scientific basis for an air quality standard for nickel

Prepared for CONCAWE by

R. J. Lewis
D. J. Caldwell
Exxon Biomedical Sciences, Inc.

Reviewed by

D. King
W. Tordoir
B. J. Simpson (Technical Coordinator)

Brussels
April 1999

CONTENTS

ABSTRACT/SUMMARY

The health effects due to nickel exposure are reviewed in this document for the purposes of understanding the scientific basis for an Air Quality Standard (AQS). The report provides an overview of two approaches for deriving a nickel AQS by presenting both a threshold/safety factor and a linear non-threshold approach. Using a threshold/safety factor approach with a lowest observed-adverse-effect-level (LOAEL) of 1000 µg Ni/m^3 for soluble nickel compounds based on the occupational epidemiology data, exposure limits of 0.6 µg Ni/m^3 for soluble nickel compounds and 6 µg Ni/m^3 for less soluble compounds (e.g., oxidic and sulfidic compounds), as an annual average, are justified on scientific grounds. Use of a single value of 0.6 µg Ni/m^3 (annual average) is recommended since it would be protective for both soluble and less soluble nickel compounds. By contrast, exposure limits derived using the animal and human data and a linear non-threshold approach are approximately an order of magnitude lower and range from 0.01-0.03 µg Ni/m^3 (annual average) for both soluble and insoluble compounds.

In general, nickel compounds are not acutely toxic. However, nickel is a proven sensitizer; therefore nickel compounds should be regarded as potential sensitizers. The primary hazard associated with exposure to certain nickel compounds is the ability to adversely affect the respiratory system and to produce respiratory cancers. This effect is consistent between animals and humans. Oral exposures do not appear to result in the biological activities exhibited by the inhalation route. Because inhalation is the most pertinent exposure route for an AQS and inhalation is the most toxic route for nickel compounds, inhalation-related health effects (excluding nickel carbonyl) and the bioavailability of the relevant forms of these compounds to relevant target tissues are considered most appropriate. In particular, the critical effect associated with nickel exposure, for the purposes of setting an ambient air standard, is respiratory cancer.

The choice of human versus animal datasets for deriving a nickel AQS does not strongly influence the final recommended value. However, the choice of extrapolation method (i.e., a threshold/safety factor versus linear non-threshold approach) has an impact on the recommended AQS value. A common weakness of both approaches is that the characteristics of nickel exposures in animal and human studies are qualitatively different from exposures present in ambient air. Specifically, the strongest respiratory cancer associations identified in the human and animal studies are with sulfidic and oxidic nickel; sulfidic nickel is not likely to be detected in ambient air while nickel oxide may be present up to a maximum of 8%.

Overall, the weight of the evidence strongly supports the use of a threshold/safety factor approach for deriving a scientifically justified and defensible AQS for nickel. Factors that support the use of the threshold/safety factor approach include the following:

- the existence of a NOAEL for pulmonary inflammation of 130 µg Ni/m^3 (nickel dust) derived from inhalation studies,
- the lack of carcinogenic response in the absence of pulmonary inflammation,
- the presence of good evidence for an empirical threshold for lung and nasal cancer in epidemiology studies of occupationally exposed groups,

- the presence of a NOAEL for pulmonary carcinogenesis of approximately 100 μg Ni/m^3 observed in recent rodent studies conducted with three nickel compounds administered by inhalation, the relevant route of exposure,

- no evidence of genotoxicity in *in vivo* studies conducted by the inhalation route of exposure in humans and rodents.

Although the finding of genotoxicity from *in vitro* studies of nickel compounds may support the use of a default linear non-threshold approach, the combined weight of the evidence suggests that this would likely produce an unduly conservative AQS value. Accordingly, a value of 0.6 μg Ni/m^3 (annual basis) is recommended as an AQS for nickel to protect the general public against carcinogenic and other potential hazardous effects associated with exposure to both soluble and less soluble nickel compounds. This value is derived from the threshold/safety factor approach.

1. INTRODUCTION/PURPOSE

The purpose of this document is to review the relevant health information so as to understand the scientific basis for an Air Quality Standard (AQS) for nickel. The document develops a recommended AQS for nickel that is based on the published literature and scientific judgement. This document is not an exhaustive review of the scientific literature on nickel compounds. Rather, it is a focused review on the data most relevant to setting a scientifically based AQS for nickel to protect human health.

The document begins with a brief overview of the different types of nickel compounds in the environment. This is followed by a brief discussion of the ambient air guidelines for nickel recommended by other organizations and the methods for developing these guidelines. In addition, mechanisms of action are briefly reviewed due to their unique and complex nature for metals such as nickel. Next, health effects associated with nickel are summarized, along with the lowest level of nickel exposure associated with each of the health effects (i.e., the lowest observed adverse effect level [LOAEL] and/or no observed adverse effect level [NOAEL]). The health endpoint upon which a nickel AQS should be based is also described, along with the scientific rationale for selecting a threshold versus non-threshold approach for developing the AQS. Finally, an AQS for nickel is recommended, and critical data gaps and recommendations to improve the basis for future nickel AQS are discussed.

Unless otherwise indicated, all concentrations refer to nickel only.

2. USE, SOURCE, AND CHARACTERISTICS OF NICKEL-BASED COMPOUNDS

Nickel is a silvery metal with a specific gravity of 8.9, a melting point of 1455°C, and a boiling point of approximately 2900°C (NAS, 1975). This metal is widely used in ferroalloys, stainless steels, and metal plating. Also, nickel compounds are used in pigments, coinage, nickel-cadmium batteries, and as catalysts (IARC, 1990).

Nickel emissions to the atmosphere from natural sources such as windblown dust, volcanoes, and vegetation are estimated to be 8.5 kg x 10^6 each year, whereas anthropogenic sources total approximately 40-50 kg x 10^6 a year. Of these emissions, 62% are ascribed to the burning of residual and fuel oil, followed by nickel metal refining, municipal incineration, steel production, other nickel alloy production, and coal combustion (ATSDR, 1997).

There are a variety of species of nickel present in the environment. These can be broadly categorized as metallic nickel, oxidic nickel (including nickel oxides, hydroxides, and carbonates, as well as complex nickel oxides), sulphidic nickel (including nickel sulphides and subsulphides), and soluble nickel compounds (including nickel sulfate, nickel chloride, and nickel nitrate) (NiPERA, 1996). The most common forms of nickel in ambient air are nickel sulfate, nickel oxide, and complex nickel-ferric oxide. Approximately 50% of the total nickel in ambient air is soluble nickel, up to 8% is nickel oxide, and the remaining nickel is in the form of complex oxides. Metallic nickel and nickel subsulfide may also be present in ambient air, but at extremely small concentrations (CEPN, 1996).

Table 1 presents the average ambient concentration of nickel reported for some European countries, the United States, and Canada. In urban areas, the average nickel concentration in Europe is 0.0115 µg/m^3. This level is similar to levels reported in the United States which range from an average of 0.017 µg/m^3 in the summer to 0.025 µg/m^3 in the fall and winter. Urban air levels in Ontario, Canada, are approximately an order of magnitude lower compared with the U.S. and Europe.

Table 1: AVERAGE AMBIENT NICKEL CONCENTRATIONS

LOCATION	NICKEL CONCENTRATION (µg/m^3)		
	Industrial	Urban	Rural/Remote
European Countries[1]	0.007	0.0115	0.0007 - 0.0025
United States		0.017 summer[2] 0.025 fall/winter	0.008[3]
Canadian	0.259[4]	0.002[5]	0.006[6]

[1] CEPN, 1996
[2] NAS, 1975
[3] Average national annual concentration, USEPA, 1986b
[4] Arithmetic annual mean concentration (1992). The highest concentration measured was 6.1 µg/m^3, as a 24-hour average, in 1988. All measurements were taken near a large nickel-producing facility, OMOEE, 1996
[5] Typical value, Hamilton, Ontario, OMOEE, 1996
[6] Typical value, Province of Ontario, OMOEE, 1996

In addition to ambient air, the general population is exposed to nickel in the diet, drinking water, and cigarette smoke. Dermal exposure through contact with a variety of nickel-containing articles is believed to be minimal (Grandjean, 1984). The estimated average daily intake of nickel ranges from 0.2 μg for inhalation and 300 μg for ingestion (**Table 2**).

Table 2: ESTIMATED DAILY INTAKE OF NICKEL BY AN ADULT[a]

MEDIA	AVERAGE AMBIENT CONCENTRATION	AVERAGE DAILY INTAKE (μg)	FRACTION ABSORBED	ESTIMATED DAILY ABSORBED INTAKE (μg)
Air	0.01 μg/m^3	0.2[b]	0.2-1.0	0.04-0.2
Food	0.5 μg/g	300	0.01-0.1	3-30
Water	5 μg/l	10[c]	0.25	2.5
TOTAL				**5.5-33**

[a] Occupational exposure not included
[b] Daily inhalation rate of 20 m^3
[c] Daily consumption rate of 2 liters
Source: New York State Department of Health, Bureau of Toxic Substance Assessment, 1989

Cigarette smoking can add to the daily nickel intake at the rate of 1 μg/pack of cigarettes (Grandjean, 1984). Cigarettes have been found to contain nickel at the concentrations of 2.2 to 2.3 μg/cigarette due to the nickel content of tobacco (Sunderman and Sunderman 1961; Szadkowski et al., 1969). The nickel content of mainstream cigarette smoke ranges from 0.005 to 0.08 μg/cigarette (Klus and Kuhn, 1982). Pipe tobacco, cigars, and snuff have been reported to contain nickel at the levels of the same magnitude (2-3 μg/g tobacco) (NAS, 1975).

Metals such as nickel have a unique and complex mechanism of action by which they exert an adverse effect on health. The toxicity of nickel is dependent on the route of exposure and the solubility of the nickel compound. Inhalation is the most significant route for nickel exposure and toxicity, with gastrointestinal and dermal exposure absorption being significantly less important (see Sections 6 and 7 for a more detailed discussion of toxicity by route of exposure). In non-occupationally exposed individuals, the lung contains the highest concentration of nickel with low levels detected in kidneys, liver, and other tissues (IARC, 1990). Individuals occupationally exposed to high levels of chromium and nickel and nickel refinery workers have elevated levels of nickel in lung and nasal mucosa (IARC, 1990).

