 12 µg Ni/kg_{bw} was identified for the nickel-sensitized women.

A number of human studies have shown that oral administration of low levels of soluble nickel over a long period of time may reduce nickel contact dermatitis. Sjovall et al. (1987) orally administered 0, 5 or 0.5 mg nickel per day to a group of patients allergic to nickel. After six weeks, they found evidence of reduced sensitization in patients exposed to 5 mg/day but not to 0.5 mg/day. Santucci et al. (1988) gave a single oral dose of 2.2 mg Ni to 25 nickel-sensitized women and found that 22 reacted to the treatment. After a 15-day rest period, the subjects were given gradually increasing doses under the following schedule: 0.67 mg Ni/day for one month, 1.34 mg Ni/day for the second month, and 2.2 mg Ni/day for the third month. In the last phase of the testing, 3/17 of the subjects had flare-ups even at the lowest dose. The other 14 subjects, however, did not respond to the highest dose, even though they had responded to that dose in the initial testing.

Neurotoxicity

A group of 35 workers were exposed to soluble nickel compounds and boric acid during one work shift through a contaminated drinking water source. The dose received by the 20 workers who reported symptoms was estimated to be 7.1-35.7 mg Ni/kg_{bw}. The neurological effects included giddiness, weariness, and headache (Sunderman et al., 1988 as cited in ATSDR, 1997).

In a study designed to determine the absorption and elimination of nickel in humans, one male volunteer who ingested a single dose of 0.05 mg Ni/kg_{bw} as nickel sulfate in drinking water lost sight in the corresponding lateral half of the eyes 7 hours later. The loss of sight lasted approximately two hours.

Genetic Toxicity

IARC (1990), IPCS (1991), and NTP (1998) have reviewed the genotoxicity effects of nickel and nickel compounds in humans. Waksvik and Boysen (1982, 1984 as cited in IARC, 1990) studied groups of nickel refinery workers (9-11 workers in each group) and observed increases in chromosomal aberrations compared to controls. Deng et al. (1988) found elevated levels of both sister chromatid exchanges and chromosome aberrations (gaps, breaks, fragments) in seven electroplating workers exposed to nickel and chromium. Kiilumen et al. (1997 as cited in NTP, 1998) 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. The significance of these study results is somewhat limited due to the small sample sizes and the possibility that some workers were exposed to genotoxic compounds other than nickel.

Carcinogenicity

Epidemiological studies of the carcinogenic effects of nickel and nickel compounds have been recently reviewed by IARC (1990), ICNCM (1990), CARB (1991), IPCS (1991), NTP (1998), and ATSDTR (1997). There is a general consensus among these scientific or regulatory bodies that inhalation exposure to some nickel compounds is carcinogenic to humans.

Two recent epidemiological studies showed that inhalation exposure to mainly soluble nickel compounds was associated with elevated risk of nasal and lung cancers. Anttila et al. (1998 as cited in NTP, 1998) studied a cohort of 1,155 workers employed at a Finnish nickel refinery. They reported elevated risks of nasal cancer (SIR=41.1; CI=4.9-148) and lung cancer (latency of 20+ years, SIR=3.4) among refinery workers. Another European study (Andersen et al., 1996 as cited in NTP, 1998) followed a cohort of 4,764 Norwegian nickel refinery workers and 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).

In a review study conducted by Doll et al. (1990 as cited in NTP, 1996a) that includes human study results of 10 different mines or refineries throughout the world, exposure to mixture of nickel compounds was found to be associated with lung and nasal sinus cancers. Doll et al. (1990 as cited in NTP, 1996a) found no evidence that inhalation exposure to metallic nickel or any of its compounds was likely to produce cancers elsewhere other than in the lung or nose.

However, there are a number of published reports suggesting that occupational exposures to nickel were associated with cancers of the stomach, larynx, liver, and large intestine. Pang et al. (1996) reported that inhalation exposure to soluble nickel compounds was associated with increased stomach cancer. They studied a cohort of 284 nickel plating industry workers who were not exposed to chromium and found weak evidence linking nickel exposure and stomach cancer (observed 8, expected 2.5, SMR=322; 95 percent CI=139-634). Lung cancer risk was not increased but there were no smoking data of the workers. The investigators noted that study was limited by its modest size, by unusually short periods of exposure (mean 2.1 years, median 0.86 years), and by a lack of dose-response relationship. It is also important to note that stomach

cancer was not found to be associated with nickel exposure in other occupational studies with a much larger sample size and with workers exposed for a much longer period of time.