The toxicity of nickel is influenced, in part, by how soluble the nickel compound is in water. In general, soluble nickel compounds are more toxic than insoluble compounds, although both types may adversely impact health under certain conditions (ATSDR, 1997). The most toxic species of nickel is nickel carbonyl. However, nickel carbonyl is not discussed in this document because human exposure is limited almost entirely to occupational settings, and nickel carbonyl has not been found in ambient air (U.S. EPA, 1986b). This is likely due to the fact that it reacts rapidly with atmospheric moisture and decomposes. Therefore, the focus of this document is on setting AQS appropriate to soluble, insoluble, and metallic species of nickel. Soluble forms of nickel considered encompass nickel sulfate as the most representative; insoluble forms include oxidic nickel (including nickel oxide and complex oxides) and sulfidic nickel (including nickel subsulphide). This covers all the major forms found in ambient air.

3. PREVIOUS NICKEL AIR QUALITY STANDARDS RECOMMENDED

Several states in the U.S. have recommended ambient AQS for nickel compounds. The U.S. Public Health Agency, Agency for Toxic Substances and Disease Registry (ATSDR, 1997) has reviewed and compiled a list of standards (see **Table 3**). Note that most of the standards vary, with many states setting limits for different species of nickel. This variation may reflect a number of factors such as differences in the interpretation of human and animal data, as well as judgements based on societal, political, or the practical impact of the standard.

Table 3: ACCEPTABLE NICKEL AMBIENT AIR CONCENTRATION REGULATIONS AND GUIDELINES FOR SELECTED U.S. STATES[a] AND A CANADIAN PROVINCE[b]

STATE/PROVINCE	AIR QUALITY GUIDELINES (µg Ni/m^3) (AVERAGING PERIOD)	
Nickel (all species)		
Connecticut	5.0	(8 hr)
Massachusetts	0.27	(24 hr)
	0.18	(annual)
North Carolina	0.006	(24 hr)
Nevada	2.0	(8 hr)
New York	3.30	(annual)
Ontario, Canada (existing)	2.0	(24 hr)
Ontario, Canada (proposed)	0.20	(24 hr)
Ontario, Canada (proposed)	0.04	(annual)
Pennsylvania (Philadelphia)	0.24	(annual)
Virginia	1.7	(24 hr)
Nickel Oxide		
Connecticut	0.30	(8 hr)
Nickel Subsulfide		
Connecticut	5.0	(8 hr)
North Carolina	0.0021	(annual)
Nevada	24	(8 hr)
New York	0.1	(annual)

[a] Source: National Air Toxics Information Clearing House (NATICH), 1996
[b] Source: Ontario Ministry of Environment and Energy (OMOEE), 1996

Another contributor to the variation in ambient AQS for nickel is differences in methods used to set standards. Most state and local AQS are set using one of three approaches. These include (a) a quantitative risk assessment using linearized multistage models applied to bioassay data, with the standard being set at some preselected de minimis risk level (usually one in a million 10^{-6}), (b) a NOAEL/LOAEL approach in which suitable animal or human data are used to define the NOAEL/LOAEL and a series of multiplicative safety or uncertainty factors are applied, or (c) an uncertainty/safety factor approach using occupational exposure standards and guidelines (Calabrese and Kenyon, 1991).

For historical perspective, the basis for selected nickel exposure limits where the appropriate data could be obtained is summarized in **Table 4**.

Table 4: NICKEL AMBIENT AIR RECOMMENDED EXPOSURE LIMITS

SOURCE/ ORGANIZATION (YEAR)	RECOMMENDED AMBIENT LIMIT (ANNUAL AVERAGE)	NICKEL COMPOUND	CRITERIA USED
American Petroleum Institute (1968)	0.03 μg/m^3	All species	Based on achievable exposure levels
New York State Department of Health (1989)	0.02 μg/m^3	Nickel sulfate	NOAEL/adjustment factor
New York State Department of Health (1989)	0.004 μg/m^3	Nickel refinery dust	10^{-6} Excess risk - human
New York State Department of Health (1989)	0.0002 μg/m^3	Nickel subsulfide	10^{-6} Excess risk - animal
New York State Department of Environmental Conservation (1988)	3.3 μg/m^3	Metallic and insoluble nickel compounds	Derived from ACGIH TWA-TLV$^+$ values
New York State Department of Environmental Conservation (1988)	3.37 μg/m^3	Nickel oxide	Derived from ACGIH TWA-TLV$^+$ values
New York State Department of Environmental Conservation (1988)	0.1 μg/m^3	Nickel sulfide	Derived from ACGIH TWA-TLV$^+$ values
World Health Organization European Region (EUR) (1998)	No safe level of exposure exists	All species	Linear extrapolation

$^+$ ACGIH TWA-TLV = American Conference of Governmental Industrial Hygienists Time Weighted Average Threshold Limit Value

4. METHODS FOR DEVELOPING AMBIENT AIR QUALITY STANDARDS

The method used to develop an ambient AQS for a compound is typically based on whether or not the agent is carcinogenic. For substances thought to be carcinogenic, a "non-threshold" effect has been adopted by some regulatory agencies as science policy (e.g., U.S. EPA). This approach assumes that exposure to any concentration of the agent may damage DNA and ultimately result in cancer. Models, such as the linearized multistage model, have been used to estimate either the risk at a given dose, or the dose associated with a given risk (Calabrese and Kenyon, 1991). However, depending upon the mechanism of action and the database for the carcinogen, other models as well as the safety factor approach have been used to develop exposure standards or toxicity benchmarks (Moolenaar, 1994). For non-carcinogenic effects, such as developmental and reproductive effects, a "threshold" is usually assumed, and limits are usually derived based on a NOAEL/safety factor approach (Calabrese and Kenyon, 1991).

There is considerable debate regarding the application of a non-threshold concept for a carcinogen. While a non-threshold model is commonly assumed for carcinogenic compounds, this approach fails to take into account the complexities of the multi-step carcinogenic process. Factors that may contribute to a threshold for carcinogenic response include metabolic activation/deactivation, distribution, nonmutagenic modes of carcinogenic action, and defense and repair mechanisms (Melnick et al., 1996; Paustenbach et al., 1990; Cohen and Ellwein 1990; Tubiana, 1992).

With regard to nickel specifically, the use of a threshold approach for calculating an AQS is supported by:

- the existence of a NOAEL for pulmonary inflammation of 130 µg Ni/m^3 (nickel dust) derived from inhalation studies,
- the lack of carcinogenic response in the absence of pulmonary inflammation,
- the presence of good evidence for an empirical threshold for lung and nasal cancer in epidemiology studies of occupationally exposed groups,
- the presence of a NOAEL for pulmonary carcinogenesis of approximately 100 µg/m^3 observed in recent rodent studies conducted with three nickel compounds administered by inhalation,
- no evidence of genotoxicity in *in vivo* studies conducted by the inhalation route of exposure in humans and rodents.

However, since some nickel compounds have tested positive by *in vitro* genotoxicity assays, it could be argued that a linear low dose extrapolation is appropriate. Thus, an AQS based on a linear, non-threshold approach for a nickel risk assessment conducted by the Centre d'Etude sur l'Evaluation de la Protection dans le Domaine Nucleaire (CEPN) is presented (CEPN, 1996).

5. OCCUPATIONAL EXPOSURE STANDARDS FOR NICKEL COMPOUNDS

Many countries have established occupational exposure standards for nickel compounds (**Table 5**). Others have established standards for nickel carbonyl alone.

The basis for these standards varies. The OSHA Permissible Exposure Limit (PEL) for soluble nickel is 0.1 mg/m^3, based primarily on evidence that exposure of experimental animals to low levels of soluble nickel causes pathological changes in the lung (OSHA, 1989). In 1998, the American Conference of Governmental Industrial Hygienists (ACGIH) revised the threshold limit value (TLV) for nickel and selected nickel compounds based on inhalable fraction. The new elemental nickel (metallic) TLV increased to 1.5 mg/m^3 (ACGIH, 1998). Additionally, TLVs of 0.2 mg/m^3 for insoluble nickel, 0.125 mg/m^3 for nickel subsulfide, and 0.1 mg/m^3 for soluble nickel were also adopted. All TLVs are expressed as milligrams of nickel per cubic meter of air.

While it is useful to review the occupational standards for nickel compounds, these standards may not be directly applicable to the community setting for several reasons. First, the daily duration of exposure is shorter in an occupational setting. Second, the occupationally exposed population is highly selected and is often healthier than the general population. Thus, AQS based on occupational exposure limits may not completely protect all members of the general population that includes possibly sensitive subgroups.

Table 5: SELECTED OCCUPATIONAL EXPOSURE STANDARDS FOR NICKEL COMPOUNDS

COUNTRY	CONCENTRATION (mg Ni/m^3 air)	NICKEL COMPOUND	BASIS[a]
Austria	0.05	Nickel metal and insoluble nickel	TWA
	0.05	Soluble nickel	TWA
Belgium	1.0	Nickel metal and insoluble nickel	TWA
	0.1	Soluble nickel	TWA
Denmark	0.5	Nickel metal	TWA
	0.5	Soluble nickel	TWA
	1.0	Insoluble nickel	TWA
Finland	1.0	Nickel metal	TWA
	0.1	Soluble nickel	TWA
France	1.0	Nickel metal and insoluble nickel	TWA
	0.1	Soluble nickel	TWA
Germany	0.5	Nickel metal and insoluble nickel	TWA
	0.05	Soluble nickel	TWA
Ireland	1.0	Nickel metal and insoluble nickel	TWA
	1.0	Soluble nickel	TWA
Italy	1.0	Nickel metal and insoluble nickel	TWA
	1.0	Soluble nickel	TWA
Luxembourg	1.0	Nickel metal and insoluble nickel	TWA
	1.0	Soluble nickel	TWA
Netherlands	1.0	Nickel metal	TWA
	0.1	Soluble nickel	TWA
Portugal	1.0	Nickel metal and insoluble nickel	TWA
	1.0	Soluble nickel	TWA
Spain	1.0	Nickel metal and insoluble nickel	TWA
	1.0	Soluble nickel	TWA
Sweden	0.5	Nickel metal	TWA
	0.01	Nickel subsulfide	TWA
	0.1	Soluble nickel	TWA
UK	0.5	Nickel metal and insoluble nickel	TWA
	0.1	Soluble nickel	TWA
U.S. - OSHA[b]	1.0	Metallic nickel	TWA
	0.1	Soluble nickel	TWA
U.S. - ACGIH[c]	1.5	Nickel metal	TWA
	0.2	Insoluble nickel	TWA
	0.125	Nickel subsulfide	TWA
	0.1	Soluble nickel	TWA
EC[d] (proposed)	1.0	Metallic nickel	TWA
	0.5	Oxidic	TWA
	0.1	Sulphidic nickel	TWA
	0.1	Soluble nickel	TWA

[a] TWA = 8-hr time weighted average; STEL = short-term exposure limit

Source: IARC 1990; HSE 1995

[b] Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit for metallic nickel (1989) and soluble nickel (1993)

[c] American Conference of Governmental Industrial Hygienists (ACGIH), 1998

[d] Occupational Exposure Limits Criteria Document for Nickel prepared for DGV of the European Commission (EC), December 1996

Source: NiPERA, 1996

6. NONCANCER HEALTH EFFECTS OF NICKEL EXPOSURE

6.1. ACUTE TOXICITY

High-level, short-term exposures to nickel compounds have produced effects in both human and animals.

6.1.1. Human studies

Ingestion of high quantities of soluble nickel compounds (>500 mg) may cause death or nausea, neurological, gastrointestinal, and other systemic effects (NIOSH, 1977; ATSDR, 1997; U.S. EPA, 1981). However, at lower levels of nickel ingestion there is relatively low oral toxicity. Inhalation of nickel has been associated with nasal and pulmonary irritation in workers exposed to nickel aerosols (NIOSH, 1977). Unfortunately, these studies do not describe chemical species and concentrations of exposure, although exposures were likely to be considerably higher than levels typically encountered in ambient air.

6.1.2. Animal studies

The soluble nickel compounds (nickel nitrate and nickel sulfate hexahydrate) are more acutely toxic than the less soluble compounds (nickel oxide and nickel subsulfide). Oral LD_{50} values have been reported for rodents for these more toxic compounds ranging from 66 to 136 mg/kg. Acute inhalation of nickel chloride or nickel sulfate (0.25 and 0.455 mg/m^3, respectively) by rodents produced immunosuppression and increased susceptibility to disease (Adkins et. al., 1979).

Inhalation studies of rats and mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide at concentrations up to 13.5 mg/m^3 (calculated as nickel) during a 6-hour exposure period for 12 days produced pulmonary inflammation, degeneration of bronchiolar mucosa, and atrophy of olfactory epithelium at all concentrations; effects were greater in rats than in mice (Benson et al., 1987, 1988).

Nickel chloride administered to rabbits at 0.3 mg Ni/m^3, 6 hours/day, 5 days/week for 1 month, caused an increase in the number and volume of alveolar epithelial cells, nodular accumulation of macrophages and laminated structures, and an increase in phospholipids in lower lobes of the lungs (Johansson et al., 1983).

In a study of rats exposed at yet lower levels (0.109 mg Ni/m^3 for nickel chloride and 0.112 mg Ni/m^3 for nickel oxide) 12 hours/day, 6 days/week for 2 weeks, Bingham et al. (1972) found hyperplastic bronchial epithelium in the nickel chloride exposure group and increases in alveolar macrophages and thickened alveolar walls in the nickel oxide exposure group.

A study of nickel metal dust, rather than nickel oxide or nickel chloride, of greater duration (4 and 8 months) at the comparable air concentration of 0.13 mg/m^3 resulted in no structural changes but did produce increased phospholipids and phosphatidylcholines (Curstedt et al., 1984).

Taken as a whole, the data suggest a threshold concentration for nickel which must be exceeded for toxicity to occur.

6.2. CHRONIC TOXICITY

Health effects in humans and animals have been reported following long-term exposures to nickel compounds, particularly by inhalation.

6.2.1. Human studies

The major categories of health hazards related to chronic exposure to nickel and its compounds can be categorized as follows: allergies, respiratory effects, and other health outcomes. Each of these categories is discussed below.

- Allergies

  Skin contact with nickel and nickel compounds is a common cause of allergic dermatitis (ATSDR, 1997; U.S. EPA, 1986a; NIOSH, 1977; NAS, 1975). Dermal sensitization most often occurs among occupationally-exposed individuals, although members of the general population may develop this condition from exposures to nickel-containing coins, jewelry, watches, and clothing fasteners. However, while nickel is a well-known skin sensitizer, there is no evidence that airborne nickel causes allergic reactions of the respiratory tract in the general population (WHO, 1998).

- Respiratory effects

  There are several reports in the literature of workers developing respiratory conditions such as chronic bronchitis, emphysema, chronic rhinitis and sinusitis, nasal perforations, increased susceptibility to chronic respiratory tract infections, reduced vital capacity, and reduced expiratory flow following exposure to nickel (ATSDR, 1997; U.S. EPA, 1986a; NIOSH, 1977). However, many of these are case reports of nickel workers in various production categories with likely high levels of exposure to various nickel compounds. In addition, concentrations of exposure at which these effects occurred are rarely reported.

  Several case reports have attributed asthmatic illnesses to nickel exposure (ATSDR, 1997; IARC, 1990; U.S. EPA, 1986a; NIOSH, 1977). However, these are only case reports, and there are no data regarding the concentrations and species of nickel at which this health effect occurred. Lin et al. (1998) recently reported a case-control study of childhood asthma hospital admissions (n=1,269 asthma admissions and n=970 controls with non-respiratory diseases) and industrial nickel emissions data obtained from the U.S. Toxic Chemical Release Inventory. The results indicated an increased risk of asthma associated with nickel exposure among older children (5-14 years old, odds ratio=1.55; 95% confidence interval=1.03-2.34), but not younger children (0-4 years old, odds ratio not reported). The authors conclude that the differences in findings by age may be attributable to differences in activity patterns according to age. However, the relevance of these findings to an AQS for nickel is uncertain due to the lack of information on specific exposure levels and the weakness of the study design (i.e., this is an ecologic study design, which lacks individual level data on exposure). Further, the increased risks observed are relatively small, which means that possible confounding factors such as

other pollutants correlated with nickel emissions cannot be ruled out. Finally, the study is only reported as an abstract. Thus, it is difficult to draw firm conclusions about any causal relationship between nickel exposure and asthma.

Two studies have reported an increased incidence of deaths due to respiratory diseases for workers occupationally exposed to $\geq$0.04 mg/m^3 of nickel, usually as nickel oxide or metallic nickel (Cornell and Landis, 1984; Polednak, 1981, cited in ATSDR, 1997). However, interpretation of these findings is difficult because workers were exposed to several other potentially toxic agents besides nickel (i.e., uranium, iron, lead, and chromium). Another study, which does not appear to suffer from confounding by other substances, examined chest radiographs among 745 nickel sinter plant workers with heavy exposure to moderately soluble and insoluble forms of nickel (nickel subsulfide and nickel oxide). Radiographs were taken annually and read and classified by five readers using the 1980 ILO protocol. Radiographs showed an increase in irregular opacities; however, the authors noted that the changes found were no different from those reported for differences in age and cigarette smoking (Muir et al., 1993). The conclusions were that workers exposed to high concentrations of insoluble and moderately soluble nickel compounds did not develop any significant inflammatory response in the lungs. Overall, the majority of data suggest that exposure to nickel at typical environmental levels is unlikely to cause adverse respiratory effects (U.S. EPA, 1986a).

- Other Health Effects Data

Several studies have examined genotoxic effects among electroplating and nickel refinery workers and welders. Waksvik and Boysen (1982), in a study of chromosomal aberrations among nickel refinery workers, found significantly increased levels of chromosomal aberrations, primarily gaps, among workers exposed to nickel monoxide and nickel subsulfide at an average concentration of 500 μg/m^3. An increased level of gaps was also noted among electroplating workers at the same plant who were exposed to nickel chloride and nickel sulfate at an average concentration of 200 μg/m^3. In both groups, however, there were no elevated levels of chromosomal breaks or sister chromatid exchanges. Also, there was no correlation between the occurrence of chromosomal gaps and plasma nickel concentration or duration of exposure (Waksvik and Boysen, 1982). Waksvik et al. (1984) also reported chromosomal aberrations among nine retired workers with known nasal dysplasia from the same nickel refinery who had been exposed to similar nickel compounds but at higher concentrations (around 1000 μg/m^3). The results showed a borderline significant increase in gaps, and a statistically significant increase in the frequency of chromatid breaks.

Deng et al. (1983, 1988) reported an increased frequency of sister chromatid exchanges and chromosomal aberrations among seven electroplating workers. This effect was observed at low levels of exposure that averaged 24 μg/m^3. However, the increase in sister chromatid exchanges among exposed workers was slight and only of borderline statistical significance.

Elias et al. (1989) observed a statistically significant increase of chromosomal aberrations among welders exposed to nickel, iron, and manganese. However, while the incidence of chromosomal aberrations correlated with length of employment, there was no correlation with measured nickel exposure.

Moreover, the presence of multiple potentially causative agents precludes any direct inferences regarding the effects of only nickel.

Kiilunen et al. (1997) examined the frequency of micronucleated epithelial cells in the buccal mucosa of 25 men working in an electrowinning tank house and 34 control subjects. Measurements of nickel concentrations in air, urine and blood showed low levels of exposure to predominately soluble nickel (airborne levels ranged from 170-460 $\mu g/m^3$). The frequency of micronucleated epithelial cells was not significantly elevated compared with referents, and there was no relationship with nickel levels in air, urine, or blood. These findings indicate that prolonged exposure to soluble nickel air concentrations of up to approximately 500 $\mu g/m^3$ does not result in clastogenic or aneuploidogenic effects in buccal mucosa of exposed workers.

Collectively, the studies described above show, at most, a small but inconsistent increase in adverse chromosomal effects. Notably, among the studies showing a positive finding, there is no evidence of a dose-response relationship. Further, several of the studies are potentially confounded by exposures other than nickel. Thus, there is little evidence to suggest that workplace nickel exposures cause genotoxic effects in exposed workers. It is noteworthy that the recent findings of Kiilunen et al. (1997) are consistent with the prediction of Doll et al. (RICNCM, 1990) in that there appears to be a threshold for carcinogenic effects (see section 11).

Although carcinogenic effects of nickel exposure are thought to be of the greatest concern, other respiratory lesions have been reported. For example, hyperplastic rhinitis has been reported in active and retired nickel workers (CRC, 1989); however, the concentration and species of nickel exposure at which these effects were observed has not been reported. For other health outcomes, a review of the scientific literature by the ATSDR revealed no human data regarding the effects of nickel inhalation exposure on the metabolic, hematologic, hepatic, neurologic, musculoskeletal, endocrine, or gastrointestinal system (ATSDR, 1997). There have been reports of increases in serum proteins involved in cell-mediated immunity, but the species and concentration of nickel exposure at which these effects have been observed is not reported (ATSDR, 1997). There have also been two Russian studies reporting increased spontaneous abortions and birth defects among women in a nickel hydrometallurgy refining plant who were exposed to primarily nickel sulfate at levels of 0.08 - 0.196 mg/m^3. However, the validity of these findings are questionable given the lack of complete reporting of study methods and the potential confounding factors of women manually lifting heavy nickel anodes and experiencing heat stress (ATSDR, 1997).