Redmond (1984) reported mortality patterns of 28,261 workers employed at 12 plants involved in the production of high nickel alloys during the late 1950s and 1960s and followed up to December 31, 1977. Overall, they did not find statistically significant increased risks for cancers of the lung, nasal sinuses, larynx or kidney. However, they found increased cancer risk of the liver (SMR = 182, $p < 0.01$) for all male workers and increased cancer risk of the large intestine (SMR = 223, p value not provided) for nonwhite males. These two cancer sites were not generally associated with nickel exposure and the authors cautioned that the elevated SMR could be attributable to exposures to substances other than nickel.

Shannon et al. (1984) studied the mortality data (1950-1976) of 11,500 nickel workers at Falconbridge, Ontario. Five cases of laryngeal cancer were observed when only 1.92 were expected (SMR = 261, $p < 0.05$). Pedersen et al. (1973 as cited in Doll, 1984) also found excess laryngeal cancer among the nickel refinery workers in Norway. They observed five cases of laryngeal cancer among the exposed when only 1.4 case was expected. However, no additional cases have been observed in the decade following the reported study (Doll, 1984).

There are two ecological studies showing that exposure to nickel in drinking water may be associated with some form of cancer. Isacson et al. (1985) studied data from the Iowa Cancer Registry and determined age-adjusted sex-specific cancer incidence rates for the years 1969-1981 for towns with a population of 1,000-10,000 and a public water supply from a single stable ground source. They found that the nickel level in drinking water was associated with increased incidence rates of bladder and lung cancers in men but not in women. Since the association held even at very low levels of nickel in drinking water ($\geq$0.5 µg/L) and only applied to men, Isacson et al. (1985) suggested that nickel was not a causal factor, but rather an indicator of possible anthropogenic contamination of other types.

Ling-Wei et al. (1988) reported that there was a highly positive correlation between trace element concentrations in drinking water and nasopharyngeal cancer morbidity among residents of the Xiangxi region of Hunan, China. They found the concentrations of nickel, zinc, cadmium, and lead in drinking water in high-incidence areas were significantly higher than those in low-incidence areas. The significance of the results is limited by the ecological nature of the study and the small sample size (15 subjects in each of the three exposed groups and 15 subjects in each of the two control groups).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Animal studies

The most sensitive noncarcinogenic end-point based on animal studies is the early mortality and growth retardation observed in offspring of rats exposed to nickel in drinking water. Schroeder and Mitchener (1971) administered 5 ppm nickel in drinking water to rats and observed increased perinatal mortality and increased number of "runts" in the offspring of the exposed groups (Table 8). The administered dose of 5 ppm nickel (430 µg Ni/kg_{bw}/day) can be considered as the LOAEL. Applying an uncertainty factor of 1,000 (a 10-fold for using a LOAEL instead of a NOAEL, a 10-fold to account for intra-species variability and another 10-fold to account for inter-species variability), a reference value of 0.43 µg Ni/kg_{bw}/day can be calculated for humans. This study was criticized by U.S. EPA (1998) for its small sample size, for the fact that matings

were not randomized and the males were not rotated, and for the possibility of interaction between nickel and other trace metals (e.g., chromium content in the diet was estimated to be inadequate).

A similar reproductive and developmental study was conducted and reported by Smith et al. (1993). They used a strain of rat similar to that used by Schroeder and Mitchener (1971) and exposed them to 0, 10, 50, or 250 ppm nickel in drinking water. The outcomes of the first breeding were different from those of the second breeding. The proportion of dead pups per litter was significantly elevated at the high dose in the first breeding and at 10 and 250 ppm in the second breeding (Tables 10 and 11). Smith et al. (1993) recommended a LOAEL of 10 ppm nickel (1.3 mg Ni/kg_{bw}/day). Applying an uncertainty factor of 1,000 (a 10-fold for using a LOAEL instead of a NOAEL, a 10-fold to account for intra-species variability and another 10-fold to account for inter-species variability), a reference value of 1.3 µg Ni/kg_{bw}/day can be estimated for humans.