6.2.2. Animal Studies

Animal data support the human data and extend the working knowledge of nickel effects on the renal, reproductive/developmental, hepatic, cardiovascular, pulmonary, and immunologic systems. A number of reports have evaluated the available animal data for nickel compounds (ATSDR, 1997; CRC, 1989; and NYSDH, 1989). From these reports it can be seen that the respiratory and immune systems are the most sensitive endpoints for nickel compounds via the inhalation pathway. This is true for acute, subchronic, or chronic exposure durations. A summary of these data is provided in **Appendix 1**.

- Renal Toxicity

  Tubular lesions resulting in aminoaciduria and proteinuria have been produced in experimental animals with exposure to various nickel compounds (≥0.8 mg ni/m^3). Nickel binding to specific sites in the glomerular basement membrane creating an ionic block may be responsible for the observed functional toxicity in filtration (CRC, 1989).

- Liver Toxicity

  Liver effects have been reported following inhalation of nickel in a variety of laboratory animals. Atrophy of the liver was observed in rats and mice exposed to 3.6 mg nickel/m^3 as nickel subsulfide (Benson et al., 1987). Some studies showed decreased liver weights with exposure to nickel but others did not (Weischer et al., 1980; Dunnick et al., 1989).

  Nickel compounds produce an acute hepatic toxicity demonstrated by hepatic pathology as well as increased serum hepatic enzymes. A number of investigations have associated enhanced lipid peroxidation in the liver with subcutaneous and intraperitoneal nickel administration (CRC, 1989).

- Developmental Toxicity

  Studies have established the embryotoxic and teratogenic effects of nickel compounds in a variety of experimental animals using various routes of exposure (CRC, 1989; NYSDH, 1989). Maternal exposure resulted in a decrease in implantation frequency, increased early and late resorption and increased frequency of stillborn fetuses. In addition, exposure to nickel during organogenesis has resulted in a variety of teratogenic effects including acephalia, exencephaly, cerebral hernia, skeletal anomalies, micromelia, club foot, cleft palate, and cystic lungs.

  Inhalation studies for developmental effects are limited. Developmental toxicity appears to be present only in the presence of maternal toxicity. A decrease in fetal body weight was observed in offspring of rats exposed to 1.6 mg nickel/m^3 as nickel oxide (Weischer et al., 1980). However, there was maternal toxicity at this exposure evidenced by decreased body and liver weights.

  Nickel may exert its effects directly and indirectly on the developing embryo/fetus. Teratogenic doses of nickel produce hyperglycemia that apparently affects the developing offspring (CRC, 1989).

- Reproductive Toxicity

  Testicular degeneration was observed in rats and mice exposed to nickel sulfate (≥1.8 mg nickel/m^3) and nickel subsulfide (≥1.8 - ≥3.6 mg nickel/m^3 in rats and mice, respectively) (Benson et al., 1987, 1988). Lower exposures for longer durations did not produce effects on sperm number, motility, or morphology (Dunnick et al., 1989). The lower exposure conditions did not effect the estrous cycle of the female rat (ATSDR, 1997).

  Pregnancy appeared to increase susceptibility to nickel toxicity as judged by a lower LD_{50} in pregnant rats than nonpregnant rats (CRC, 1989).

- Respiratory Toxicity

  Studies in both humans and animals indicate that the respiratory system is a primary target of nickel toxicity following inhalation exposure. In addition to cancer, numerous studies have demonstrated nickel-induced pulmonary toxicity. In general, the toxicity depends on the solubility of the compounds and not on lung burden. The studies indicate the following toxicity ranking: nickel sulfate > nickel subsulfide > nickel oxide. In addition, rats appear to be more sensitive than mice to nickel toxicity.

  A variety of pulmonary endpoints are affected by inhalation of nickel compounds (ATSDR, 1997; NYSDH, 1989). The degree of pulmonary toxicity is a function of dose and duration of exposure. Morphologically, bronchial gland hyperplasia, chronic inflammation, fibrosis, and interstitial infiltrates have been observed. Clinically, increased lung weights, pneumonia, pneumonitis, atelectasis, bronchitis, bronchiectasis, and emphysema have been noted. Although these findings occur at lower doses than those associated with cancer (see **Appendix 1**), there is no consistent evidence of increased noncancer respiratory disease in humans associated specifically with exposure to nickel.

- Immune Toxicity

  In addition to eliciting an immune response resulting in contact dermatitis or asthma (only in occupationally exposed persons), nickel appears to cause a suppression of cellular and humoral immune systems in animals (ATSDR, 1997). Numerous animal studies indicate that nickel in high concentrations is toxic to alveolar macrophages. Alveolar macrophages appear to play an essential role in the pulmonary toxicity induced by nickel exposure. Alterations in macrophage function and morphology have been reported with high nickel exposures (ATSDR, 1997; NYSDH, 1989). Other components of the immune system have been affected as well. An important consequence of the impaired immune response following nickel exposure is the observed increased susceptibility to respiratory infections seen in mice (Adkins et al., 1979). Furthermore, immunologic studies suggest that nickel may exert a carcinogenic effect by suppressing natural killer (NK) cell activity and interferon production (Shen and Zhang, 1994).

- Genotoxicity

  The *in vitro* and *in vivo* genotoxicity data (**Appendix 2**), indicate that some forms of nickel are genotoxic. Equivocal results of mutagenicity tests have been found and probably reflect the variation in sensitivity of bacterial strains and different conditions. The *in vivo* studies were conducted by the oral or intraperitoneal route of exposure. With exception of one study of soluble nickel salts conducted by the oral route (Sobti and Gill, 1989), there are no positive *in vivo* studies in mammalian cells. Furthermore, no genotoxicity has been found by *in vivo* (inhalation) mouse micronucleus studies (the most relevant route of exposure) in which nickel and its insoluble or soluble inorganic compounds have been tested. Toxicokinetic studies of radiolabeled nickel aerosols indicate that the highly soluble nickel sulfate is rapidly cleared from the lungs to other body tissues, and is excreted primarily through the feces. Conversely, the insoluble nickel oxide was not detected outside the respiratory tract (except for the gastrointestinal tract). Therefore, it is unlikely that insoluble nickel compounds reached the target organ (bone marrow) (Benson et al., 1991). Other studies have evaluated micronulei formation, chromosome aberrations,

dominant lethality, gene mutations, and recessive lethality (Rodriguez-Amaiz and Ramos, 1986; Rasmuson, 1985; Deknudt and Leonard, 1982; Mathur et al., 1977). Taken together with the human genetic toxicology studies (Waksvik and Boysen, 1982; Waksvik et al., 1984; Deng et al., 1983, 1988; Elias et al., 1989; Kiilunen et al., 1997), the weight of the evidence indicates nickel is unlikely to be genotoxic to humans by the inhalation route of exposure.

7. CANCER HEALTH EFFECTS OF NICKEL EXPOSURE

The most serious human health concern related to nickel exposure is an increased risk of respiratory disease including cancer. The epidemiology studies completed to date have examined mortality primarily among persons occupationally exposed to nickel during the refining and use of nickel compounds. A number of reviews of these studies have been completed, and there is general agreement that certain nickel refining operations are associated with an increased risk of lung and nasal cancer (RICNCM, 1990; Grandjean et al., 1988; IARC, 1990; NIOSH, 1977; Shen and Zhang, 1994; U.S. EPA, 1986a). Evidence for the use of nickel in other industries being carcinogenic to humans is less clear.

A number of organizations have classified the carcinogenicity of various nickel compounds to humans. These classifications are summarized in **Table 6**. In general, all of the nickel compounds assessed have been classified as being either possible or known carcinogens.

Table 6: CARCINOGENICITY CLASSIFICATIONS FOR NICKEL COMPOUNDS

ORGANIZATION	TYPE OF NICKEL	CANCER CLASSIFICATION/RISK PHRASE[b]
European Union[a]	Nickel Sulfate	Category 3 / Xn, R 22, R 40, R 42/43
European Union[a]	Nickel Oxide	Category 1 / T, R 43, R 49
European Union[a]	Metallic Nickel	Category 3 / Xn, R 40, R 43
European Union[a]	Nickel Subsulfide	Category 1 / T, R 43, R 49
International Agency for Research on Cancer (IARC, 1990)	Nickel Compounds	Group 1 / Carcinogenic to Humans
International Agency for Research on Cancer (IARC, 1990)	Metallic Nickel	Group 2B / Possibly Carcinogenic to Humans
National Institute of Occupational Safety and Health (NIOSH, 1977)	Nickel Metal and All Inorganic Nickel Compounds (airborne)	No Formal Category Number / Carcinogenic to Humans
United States Environmental Protection Agency (USEPA, 1986a b)	Nickel Refinery Dust and Nickel Subsulfide	Group A / Human Carcinogen
United States Environmental Protection Agency (USEPA, 1986a b)	Nickel Carbonyl	Group B2 / Probable Human Carcinogen

[a] European Commission Dangerous Substances Directive, 67/548/EEC, Annex 1

[b] Category 1 = Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer

Category 2 = Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a

substance may result in the development of cancer, generally on the basis of: appropriate long-term animal studies, other relevant information

Category 3 = Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2

Xn = Harmful
T = Toxic
R 22 = Harmful if swallowed
R 40 = Possible risk of irreversible effects
R 42/43 = May cause sensitization by inhalation or skin contact
R 43 = May cause sensitization by skin contact
R 49 = May cause cancer by inhalation

In general, the epidemiology data are limited by a lack of information regarding the magnitude and species of nickel to which workers were exposed. Consequently, many of the investigations were unable to separate effects of exposure to individual nickel species, or to determine exposure levels at which risk was increased. Furthermore, in some instances, there was exposure to other potentially toxic materials, thereby possibly confounding the association of interest. Finally, many of the studies did not take smoking into account, an important consideration when examining respiratory cancer risk. A brief review of the epidemiology studies by type of working population is provided below.

7.1. CANCER IN NICKEL REFINERY WORKERS

Epidemiology studies of nickel refinery workers have been conducted in Canada, Wales, Norway, Finland, New Caledonia, and the United States (RICNCM, 1990; IARC, 1990; Grandjean et al., 1988). Many of these studies have reported large increased risks of lung and nasal cancer associated with certain nickel refining operations. The greatest risks observed have been for nasal cancer, although it is clear that certain nickel refining exposures may increase the risk of lung cancer as well.

The nickel refining operations associated with the greatest excess risk have been calcining, smelting, and roasting processes of nickel matte refining (RICNCM, 1990; Grandjean et al., 1988; U.S. EPA, 1986a). While the exact species of nickel responsible for the excess lung and nasal cancer risk cannot be determined, the primary exposures during these operations are sulfidic nickel and oxidic nickel.

7.2. CANCER IN WORKERS USING NICKEL

Workers who use nickel have also been studied in several epidemiologic investigations. These include workers involved in electroplating, stainless steel welding, powder metallurgy and the production and use of high-nickel alloys (RICNCM, 1990; IARC, 1990; Grandjean et al., 1988). Because of the variety of operations and processes represented in these studies, interpretation is difficult due to the presence of potentially carcinogenic substances other than nickel. Also, there is a general lack of data on the concentration of nickel exposure among the workers studied. At this

time, there are no data that confirm increased cancer risks in nonnickel refining workers exposed to nickel only (HSE, 1988).

7.3. SUMMARY OF EPIDEMIOLOGIC EVIDENCE FOR CARCINOGENICITY OF NICKEL REFINING AND USE

In 1984, the International Committee on Nickel Carcinogenesis in Man (ICNCM) was convened by Sir Richard Doll to review the epidemiologic evidence regarding cancer risk and occupational exposure to nickel and its compounds (RICNCM, 1990). This committee performed an exhaustive assessment of cancer risk in relation to specific forms and concentrations of nickel using data from 10 previously studied cohorts representing approximately 80,000 men involved in the production and use of nickel. A detailed description of the 10 cohorts included in this analysis is available elsewhere (RICNCM, 1990). Based on this assessment, the committee concluded the following:

1. Most of the excess lung and nasal cancer risk among nickel workers is attributable to exposure to sulfidic nickel; however, exposure to oxidic nickel and soluble nickel are also associated with increased risks of these cancers.

2. Exposure to metallic nickel does not increase cancer risk.

3. Cancers of the lung and nasal sinus are the only cancer sites associated with occupational exposure to nickel.

4. While dose-specific estimates of risk for individual nickel species were not possible, the "evidence from this study suggests that respiratory cancer risks are primarily related to exposure to soluble nickel at concentrations in excess of 1 mg Ni/m^3 and to exposure to less soluble forms at concentrations greater than 10 mg Ni/m^3." The ICNCM concludes that "the risk to the general population from exposure to the extremely small concentrations (less than 1 μg/m^3) to which it is exposed in the ambient air is minute, if indeed there is any risk at all" (RICNCM, 1990).

Recently, Anttila et al. (1998) reported an increased incidence of nasal and lung cancer among 418 Finnish nickel refinery workers exposed primarily to nickel sulfate at levels below 0.5 mg/m^3 as well as to low concentrations of other nickel compounds. These results suggest carcinogenic effects at exposure levels below those associated with respiratory cancer in the much larger, more detailed study performed by Doll et al. (RICNCM, 1990). However, compared with the Doll et al. (RICNCM, 1990) assessment, the Finnish study is based on very small numbers of workers (n=418) and cases (only n=2 nasal cancers and n=6 lung cancers). As a result, the risk ratios are very imprecise, with the 95% confidence interval for nasal cancer ranging from 4.97 to 148 (standardized incidence ratio=41.1). Further, the results are not internally consistent because, unlike nasal cancer, lung cancer risk does not increase with increasing duration of employment. Finally, while exposures in the Finnish refinery are reported to be below 0.5 mg/m^3 there are some data to indicate that historical exposures may have been in the range of 0.5 to 1.5 mg/ m^3, which is consistent with Doll et al. (RICNCM, 1990). A detailed review of Anttilla et al. (1998) and exposure levels in this study is available in Appendix 3.

7.4. ANIMAL STUDIES ON CANCER

The carcinogenicity of nickel varies with the route of administration as well as the nickel compound. In contrast to the higher toxicity of soluble nickel compounds in acute and repeated dose toxicity tests, the more insoluble nickel compounds are of lower systemic toxicity but generally are more carcinogenic than soluble nickel compounds following parenteral (i.e., subcutaneous or intramuscular injection) administration (Gilman, 1962; Kasprzak et al., 1983; Lumb and Sunderman, 1988; Smialowicz et al., 1985; Sunderman and McCully, 1983). However, this route of exposure (parenteral) is obviously irrelevant in deriving an AQS for nickel compounds.

Efforts to produce carcinogenic responses on injection, instillation, or implantation are consistently positive, however, inhalation studies are more limited. Multiple intratracheal instillation of nickel subsulfide induced malignant lung tumors in female Wistar rats (Pott et al., 1987) and in female Fisher 344 rats (Yarita and Nettenheim, 1978), while intratracheally instilled nickel subsulfide did not induce lung tumors in Syrian hamsters (Muhle et al., 1992). In an inhalation study, nickel subsulfide produced pulmonary carcinogenesis in 14% of rats exposed at 0.97 mg Ni/mg^3 for 78 weeks followed by a 30-week observation period compared to 1% of control animals (Ottolenghi et al., 1974). However, the study only examined one species, one concentration of nickel, and did not employ lifetime exposure. Chronic inhalation studies were carried out with male and female F-344 rats and B6C3F1 mice of both sexes to investigate the carcinogenic potential of lifetime exposure to insoluble and soluble forms of nickel. The insoluble green nickel oxide (NiO), slightly soluble nickel subsulfide (Ni_3S_2), and soluble nickel sulfate hexahydrate ($NiSO_4 \bullet 6H_2O$) were studied by the U.S. National Toxicology Program (NTP, 1996a,b,c). The results of these studies are summarized in **Table 7** below.

Table 7: SUMMARY OF RECENT NATIONAL TOXICOLOGY PROGRAM NICKEL STUDIES: CARCINOGENICITY BY INHALATION ROUTE OF EXPOSURE AND GENOTOXICITY

CHEMICAL FORM	SOLUBILITY	DOSE RANGE (mg Ni/m^3) [a]	NOAEL[g] (mg Ni/m^3)	CARCINOGENICITY RESULT[b]	GENOTOXICITY *IN VIVO/ IN VITRO*
NiO	Insoluble	0.5, 1.0, 2.0 (R) 1.0, 2.0, 4.0 (M)	0.5 (R) 1.0 (M)	SE - R - m/f NE - M – m EE - M - f	Negative[c]/ND[d]
Ni_3S_2	Slightly soluble	0.11, 0.73 (R) 0.44, 0.88 (M)	0.11 (R) 0.88 (M)	CE - R - m/f NE - M - m/f	Negative[c]/ equivocal[e]
$NiSO_4$	Soluble	0.03, 0.06, 0.11 (R) 0.06, 0.11, 0.22 (M)	0.11 (R) 0.22 (M)	NE - R - m/f NE - M - m/f	ND/positive[f]

[a] The 8-hour time-weighted average concentration of inhalable nickel particulate
[b] Carcinogenicity codes: CE = Clear evidence, SE = Some evidence, NE = No evidence, EE = Equivocal evidence, R = Rats, M = Mice, m = Male, f = Female
[c] Mouse micronucleus assay
[d] ND = no data
[e] In the *Salmonella* gene mutation assay, sporadic weakly positive and equivocal responses were obtained in strain TA100 with and without S9 metabolic activation enzymes; all other strains/activation combinations gave negative results
[f] 5178Y mouse lymphoma cell assay (without S9)
[g] NOAEL = no observable adverse effect level

Exposure of rats to insoluble nickel oxide for 2 years at concentrations of 0, 0.62, 1.25, or 2.5 mg/m^3 (equivalent to 0.5, 1.0, or 2.0 mg Ni/m^3) resulted in inflammation and pigmentation in the lung, lymphoid hyperplasia and pigmentation in the bronchial lymph nodes, and hyperplasia of the adrenal medulla (females). Exposure of mice to 0, 1.25, 2.5, or 5.0 mg/m^3 (equivalent to 1.0, 2.0, or 4.0 mg Ni/m^3) resulted in bronchialization (i.e., deposition and localization in the conducting airways of the lung), proteinosis, inflammation, and pigmentation in the lung and lymphoid hyperplasia and pigmentation in the bronchial lymph nodes. The NTP concluded that the 2-year rat inhalation studies showed some evidence of carcinogenicity in both male and female rats, no evidence of carcinogenicity in male mice, and equivocal evidence of carcinogenicity in female mice based on a statistically significant increase in the combined incidence of alveolar or bronchiolar adenoma or carcinoma (p=0.01). The combined incidence of alveolar or bronchiolar adenoma or carcinoma in the low dose was not different from that observed in controls, and none of the individual tumor incidences (adenoma, carcinoma) were different from control animals at any dose. Moreover, with the exception of 1 adenoma in a single female mid-dose mouse, no alveolar or bronchiolar adenomas or carcinomas were observed in any treated animal at the 7 or 15 month interim sacrifice; this tumor type was also observed in one male control mouse at each interim sacrifice.

The nickel subsulfide studies were conducted at air concentrations of 0, 0.15, or 1 mg/m^3 (equivalent to 0.11 or 0.73 mg Ni/m^3) in rats and 0, 0.6, or 1.2 mg/m^3 (equivalent to 0.44 or 0.88 mg Ni/m^3) in mice. There was clear evidence of carcinogenicity in male and female rats with significant increases in lung carcinomas and adenomas at the high exposure. There was no evidence of carcinogenicity in mice despite exposure at concentrations in the range of maximum tolerated exposures (MTE).

Rats were exposed to nickel sulfate at concentrations of 0, 0.12, 0.25, or 0.5 mg/m^3 (equivalent to 0. 0.03, 0.06, or 0.11 mg Ni/m^3) and mice at concentrations of 0, 0.25, 0.5, and 1.0 mg/m^3 (equivalent to 0, 0.06, 0.11 or 0.22 mg Ni/m^3). These concentrations represented the MTE. Rats exposed at 0.06 and 0.11 mg Ni/m^3 showed chronic, active pulmonary inflammation; macrophage hyperplasia; alveolar proteinosis; fibrosis; hyperplasia of the bronchial lymph nodes; and atrophy of the olfactory epithelium. Similar inflammatory changes were seen in mice exposed at 0.11 and 0.22 mg Ni/m^3 concentrations. Despite lifetime exposures which were sufficient to produce inflammatory changes, there was no evidence of carcinogenic effects from $NiSO_4$.