Human studies

The most sensitive noncarcinogenic endpoint based on human studies is the aggravation of nickel dermatitis in people sensitized towards nickel. Cronin et al. (1980) and Nielsen et al. (1999) demonstrated that oral administration of nickel could aggravate hand eczema in people sensitized towards nickel. Nielsen et al. (1999) reported that nine of 20 nickel allergic eczema patients experienced aggravation of hand eczema after nickel administration (3 µg/ml or 12 µg Ni/kg_{bw}), and three also developed a maculopapular exanthema. No exacerbation was seen in the control group. Based on the data of this study, a NOAEL of 1.2 µg Ni/kg_{bw} is identified for nickel-sensitized patients. This result is obtained by applying an uncertainty factor of 10 to account for the uncertainty in extrapolating from LOAEL to NOAEL.

Cronin et al. (1980) gave groups of five fasting female patients that had hand eczema a gelatine-lactose capsule containing 0.6 mg, 1.25 mg, or 2.5 mg nickel as nickel sulfate and observed worsening of nickel dermatitis within 24 hours. Assuming a body weight of 70 kg and the lowest oral dose that aggravated nickel dermatitis is 0.6 mg, a LOAEL of 8.6 µg Ni/kg_{bw} is estimated. Applying an uncertainty factor of 10 to account for the uncertainty in extrapolating from LOAEL to NOAEL yields a NOAEL of 0.86 µg Ni/kg_{bw}. The small number of patients in the exposed groups limits the confidence of this estimate.

It is important to point out that an additional uncertainty factor of 10 to account for intra-species variability was not used in the derivations of the two reference values described in this section. This is because the aggravation of skin conditions reported by Cronin et al. (1980) and Nielsen et al. (1999) were found in individuals who were allergic to nickel. For the identified adverse health effect, these individuals are the sensitive sub-population. Furthermore, the subjects in the studies reported by Cronin et al. (1980) and Nielsen et al. (1999) were in fasting condition when they were administered with the nickel dose. As discussed in the section on absorption, gastrointestinal absorption of soluble nickel in fasting subjects can be 10 to 30 times higher than that observed when nickel was administered with food. For the general population, it is unlikely that all the exposures are under fasting condition, therefore, the two reference values derived from the Nielsen et al. (1999) and Cronin et al. (1980) studies should be considered upper-bound estimates (Table 19).

Based on the animal and human toxicity data discussed in this section, two reference values and two NOAELs are estimated and summarized in Table 19. For comparison purposes, the LOAEL and NOAEL used by U.S. EPA (1998) for the development of an oral reference dose for soluble salts of nickel are also included.

Table 19. Nickel toxicity - a summary of the NOAELs and reference values estimated.

Study	Dose regime/ species	LOAEL identified (µg Ni/kg_{bw}/day)	Uncertainty factor applied	Calculated reference value or NOAEL (µg Ni/kg_{bw}/day)
Nielsen et al. (1999)	Single oral dose/ humans	12	10	1.2
Cronin et al. (1980)	Single oral dose/ humans	8.6	10	0.86
Schroeder and Mitchener (1971)	Continuous dosing/rats	430	1,000	0.43
Smith et al. (1993)	Continuous dosing/rats	1,300	1,000	1.3
Ambrose et al. (1976)	Continuous dosing/rats	50,000/5,000 *	300	17

* A LOAEL of 50,000 µg Ni/kg_{bw} and a NOAEL of 5,000 µg Ni/kg_{bw} were used by U.S. EPA in a 1996 evaluation for the development of an oral reference dose for soluble salts of nickel (U.S. EPA, 1998). U.S. EPA is currently reviewing existing toxicological data for soluble nickel salts and has not made any final decision regarding the key study to be used in the risk assessment for soluble nickel salts.

After evaluating the data presented in Table 19, a LOAEL of 1,300 µg Ni/kg_{bw}/day derived from a reproductive and developmental study reported by Smith et al. (1993) was selected for the development of a PHG for nickel in drinking water. This study was chosen because of the high quality of the study, rats in the study were exposed through a relevant medium (drinking water), and the reference value derived from the study is within the range of values calculated for the other three studies (Table 19).

The study reported by Nielsen et al. (1999) was not chosen for the development of PHG because the human subjects were exposed to a single oral dose of nickel.