All three studies showed evidence of atrophy of the olfactory epithelium with long-term inhalation of Ni in both rats and mice, indicating a MTE was achieved. Moreover, three NTP studies indicate an apparent NOAEL for carcinogenesis of at least 0.1 mg/m^3 (as Ni) which is similar to the NOAEL of 0.13 mg/m^3 (as Ni) for noncarcinogenic effects observed in the Curstedt et al. study (1984).

8. MECHANISMS OF CARCINOGENICITY

Bioavailability of nickel appears to be key to understanding carcinogenic activity of nickel compounds. Water soluble nickel compounds are not carcinogenic in animal studies *in vivo,* however the water soluble nickel sulfate is carcinogenic in epidemiological studies. One of the reasons for this is the poor bioavailability of nickel ions *in vivo* (Costa, 1989). This is partially due to anatomic differences between the respiratory tracts of rats and humans. There is greater deposition in the upper respiratory tracts of rodents compared to humans resulting in a lower absorbed dose in the lower regions of the respiratory tract. Presumably if the nickel compound is bioavailable, there is a potential for carcinogenicity.

Although the mechanism of nickel-induced carcinogenicity is unclear, several studies have implicated the nickel ion as the ultimate carcinogenic form. Potency differences among the various carcinogenic forms of nickel following parenteral injection have been correlated with the percentage of nickel in the compound, the dissolution rate in biological fluids, and the ability to be actively phagocytized by cells. The most potently carcinogenic nickel compound, nickel subsulphide, has been shown to be actively phagocytized by cells, and once in the cell, dissociates relatively quickly ($t_{1/2}$ = 34 days). Other nickel compounds, such as metallic nickel and nickel oxide although taken up by cells, had longer dissolution rates ($t_{1/2}$ >11 years) and were less potent carcinogens. Soluble nickel salts which rapidly dissociated but had poor cellular uptake (nickel sulfate) were not carcinogenic.

The molecular effects of nickel are complex. Nickel has been reported to interact with DNA, resulting in crosslinks and strand breaks (Ciccarelli and Wetterhahn, 1982; Patierno and Costa, 1985; Robinson and Costa, 1982). Nickel has a greater binding affinity for proteins than DNA and preferentially damages heterochromatic regions of the chromatin. Studies indicate that nickel binds directly to DNA in chromatin and results in formation of stable, inert nickel-DNA and or nickel-DNA protein complexes. Nickel salts inhibit DNA replication and transcription *in vitro* and *in vivo* and may also produce effects in the cell by altering the structure of DNA. Carcinogenesis may result from a misreplication process related to the nickel ions or DNA damage or may be the result of DNA rearrangements or alterations in DNA-protein interactions (CRC, 1989). However, recent *in vivo* studies with nickel oxide and nickel subsulfide did not produce genotoxicity in the *in vivo* mouse micronucleus assay (NTP, 1996a,b).

9. SUSCEPTIBLE POPULATIONS

Certain subpopulations may exhibit a different or enhanced response to nickel than the general population exposed to the same level because of genetic make-up, developmental stage, age, health and nutritional status, and chemical exposure history (particularly to other metals). In addition, pregnancy may enhance individuals' susceptibility to the acute toxicity of nickel compounds. Another group potentially more susceptible to the effects of nickel exposure are smokers. Cigarette smoking results in the release of nickel into mainstream cigarette smoke (NAS, 1975). A study of nickel refinery workers in Norway suggests that the effect of smoking and nickel refining on lung cancer risk may be additive (Mangus et al., 1982).

10. HEALTH ENDPOINT SELECTION FOR DEVELOPING AN AQS FOR NICKEL

The selection of a health endpoint for developing an AQS for nickel must consider several factors. First, the quality of available human and animal data must be considered. Only data from well conducted, well-controlled studies with valid data on exposure and health outcome should serve as the basis for an AQS. In the absence of valid human data, animal data, appropriately qualified, can be used. In addition, the studies must provide information about disease occurrence in relation to specific concentrations and species of exposure to be useful for setting an AQS.

Once the appropriate animal and human database is defined, the most critical effect must be delineated. The critical health effect is broadly defined as the health endpoint of most concern to the population. Selection of the critical effect depends on a true cause-effect relationship, replicability, relevance to humans, and the "adversity" or seriousness of the effect (i.e., degree of impact on health).

Accordingly, the most scientifically justifiable and defensible endpoint to base an ambient AQS for nickel on is respiratory cancer. While other systems have been identified as being targets of nickel by the inhalation route, they are either affected at higher doses than required for respiratory effects, inconsistently found to be effected, produced by unknown nickel concentrations, or compromised by co-exposures to other substances. The CEPN, which estimated respiratory cancer risk associated with ambient nickel exposures using a non-threshold model, also believes respiratory cancer is the critical endpoint (CEPN, 1996).

There have been reports of adverse noncarcinogenic effects of nickel on the respiratory tract of humans exposed to nickel compounds. In humans, conditions such as chronic bronchitis, emphysema, chronic rhinitis and sinusitis, asthma, and related conditions have been reported to be associated with nickel exposure. However, many of these are case reports of nickel workers in various production categories with exposure to various nickel compounds that are likely to be considerably higher than those encountered in ambient air. In addition, concentrations of exposure at which these effects occurred are rarely reported. The only studies reporting adverse respiratory effects at quantitative levels of exposure (Cornell and Landis, 1984; Polednak, 1981, cited in ATSDR, 1997) are possibly confounded by the presence of multiple, potentially causative agents other than nickel (i.e., uranium, iron, lead, and chromium). Indeed, a 1992 study of nickel sinter workers concluded that nickel did not result in any significant non-malignant respiratory response (Muir et al., 1993). There have also been a few inconsistent reports in humans of chromosomal damage at nickel exposures lower than those associated with respiratory cancer, but these studies have lacked a dose-response, shown only small increases in adverse chromosomal effects compared with controls, and/or been potentially confounded by exposures other than nickel.

Studies in laboratory animals have also resulted in carcinogenic and noncarcinogenic respiratory effects. The doses associated with these effects have at times been less than those estimated to elicit disease in humans. However, several factors indicate that these findings should be used as supportive of the human data rather than definitive for the purposes of deriving an AQS. As reviewed in this document, valid human data exist and doses can be quantified for the carcinogenic responses. Although carcinogenic effects have been noted in laboratory animals, the mechanism of action of nickel is complex and does not appear to involve a "classic" mutation

pathway. With additional consideration of differences in repair mechanisms and efficiencies as well as bioavailability, the direct relevance of the animal studies is uncertain. Thus, a quantitative derivation of an AQS appears to be more soundly based on the human data. The CEPN has derived unit risk estimates for nickel and respiratory cancer based on both human and animal data and found the results to be similar (CEPN, 1996). This suggests that the choice of human versus animal data to derive a nickel AQS does not strongly influence the final value.

The low dose noncarcinogenic responses noted in animals have been used to derive an ambient air standard for nickel by some organizations (e.g., the New York State Department of Health recommended a value of 0.02 $\mu g/m^3$)(NYSDH, 1989). However, this approach appears to be unduly conservative. The endpoint in question was pulmonary inflammation. This endpoint appears to have been representative of normal physiological functioning to remove foreign agents from the lung and the applied 1000-fold uncertainty factor likely overestimates any potential noncancer hazard from low level nickel exposures in the air. Two authoritative reviews of the literature have concluded that exposure to nickel at typical environmental levels is unlikely to cause adverse respiratory effects (U.S. EPA, 1986a).

In conclusion, cancer of the respiratory system has been observed in both humans and animals and is the critical adverse health effect associated with nickel exposure.

11. DERIVATION OF A NICKEL AIR QUALITY STANDARD USING A THRESHOLD/SAFETY FACTOR APPROACH

As described above, quantitative derivation of an AQS for nickel appears to be most scientifically justifiable and defensible based on respiratory cancer in human epidemiology studies. The data on respiratory cancer in humans comes from studies of workers occupationally exposed to nickel during the refining and use of nickel compounds. These epidemiology studies involved a large number of workers with many years of mortality follow-up. Also, recent work by Doll (RICNCM, 1990) to characterize exposures among these workers has tremendously improved the available epidemiologic database on nickel exposure to the point that these data can be used to develop an AQS for nickel.

While Doll's (RICNCM, 1990) analysis suggests a threshold for respiratory cancer risk in humans, precise definition of a NOAEL and/or LOAEL based on these data is difficult due to the uncertainty in estimates of the types and levels of nickel to which workers were exposed. Additionally, most workers had either modest or very intense exposures, further complicating the definition of a NOAEL and/or LOAEL. Nevertheless, in their discussion of respiratory cancer risk at low-level nickel exposures, the authors conclude there is "no definitive evidence of increased cancer risk associated with exposure to metallic nickel, oxidic nickel, or sulfidic nickel at concentrations of less than 1 mg Ni/m^3". This statement could be interpreted as a NOAEL at 1 mg Ni/m^3; however, the authors go on to state that soluble nickel exposures "close to 1 mg Ni/m3 resulted in increased lung and possibly increased nasal cancer risks". Accordingly, given the uncertainty in the exposure estimates, it is most prudent to conclude that 1 mg Ni/m^3 represents a LOAEL in humans. A very small study in Finnish nickel refinery workers (Anttila et al., 1998) has recently reported increased nasal and lung cancer risks below 0.5 mg/m^3. However, as discussed earlier, the limitations of this study, along with possibly higher historical exposures argues against basing an AQS on this study. Further, the observation of clear NOAELs at exposures of at least 0.1 mg Ni/m^3 in animal studies where exposures are well characterized strongly supports the value of 1 mg Ni/m^3 as a LOAEL in humans.

An important factor to consider in using the occupational epidemiology data to derive an AQS is that nickel refinery dust exposures differ in composition from ambient air. For example, nickel refinery dust may be comprised of 1-50% nickel, whereas dust in ambient air is comprised of only approximately 0.01% nickel. Further, nickel refinery dusts have a strong presence of sulfidic nickel and oxidic nickel including nickel oxide; sulfidic nickel in ambient air is unlikely to be present in detectable quantities, whereas nickel oxide, if present, will be at a maximum of 8% (CEPN, 1996). (Further discussion of the differences between occupational and ambient nickel exposures is provided in Section 13 and Table 9). However, because nickel refinery workers experienced more "severe" exposures than the general population, the occupational epidemiology data are likely to overestimate the true cancer risk to the general population.

11.1. ADJUSTMENT FACTORS

The use of adjustment factors for establishing health-based exposure criteria are generally accepted and based on a scientific rationale (Dourson and Stara, 1983; Lewis et al., 1990; Health Council of the Netherlands, 1997; ECETOC, 1995). In

setting an AQS for nickel, application of several adjustment factors to the best estimate of the LOAEL for respiratory cancer is warranted. First, because epidemiology data for populations occupationally exposed to nickel are being used as the basis for the AQS, an adjustment factor to adjust for differences between occupational and environmental exposures is justified. The most common adjustment factor used is a factor of 4.2 (168 hours per week over 40 working hours per week).

It is also necessary to apply an adjustment factor to adjust for the shorter time spent in an occupational versus residential setting. Previous risk assessment have traditionally used 70 years as the average lifetime duration and 40 years as the average working career duration; this results in an adjustment factor of 1.75. However, this must be adjusted to account for the fact that the average working time in the epidemiology studies was less than 40 years. This adjustment is performed by dividing the 70 year lifetime figure by the average duration of employment in the cohort upon which the risk estimates are based. However, the epidemiology analysis by Doll (RICNCM, 1990), which defines the LOAEL for respiratory cancer based on ten separate studies, does not provide information about duration of employment for all ten studies. A review of publications for each of the studies included in Doll's assessment (RICNCM, 1990) resulted in acquisition of data on average duration of employment for only three of the studies (Goldberg, et al., 1987; Cragle et al., 1984; Cox et al., 1981). Consequently, average duration of employment was estimated for the remaining investigations based on the three studies that had relevant data reported.

The approximate average duration of employment was based on the ratio of average years employed to the minimum employment time required to be included in the cohort for the three studies where data were reported. A weighted mean was then calculated for all studies combined (the number of employees in each cohort served as the weighing factor).

Based on the above calculations, the average duration of employment in the Doll assessment (RICNCM, 1990) was 7.2 years. Using this estimate, the revised uncertainty factor to account for time spent in an occupational versus residential setting is 9.7 (70/7.2). When this is multiplied by 4.2, the overall occupational adjustment factor is 40.7.

It is also important to adjust for the total intake of nickel. A respiration volume of 18 m^3 is typical (EBSI, 1994) for a 24 hour day, while 8 m^3 has been used for an occupational breathing volume. However, these figures must be normalized to avoid over adjusting for the factors already used. This can be accomplished by dividing the volumes by the length of exposure to arrive at rates. This results in an environmental breathing rate of 18/24 = 0.75 m^3/hour and an occupational breathing rate of 8/8 = 1.0 m^3/hour. The ratio between these two rates is 0.75.

Another important adjustment factor is one to protect subpopulations with a potentially heightened susceptibility to the effects of nickel. Some individuals in the general population may be particularly responsive to nickel due to their genetic make-up, developmental stage, age, health status, and chemical exposure history. Subpopulations with possibly greater susceptibility to the effects of nickel include the elderly, the very young, and the developing embryo/fetus due to compromised detoxification and elimination mechanisms.

Typically, an adjustment factor between 1 and 10 is used to account for susceptible populations (Dourson and Stara, 1983), unless the NOAEL is based on a study in a sensitive at risk human population. U.S. EPA used an adjustment factor of 3 applied

to the results of an epidemiologic study consisting of a large cohort exposed to arsenic (U.S. EPA, 1995). The large cohort covered in the epidemiology analyses (RICNCM, 1990) can be assumed to contain some susceptible individuals since respiratory cancer was found in the study, thus a less than 10 fold factor is justified.

Additional justification for application of a less than 10 fold adjustment factor for individual differences exists. Factors of 3 to 6 have been reported to provide adequate protection for nearly all individuals (approximately 99.9%) in animal populations (Lewis et al., 1990). Renwick (1993) and Hattis, et al. (1987) reviewed individual differences in kinetics determining that for most chemicals the individual differences are in the range of 2-4 fold. Individual variation (metabolic kinetics) would be less influential for the selected endpoint. Renwick (1991) reviewed the interindividual differences in dynamics (i.e., toxicodynamics - target organ sensitivity). The maximum to mean ratio of sensitivity ranged from 1.5 to 6.9.

Because of the large cohort and the mechanism of action of nickel, the midpoint interval (i.e., 5.0) is appropriate to protect various susceptible subgroups for the critical effect of cancer. A factor of 10.0 would likely over-adjust for susceptibility because this AQS is based on data from epidemiology studies of occupational populations that likely include some susceptible individuals. However, a factor of 1.0 would probably under-adjust for susceptibility because occupational populations, while including some susceptibles, are primarily comprised of individuals who are healthier than the general population (McMichael, 1976). Thus, the midpoint value of 5.0 is a reasonable choice for a susceptibility adjustment factor.

Finally, an adjustment must be made to account for the use of a LOAEL rather than a NOAEL. This adjustment assumes that the LOAEL is reasonably close to the projected NOAEL, and that the use of an adjustment factor will drop the LOAEL into the range of the expected NOAEL (Dourson et al., 1996). Based on analyses of toxicology study findings, a factor of 10 or lower is scientifically defensible (Dourson and Stara, 1983; Lewis et al., 1990; Pohl and Abadin 1995; Dourson et al., 1996), although these studies involved non-carcinogenic chemicals. For nickel, there is little precedence for determining the appropriate LOAEL-to-NOAEL adjustment factor given that human data and respiratory cancer risk are being considered. However, if the NOAEL for respiratory cancer based on animal studies is assumed to be representative of the projected NOAEL in humans, then a 10-fold adjustment factor is warranted since this would “drop” the LOAEL into the range of the expected human NOAEL (NOTE: the NOAEL in animals is at a minimum 0.1 mg Ni/m^3 and the LOAEL in humans is 1 mg Ni/m^3). Further, the severity of the critical health effect (i.e., respiratory cancer) suggests the use of a 10-fold adjustment versus a lower value is appropriate.

11.2. RECOMMENDED AIR QUALITY STANDARD FOR NICKEL

The available epidemiology data suggest two different LOAELs for respiratory cancer and different species of nickel. Below is a description of the adjustment factors applied to these two NOAELs (note: several adjustment factors are rounded).

Occupational to environmental dosimetry: 31 = (9.7 X 4.2 X 0.75)

YEARS EXPOSED 70/7.2	=	9.7
HOURS EXPOSED 168/40	=	4.2
BREATHING RATE 0.75/1.0	=	0.75
SUSCEPTIBLE SUBPOPULATION	=	5.0
LOAEL to NOAEL	=	10

The total of the above adjustment factors is 1550 = (31 x 5 x 10). Proposed AQS based on epidemiologic data:

1.0 mg/m^3 soluble nickel compounds / 1550 = 0.0006 mg/m^3 or 0.6 µg/m^3

10.0 mg/m^3 less soluble nickel compounds / 1550 = 0.006 mg/m^3 or 6 µg/m^3

Based on the available scientific evidence and judgement, an appropriate AQS for nickel compounds is 0.0006 mg/m^3 or 0.6 µg/m^3, as an annual average. Assuming European ambient air levels range from 0.001 to 0.03 µg/m^3 (CEPN, 1996), this AQS would provide for a large margin-of-exposure (calculated as the estimated NOAEL divided by the estimated ambient exposure level) which is in excess of 3,000. A margin of exposure greater than 100 is presumed to represent a "*de minimis*" level of risk by the United States Environmental Protection Agency. The recommendation of an annual average is justified given that AQS primarily based on chronic effects are typically defined on an annual basis. Further, the cancer cases in the epidemiologic studies used to develop the nickel AQS were exposed to nickel compounds for many years (at least 5 to 10 years) (RICNCM, 1990).

12. DERIVATION OF A NICKEL AIR QUALITY STANDARD USING A LINEAR NON-THRESHOLD APPROACH

The CEPN performed a risk assessment for nickel based on respiratory cancer in both humans and animals using a linear non-threshold approach (CEPN, 1996). The epidemiology studies on occupational exposures led to a unit risk estimate of 2.5 10^{-4} for lung cancer, for a full lifetime continuous exposure to 1 $\mu g/m^3$. To account for physical and chemical differences in exposure between nickel refinery workers and the general population, adjustments were made to the unit risk estimate using the results from animal studies which permitted a distinction between the effects of nickel oxide and nickel subsulfide. These calculations suggested a unit risk of 0.4 10^{-4} for lung cancer, for a full lifetime continuous exposure to 1 $\mu g/m^3$ of nickel oxide, and 3 10^{-4} for lung cancer, for a full lifetime of continuous exposure to 1 $\mu g/m^3$ of nickel subsulfide. It is noteworthy that the unit risk estimates derived based on the human information are very similar to those derived based on the animal data.

The CEPN concludes that "considering the fact that in the case of ambient air exposures, Ni_3S_2 is not the relevant nickel compound, and that there is a maximum of a few percents of total nickel as NiO, if any, the unit risk of lung cancer of 1 10^{-7} for an exposure of 1 ng/m^3 is proposed as a precautionary value for assessing the risk in ambient air for the general public." The CEPN also selected representative emission values for nickel ambient air levels in European countries and calculated the predicted lifetime and average annual risk of lung cancer. The results of these calculations are shown in **Table 8** below.

Table 8: EUROPEAN AMBIENT NICKEL EXPOSURE LEVELS AND ESTIMATED LIFETIME AND AVERAGE ANNUAL RISK OF LUNG CANCER

REPRESENTATIVE VALUE OF AMBIENT AIR LIFETIME EXPOSURE LEVEL ($\mu g/m^3$)	LIFETIME RISK OF LUNG CANCER	AVERAGE ANNUAL RISK OF LUNG CANCER
0.001	10^{-7}	1.4 10^{-9}
0.01	10^{-6}	1.4 10^{-8}
0.03	3 10^{-6}	4.3 10^{-8}

Source: CEPN, 1996

The CEPN states that the individual level of risk based on the above calculations "are far below the level considered as significant. An annual risk of death in the range of 10^{-6} to 10^{-7} is generally considered as a negligible level of risk". However, the CEPN suggests that risk managers may consider that, based on the size of the 1990 European population (327 million), nickel exposures would lead to an annual collective risk of about 4 to 5 cases of lung cancer in excess per year for the whole European population, for an exposure level of 0.01 $\mu g/m^3$. For perspective there are about 120,000 lung cancers per year in Europe.