Carcinogenic Effects

In the overall evaluation, IARC (1990) determined that nickel compounds are Group 1 carcinogens. In a draft report to the Carcinogens Subcommittee of the NTP Board of Scientific Counselors, NTP (1998) made the recommendation of upgrading nickel compounds to a known human carcinogen. They suggested 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. There are human and animal data that support as well as refute the identification of soluble nickel as an oral carcinogen. The data that support such an identification are summarized below:

1. It has been demonstrated that soluble nickel compounds were mutagenic and clastogenic in mammalian cells in vitro (Table 13). Evidence points to ionic nickel as the ultimate toxic agent of nickel compounds, water soluble as well as water insoluble. There is information indicating that cellular uptake and intracellular transport of soluble nickel are different from those of insoluble nickel. These differences may explain the variation in genotoxic potency among the soluble and insoluble nickel compounds (NTP, 1998).
2. It has been demonstrated that soluble nickel compounds were also genotoxic in vivo, producing DNA damage, chromosomal aberrations, and increased micronuclei frequency (Table 13).
3. It has been shown in many epidemiological studies that inhalation exposure to soluble and insoluble nickel compounds was associated with increased incidence of nasal and lung cancers (IARC, 1990).
4. There are limited data suggesting occupational exposure to nickel compounds was associated with other cancers such as stomach cancer, pharyngeal cancer, liver cancer, and cancer of the large intestine (Pang et al., 1996; Redmond, 1984; Shannon et al., 1984). However, workers in these studies might have been exposed to other chemicals besides nickel.
5. There is limited evidence suggesting occupational exposure to nickel compounds was associated with increased chromosomal aberrations. This shows that soluble nickel compounds may be clastogenic in humans (Deng et al., 1988; Waksvik and Boysen, 1982 and 1984 as cited in IARC, 1990).
6. In two inhalation bioassays (NTP, 1996a and b), male and female rats exposed to nickel subsulfide or nickel oxide showed significantly higher incidence of pheochromocytomas of the adrenal medulla than the controls. These data indicate that some forms of nickel (e.g., free nickel ion or chelated nickel ion) were able to reach and induce cancer in a distal target organ.
7. Soluble nickel has been shown to be a complete transplacental carcinogen in rats. Increased pituitary tumors were observed in rats given nickel acetate prenatally (Diwan et al., 1992). However, the dose used in this experiment was very high; when the dose was doubled in the same study, all prenatally exposed rats died within 72 hours after birth. Furthermore, injection method used in the study might have affected the distribution of nickel among body organs.
8. It has been shown that soluble nickel is a cancer initiator in rats. Kasprzak et al. (1990) reported that a combined injection of soluble nickel and oral exposure to sodium barbital significantly increased renal cortical epithelial tumors in male rats. Diwan et al. (1992) reported increased incidences of renal cortical epithelial and renal pelvis transitional epithelial tumors in male rats exposed to nickel acetate prenatally and sodium barbital in drinking water. Near toxic doses were used in both of these two studies.
9. In three separate studies, Pott et al. (1989, 1990) demonstrated that repeated intraperitoneal injection of soluble nickel compounds caused local tumors in rats.

There are human and animal data that either do not support soluble nickel is an oral carcinogen or indicate that if soluble nickel were an oral carcinogen, its cancer potency is relatively low:

1. Only tumors at the site of contact, nasal sinus and lung, have been consistently shown to be associated with occupational exposure to nickel and nickel compounds despite the fact that the serum nickel levels measured in the exposed workers were significantly higher than those measured in the non-exposed subjects (Table 20). ICNCM (1990) reviewed the study results of 10 different mines or refineries throughout the world, and found no evidence that inhalation exposure to metallic nickel or any of its compounds was likely to produce cancers elsewhere other than in the lung or nose. However, at least one occupational study has associated systemic cancers (liver and large intestine) with working in facilities involved in the production of high nickel alloys (Redmond, 1984), but these findings were not confirmed in other epidemiological studies.

Table 20. Nickel concentrations in specimens from non-exposed and exposed adults.

Population Exposed and non-exposed	Specimen	Number of subjects	Nickel levels, mean (µg/L)	Nickel levels, range (µg/L)	References
Non-exposed	Serum	20	NA	0.06-0.55	Nielsen et al., 1999
	Serum	38	0.14±0.09		Nixon et al., 1989
	Serum	10	0.32±0.17	0.1-0.6	Sunderman et al., 1989
	Serum	43	0.2±0.2	<0.05-1.0	Hopfer et al., 1989 as cited in IPCS, 1991
	Whole blood Serum	30 30	0.34±0.28 0.28±0.24	<0.05-1.05 <0.05-1.08	Linden et al., 1985 as cited in IPCS, 1991
	Serum	71	NA	0.6-3.0	Drazniowsky et al., 1985
Exposed workers	Serum Serum Serum	37 25 6	8.9±5.9 7.2±4.8 9.0±3.7		Morgan and Rouge, 1984
	Plasma Plasma Plasma	97 144 77	5.2±2.7 8.1±6.0 4.3±2.2		Torjussen and Andersen, 1979 as cited in IPCS, 1991
	Plasma Plasma Plasma	24 90 13	7.2±2.8 11.9±8.0 6.4±1.9		Hogetveit et al., 1978 as cited in IPCS, 1991

NA = information not available.

There are monitoring data suggesting that the impact of nickel in drinking water to the overall body burden of nickel is relatively small. Hopfer et al. (1989) reported that nickel content of tap water in Sudbury, Ontario (average 109±46 µg/L, range 65 to 179 µg/L), a city with extensive nickel mines and smelters, was significantly higher than that in Hartford, Connecticut (average 0.4±0.2 µg/L, range 0.2 to 0.6 µg/L). However, the serum nickel levels in 22 healthy hospital workers (average 0.6±0.3 µg/L, range 0.2 to 1.3 µg/L) in Sudbury were only slightly higher than those measured in 43 healthy hospital workers (average 0.2±0.2 µg/L, range <0.05 to 1.0 µg/L) in Hartford. The data set is limited by the small number of water samples (5) taken from each study area. It should also be noted that residents of Sudbury, Ontario were probably also exposed to higher levels of nickel in air, besides being exposed to higher levels of nickel in water.

2. All four oral cancer bioassays reported in the literature failed to show that soluble nickel is an oral carcinogen (Schroeder et al., 1964 and 1974; Schroeder and Mitchener, 1975; Ambrose et al., 1976). Relatively low concentration of soluble nickel in drinking water (5 ppm nickel) was used in the rats and mice studies reported by Schroeder and his co-workers. However, doses close to or exceeding the maximally tolerated dose were used in the dietary study reported by Ambrose et al. (1976).

3. When soluble nickel compounds were repeatedly injected intramuscularly to rodents, no significant increase of tumor at any site was observed. When soluble nickel compounds were repeatedly injected into the peritonea of rats, they induced local tumors (Pott et al., 1989, 1990). IARC (1990) attributed the latter findings to the repeated exposure of peritoneal target cells to high concentrations of nickel ion. Similar situation did not occur when the nickel was repeatedly injected intramuscularly as different muscle cells were likely to come into contact with high concentrations of nickel ion at each injection.

4. Numerous injection and implantation studies of nickel subsulfide and nickel sulfide at various organ sites demonstrated that these chemicals did not induce tumors in tissues away from the site of contact in rodents (NTP, 1996c). Yet when these compounds were injected or implanted in skin, muscle, kidney, lung, and testis, they induced local tumors in all these different organs/tissues (NTP, 1996c), showing that none of these tissues are non-responsive to the carcinogenic effect of nickel. One plausible explanation is that these studies did not have the statistical power to detect low cancer incidences. Another plausible explanation is that nickel carcinogenesis requires certain conditions (such as high concentration and long contact time) and these conditions were not met in organs away from the site of contact. There are three exceptions. NTP (1996a and b) showed that inhalation exposure to nickel oxide or nickel subsulfide induced benign or malignant pheochromocytomas of the adrenal medulla in rats. Diwan et al. (1992) demonstrated that injection of high doses of nickel acetate to pregnant rats induced pituitary gland tumors in the offspring.

5. In the same series of inhalation studies where nickel oxide and nickel subsulfide were shown to induce pheochromocytomas in rats, a much more water-soluble compound, nickel sulfate hexahydrate, did not induce any tumor in the tested animals (NTP, 1996c). At the same nickel concentration, 0.11 mg Ni/m^3, the pheochromocytoma rate in male rats exposed to nickel subsulfide (30/53) was significantly higher ($p<0.001$) than that in male rats exposed to nickel sulfate (12/55).

6. In several in vitro studies, it has been shown that the presence of L-histidine and albumin at physiological concentrations inhibited the cellular uptake of nickel ion by 70-90 percent (Nieboer et al., 1984; Abbracchio et al., 1982). The chelation of nickel ion by organic ligands has been shown to reduce the cellular uptake of nickel and contribute to the rapid excretion of nickel. This phenomenon may lower the potential carcinogenicity of soluble nickel absorbed through the gastrointestinal tract.

In order to estimate the potential cancer risk associated with oral exposure to soluble nickel, two screening evaluations were performed.

(1) Three hypothetical nickel doses resulting from the consumption of drinking water ranged between 1 and 100 µg/L (ppb) were compared with the highest dose used in the oral rat cancer bioassay reported by Ambrose et al. (1976)(Table 21). As shown in the table, the hypothetical absorbed nickel doses that resulted from the consumption of drinking water at 1 or 10 µg/L were approximately 4 to 5 orders of magnitude lower than the highest dose used in the cancer bioassay. Since no significant increase of cancer rates was observed in the rat cancer bioassay, cancer risk associated with the consumption of water with soluble nickel in the 1 to 10 µg/L (ppb) range is believed to be small.

(2) A similar comparison was made between the nickel doses received by rats in a series of inhalation studies reported by NTP (1996a, b, c) and a hypothetical nickel dose resulted from the consumption of drinking water. In this series of studies, the lowest dose at which an increased incidence of pheochromocytoma was observed occurred in rats exposed to 0.11 mg Ni/m^3 of nickel subsulfide. Assuming an inhalation rate of 0.3 m^3/day, a body weight of 350 g, and that half of the inhaled particles was eventually absorbed, an absorbed dose of 47 µg Ni/kg_{bw}-day was estimated. Applying a body weight adjustment factor of 0.26, the human equivalent dose was calculated to be 12 µg Ni/kg_{bw}-day. This value is about 4,000 fold higher than the absorbed nickel dose (0.003 µg Ni/kg_{bw}-day) which resulted from the consumption of drinking water at 1 µg/L (ppb).

Due to the lack of a suitable cancer bioassay for quantitative dose-response evaluation, a detailed cancer risk analysis was not performed. Considering the overall evaluation of IARC (1990) and the recommendation of NTP (1998) which both determined that nickel compounds as a group are known human carcinogens, an uncertainty factor of 10 to account for the potential carcinogenicity of nickel is used in the derivation of the PHG.

Table 21. Comparison of three hypothetical nickel doses resulting from the consumption of drinking water with the highest dose used in the negative oral cancer bioassay reported by Ambrose et al. (1976).

Hypothetical concentration of soluble nickel in drinking water (µg Ni/L)	Hypothetical absorbed nickel dose resulted from the consumption of drinking water at 2L/day (µg Ni/kg_{bw}-day) *	Estimated nickel dose absorbed by the highest dosed rats in the oral cancer bioassay reported by Ambrose et al. (1976) (µg Ni/kg_{bw}-day) **	Estimated human equivalent dose absorbed by the rats (µg Ni/kg_{bw}-day) †	Ratio of human equivalent dose absorbed by the rats and the hypothetical absorbed nickel dose that resulted from the consumption of drinking water
1	0.003	1,250	325	110,000
10	0.03	1,250	325	11,000
100	0.3	1,250	325	1,100

*Assuming 10 percent of the soluble nickel in drinking water was absorbed through the gastrointestinal tract and an adult body weight of 70 kg.

**Assuming 1 percent of the soluble nickel in diet was absorbed through the gastrointestinal tract.

†A body weight scaling factor of 0.26 was used to convert the animal dose to the human equivalent dose.

CALCULATING OF PHG

Calculation of concentrations of chemical contaminants in drinking water associated with negligible risks as carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses which may result in dermal and inhalation exposures.

Noncarcinogenic Effects

Based on an animal study reported by Smith et al. (1993), a LOAEL of 1,300 µg Ni/kg_{bw}/day was selected for the calculation of a PHG for noncarcinogenic effects. Calculation of a public health-protective concentration (C, in µg/L) for nickel in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{LOAEL \times BW \times RSC}{UF \times L_{eqs}/day}$$

$$= \frac{1{,}300\ \mu g\ Ni/kg_{bw}/day \times 70\ kg \times 0.2}{10{,}000 \times 2\ L/day}$$

$$= 0.9\ \mu g\ Ni/L \text{ or (rounded to } 1\ \mu g\ Ni/L \text{ or } 1\ ppb)$$

Where:

LOAEL	=	Lowest-observed-adverse-effect-level, 1,300 µg Ni/kg_{bw}/day;
BW	=	Adult body weight, a default of 70 kg for adults;
RSC	=	Relative source contribution (a default of 20 percent to 80 percent), 20 percent is used as food is an important source of nickel;
UF	=	An overall uncertainty factor of 10,000 is used. A factor of 10 to convert LOAEL to NOAEL, a factor of 10 to account for the uncertainty in inter-species extrapolation, a factor of 10 for intra-species variability, and a factor of 10 to account for the potential carcinogenicity of soluble nickel; and
L_{eqs}/day	=	Adult daily water consumption rate, 2 L/day.

For PHGs, the use of the RSC has, with a few exceptions, followed U.S. EPA drinking water risk assessment methodology. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For noncarcinogens, reference doses (RfDs, in mg/kg_{bw}/day), drinking water equivalent levels (DWELs, in mg/L) and MCLGs (in mg/L) are calculated using body weights, water consumption rates (L/day), and RSC. The range of RSC can vary from 20 percent to 80 percent (0.2 to 0.8) depending on scientific evidence.

Thus the health protective concentration for soluble nickel in drinking water based on noncarcinogenic effects would be 1 µg/L, 1 ppb.

RISK CHARACTERIZATION

Nickel is a natural occurring element and is ubiquitous in the environment; it has been detected in surface water, groundwater, air, soil, and food. Nickel compounds can be divided into two broad categories, those that are soluble in water and those that are not soluble in water. The hazard evaluation described in this document is mostly related to the ingestion of soluble nickel in drinking water.

The acute toxic effects of soluble nickel compounds, observed in experimental animals and humans, are relatively well studied. A 2-year-old child died after accidentally ingesting an oral dose of approximately 216 mg Ni/kg_{bw} as nickel sulfate. In another accident, 35 workers drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid. The symptoms reported by the workers included nausea, abdominal cramps, diarrhea, and vomiting. The dose to which the workers with symptoms were exposed was estimated to be 7.1- 35.7 mg Ni/kg_{bw} (Sunderman et al., 1988 as cited in ATSDR, 1997).

A relatively common adverse health effect of exposure to nickel either by skin contact or through oral ingestion is allergic skin reactions. It has been estimated that between 1 and 2 percent of males and between 8 and 11 percent of females showed a positive skin reaction to patch testing with nickel sulfate (Sunderman et al., 1984).

Single or repeated oral administration of soluble nickel compounds to experimental animals produced adverse effects mainly on the kidney, lung, and the immune and endocrine systems. The single oral LD_{50}s for two soluble nickel compounds, nickel sulfate and nickel acetate, ranged from 39 to 141 mg Ni/kg_{bw} in rats and mice. Chronic oral administration of soluble nickel compounds has been shown to produce adverse reproductive and developmental effects in rats (Smith et al., 1993; Schroeder and Mitchener, 1971; RTI, 1987 as cited in U.S. EPA, 1998).

The carcinogenicity of nickel and nickel compounds has been evaluated by several scientific and regulatory bodies. In the overall evaluation, IARC (1990) identified nickel compounds as Group 1 carcinogens. IARC (1990) found there is sufficient evidence in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry. IARC (1990) found there is inadequate evidence in humans for the carcinogenicity of metallic nickel and nickel alloys. There is sufficient evidence in experimental animals for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides and crystalline nickel sulfides. IARC (1990) also found there is limited evidence in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides and nickel telluride.

In a draft cancer identification document on nickel compounds, NTP (1998) recommended upgrading nickel compounds to a known human carcinogen. It was suggested 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.

U.S. EPA has not evaluated soluble nickel compounds for potential human carcinogenicity (U.S. EPA, 1998). CARB (1991) determined that the evidence for carcinogenicity in humans from inhaled nickel is strong. U.S. Food and Drug Administration considered low levels of elemental nickel in food as “generally recognized as safe” or GRAS (21CFR184.1537), and proposed a nickel level of 0.1 mg/L (100 ppb) for bottled water (ATSDR, 1997).

Many studies have shown that soluble nickel compounds were genotoxic and clastogenic in vitro as well as in vivo. From epidemiological studies, it has been shown that inhalation exposure to nickel compounds was associated with increased incidences of nasal and lung cancers

(IARC, 1990; IPCS, 1991). In two inhalation bioassays (NTP, 1996a and b), male and female rats exposed to nickel subsulfide and nickel oxide had significantly higher incidence of pheochromocytomas of the adrenal medulla, indicating some forms of nickel were able to reach and induce cancer in a distal target organ. Intraperitoneal injection of a soluble nickel compound at half the lethal dose to pregnant rats has been shown to cause pituitary gland tumors in offspring (Diwan et al., 1992). Pott et al. (1989, 1990) demonstrated that intraperitoneal injection soluble nickel compounds at high doses induced local tumors in rats.

If soluble nickel absorbed through the oral route were carcinogenic, its potency is likely to be lower than that estimated from occupational exposures. Epidemiological data showed that inhalation exposure to nickel compounds caused tumors at the site of contact, mostly nasal and lung tumors. Some studies have suggested the association of other systemic tumors (such as liver and large intestine) with occupational exposure to nickel but these findings were not confirmed in other epidemiological studies.

All four oral cancer bioassays reported in the literature failed to show that soluble nickel is an oral carcinogen. The nickel doses used in one of the studies (Ambrose et al., 1976) were close to or exceeded the maximally tolerated dose.

Several researchers (Nieboer et al., 1984; Abbracchio et al., 1982) found that certain amino acids, peptides, and proteins are excellent chelators of nickel ion and even at physiological concentrations can significantly inhibit cellular uptake of nickel ion. This phenomenon may reduce the carcinogenic potential of soluble nickel absorbed through the gastrointestinal tract. Animal data showed that nickel is an essential nutrient in many mammalian species, including cow, goat, pig, rat, and sheep (IPCS, 1991). Nickel is essential for the proper growth and wellbeing of rats; however, at high doses soluble nickel also induced tumors in the animal.

A PHG of 0.001 mg/L (1 µg/L or 1 ppb) is proposed for soluble nickel in drinking water. The PHG is based on a rat study by Smith et al. (1993) who reported increased frequency of perinatal death in offspring of rats exposed to nickel chloride in drinking water at 10 ppm (1.3 mg Ni/kg_{bw}). An uncertainty factor of 1,000 was used to convert the animal LOAEL to a human reference level of 1.3 µg Ni/kg_{bw}. It includes a factor of 10 for converting LOAEL to NOAEL, a factor of 10 for inter-species extrapolation, and a factor of 10 for intra-species variability. The PHG was calculated by assuming a relative source contribution of 20 percent, a water consumption rate of 2 L/day, and an adult body weight of 70 kg. In several laboratory and animal studies, nickel compounds have been shown to be genotoxic as well as carcinogenic. For this reason, an additional uncertainty factor of 10 was used in this evaluation to account for the potential carcinogenicity of soluble nickel.

The proposed PHG is also believed to be protective of persons who are allergic to nickel. In two human studies, Cronin et al. (1980) and Nielsen et al. (1999) demonstrated that oral administration of nickel could aggravate hand eczema in people sensitized towards nickel. The human NOAELs derived from these studies ranged from 0.86 to 1.2 µg Ni/kg_{bw}; the values are considerably higher than the estimated nickel dose associated with the consumption of soluble nickel in drinking water at the proposed PHG level.

OTHER REGULATORY STANDARDS

U.S. EPA promulgated a MCLG of 0.1 mg/L and a MCL of 0.1 mg/L (100 ppb) for nickel (U.S. EPA, 1999). However, the MCL and MCLG for nickel were remanded on February 9, 1995. This means that while U.S. EPA is reconsidering the limit on nickel, there is currently no U.S. EPA limit on the amount of nickel in drinking water (U.S. EPA, 1999).

The remanded MCLG was based on a chronic rat feeding study by Ambrose (1976). A NOAEL of 5 mg Ni/kg_{bw} was obtained from the study based on decreased body weight, increased relative heart weight, and decreased relative liver weight in female rats. The MCLG of 0.1 mg/L was calculated assuming 70-kg body weight, 20 percent relative source contribution, an uncertainty factor of 100, and a water consumption rate of 2 L/day. An additional "modifying factor" of three was incorporated to account for uncertainty regarding the possible reproductive effects of nickel.

The California Department of Health Services adopted a primary MCL for nickel of 0.1 mg/L [California Code of Regulations (CCR) Title 22 for inorganic chemicals Section 64431]. U.S. Food and Drug Administration proposed a nickel level of 0.1 mg/L for bottled water (ATSDR, 1997).

Arizona, Kansas, Maine, Minnesota, New Hampshire, Rhode Island, and Vermont promulgated a drinking water quality standard of 150 µg/L for nickel (ATSDR, 1997). Various drinking water supply standards of nickel have been developed by different states (Table 20).

Table 22. Drinking water supply standards of nickel developed by different states (from ATSDR, 1997).

State	Drinking water supply standards (µg/L)
Arizona	140
Indiana	13.4
Kentucky	13.4
Mississippi	607
West Virginia	510
Wisconsin	100 *

* Public health groundwater quality standards (Wisconsin Department of Natural Resources, 1999)

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