The CEPN does not recommend a specific AQS for nickel based on their calculations. However, based on the unit risk values calculated and the assumed representative ambient exposure levels, it appears that an exposure range between 0.01 and 0.03 $\mu g/m^3$ would be protective of the public's health.

The World Health Organization (WHO, 1998) has also performed a risk assessment for nickel based on respiratory cancer in one occupationally exposed cohort, using a linear non-threshold approach. The lifetime risk was estimated at 3.8×10^{-4} for continuous lifetime exposure to 1 $\mu g/m^3$. The WHO states that the assumption of a linear dose response precludes a recommended safe level for nickel compounds.

13. DISCUSSION AND CONCLUSION

This report provides an overview of the two approaches for deriving a recommended AQS for nickel. A threshold/safety factor approach is presented, along with a linear non-threshold approach developed by the CEPN (CEPN, 1996). Using these two approaches, recommended AQS values of 0.01 $\mu g/m^3$ to 0.6 $\mu g/m^3$ were derived.

Both approaches indicate that respiratory cancer is the critical health effect for deriving an AQS. Also, the choice of human versus animal datasets for developing the AQS does not strongly influence the final recommended value. However, the choice of extrapolation method (i.e., a threshold/safety factor versus linear non-threshold approach) has an impact on the recommended AQS value. Using the threshold/safety factor approach, a 0.6 $\mu g/m^3$ (annual average) AQS is recommended to protect the public's health from both carcinogenic and noncarcinogenic health effects. In contrast, a recommended AQS range of 0.01 to 0.03 $\mu g/m^3$ (annual average) was derived based on the linear non-threshold unit risks developed by CEPN; this range of possible AQS values is approximately an order of magnitude lower than the value derived using a threshold/safety factor approach.

There are strengths and weaknesses associated with each of the approaches described above. A common weakness of both approaches is that nickel exposures in animal and human studies are qualitatively different from exposures present in ambient air. As the summary table below (**Table 9**) indicates the strongest evidence from epidemiology studies is for nickel subsulfide which has very limited relevance for risk assessment of ambient air nickel compounds. Further, the contributory evidence in the epidemiology studies on oxidic nickel, which includes nickel oxide, relates to only a portion of ambient nickel. The evidence from animal studies is also limited in that nickel oxide and nickel subsulfide are only present in minimal to small quantities in ambient air. Thus, the evaluation of the carcinogenicity of nickel compounds in ambient air is limited by the fact that exposures in the health datasets do not qualitatively match ambient exposures. However, as exposures in human studies tend to represent a "worst case" scenario, any recommended AQS based on these data is likely to offer an additional margin-of-safety.

Another factor to consider is the lack of correlation between nickel solubility and carcinogenicity between animals and humans. In particular, occupational epidemiology studies indicate that soluble nickel compounds are associated with respiratory cancer while animal studies of soluble nickel compounds do not demonstrate carcinogenicity. This lack of correlation between nickel solubility and carcinogenicity may be due to differences in exposure between animals and humans (i.e., workers in occupational epidemiology studies may have been exposed to compounds other than nickel or the dose to which animals were exposed were under the threshold for carginogenicity). Additionally, differences in regional deposition and uptake of airborne nickel compounds in the airways of animals and humans may account for differences in biological response.

Table 9: COMPARISON OF NICKEL EXPOSURES FROM AMBIENT AIR AND NICKEL EXPOSURES IN STUDIES OBSERVING A RESPIRATORY CANCER RISK

NICKEL COMPOUND	NICKEL COMPOUNDS IN AMBIENT AIR (% OF TOTAL NICKEL CONCENTRATION)	EU CARCINOGEN CLASSIFICATION	SOLUBILITY	OCCUPATIONAL EPIDEMIOLOGY RESULTS*	ANIMAL STUDY RESULTS (NATIONAL TOXICOLOGY PROGRAM)*	
					RAT	MOUSE
Nickel Sulfate	Approximately 50%	Category 3	Soluble	+	-	-
Nickel Oxide	Maximum of 8%	Category 1	Insoluble	+	+	-
Metallic Nickel	Minimal	Category 3	Insoluble	-	-	-
Nickel Subsulfide	Minimal	Category 1	Slightly soluble	++	+	-

CEPN, 1996 - Source for information on nickel compounds in ambient air

* Strength of evidence of a respiratory cancer risk denoted as - (no association or not tested), + (positive evidence), or ++ (strong positive evidence)

Overall, the weight of the evidence strongly supports the use of a threshold/safety factor approach for deriving a scientifically justified and defensible AQS for nickel. Factors that strongly support the use of the threshold/safety factor approach include:

- the existence of a NOAEL for pulmonary inflammation of 130 μg Ni/m^3 (nickel dust) derived from inhalation studies,
- the lack of carcinogenic response in the absence of pulmonary inflammation,
- the presence of good evidence for an empirical threshold for lung and nasal cancer in epidemiology studies of occupationally exposed groups.
- the presence of a NOAEL for pulmonary carcinogenesis of approximately 100 μg/m^3 observed in recent rodent studies conducted with three nickel compounds administered by inhalation, the relevant route of exposure.
- no evidence of genotoxicity in *in vivo* studies conducted by the inhalation route of exposure in humans and rodents.

In addition, a recent paper exploring non-cancer risk assessment for nickel compounds provides additional support for the existence of a threshold for nickel toxicity (Haber et al., 1998). Using benchmark response modeling techniques and the NTP chronic bioassay data, a benchmark concentration of 0.48 μg/m^3 for nickel sulfate was derived for the most sensitive endpoint, atrophy of olfactory epithelium in female rats. Inclusion of a threshold parameter improved the fit of the model. Furthermore, in the low dose region of the dose-response curve, the model estimated the same response as background for the observed effect (i.e., atrophy of olfactory epithelium). This demonstrates a lack of biological response below a certain threshold of nickel exposure.

Finally, the derived value is consistent with the conclusion of an international expert panel of scientists that the risk to the general population from exposure to small concentrations of nickel compounds is negligible (RICNCM, 1990). Also, the margin-of-exposure between the estimated NOAEL based on the occupational epidemiology data and levels of nickel present in European ambient air is large (greater than 3,000). Further, existing chemical composition differences between exposures in the occupational epidemiology studies versus ambient air are likely to provide an additional margin-of-safety. While the uncertainty regarding genotoxicity of nickel compounds may support the use of a linear non-threshold approach, the combined weight of the evidence suggests that this approach would likely produce an unduly conservative AQS value. Accordingly, a value of 0.6 $\mu g/m^3$ (annual basis) is recommended for nickel to protect the general public against carcinogenic and other potential hazardous effects associated with exposure to both soluble and less soluble nickel compounds.

14. DATA GAPS AND FUTURE RECOMMENDATIONS

An AQS for nickel could be enhanced by addressing several key data gaps. First, more detailed characterization of exposure in the epidemiology studies of workers involved in nickel refining and use is needed to completely assess the dose-response relationships for specific nickel compounds. Future studies should concentrate on assessing the particle size, presence of confounding exposures, and species and concentration of nickel exposure in more current time periods. With these data, the potential health effects of all nickel species could be more completely assessed.

Another existing data gap is the lack of morbidity information for nickel exposed populations. The majority of epidemiology studies have examined mortality among workers occupationally exposed to nickel. Analytical epidemiology studies of morbidity, particularly pulmonary health outcome, would be useful to more completely assess the health impact of nickel exposure. Also, it would be beneficial if these data were collected for non-occupationally exposed populations. The epidemiology data to date have been collected almost solely for occupationally exposed groups; thus, these data may not represent sensitive subpopulations such as the very young or elderly, although these populations were taken into account through the use of safety margins

Further data are also needed regarding the effects of smoking and nickel exposure on cancer risk. The RICNCM (1990) and Shen and Zhang (1994) have both noted the need for further research regarding the relationship between cigarette smoking and nickel-induced lung cancer. This research is justified based on the high percentage of smokers among nickel-exposed workers and the carcinogenic effect of cigarette smoking on lung cancer. These types of data would allow for a more complete characterization of carcinogenic risk by allowing investigators to examine whether exposure to carcinogens from cigarette smoking, when combined with nickel exposures from other sources, has a synergistic effect on cancer risk.

Yet another data gap relates to the lack of information on personal exposures and internal dose among members of the general population. Measurements on factors such as DNA alkylation and Hb alkylation could possibly provide useful information on personal exposures in terms of target dose, which may be beneficial in assessing risks of nickel exposures to the general population.

Finally, the carcinogenicity of nickel compounds other than those covered in this review is an important area that has not been completely investigated. In particular, further research may be warranted regarding cancer risk among nickel users. To date, the epidemiology studies of these workers have not shown a clear indication of an increased cancer risk, although several studies have found possible indications of a risk.

15. REFERENCES

Adkins, B. Jr., Richards, J.H. and Gardner, D.E., "Enhancement of Experimental Respiratory Infection Following Nickel Inhalation," *Environ. Res.*, 1979, 20:33-42.

Agency for Toxic Substances and Disease Registry (ATSDR), "Toxicological Profile for Nickel (update)," U.S. Dept. Health and Human Services, Public Health Service, ATSDR, 1997.

Amacher, P., "Induction of Trifluorothymidine Resistant Mutants by Metal Ions in L5178Y/TK+/- Cells," *Mutat. Res.*, 1980, 78:279-288.

American Conference of Governmental Industrial Hygienists (ACGIH), Threshold Limit Values for Chemical Substances and Physical Agents, Cincinnati, ACGIH, 1998.

American Petroleum Institute (API), "Air Quality Monographs: Monograph No. 70-14 Nickel," Washington, DC, API, 1968.

Andersen, O., "Effects of Coal Combustion Products and Metal Compounds on Sister Chromatid Exchange (SCE) in a Macrophage Cell Line," *Environ. Health Perspect*., 1983, 47:239-253.

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

Arlauskas, A., Baker, R.S., Bonin, A.M., et al., "Mutagenicity of Metal Ions in Bacteria," *Environ. Res*., 1985, 36:379-388.

Benson, J.M., Cheng, Y.S. and Medinsky, M.A., "Toxicokinetics of ^{63}Ni After Inhalation of Nickel Sulfate Hexahydrate and Nickel Oxide," Annual Report of the Inhalation Toxicology Research Institute, December 1991, pp. 42-43.

Benson, J.M., Burt, D.G., Cheng, Y.S., et al., “Biochemical Responses of Rat and Mouse Lung to Inhaled Nickel Compounds,” *Toxicology*, 1989, 57:255-266.

Benson, J.M., Burt, D.G., Carpenter, R.L., et al., "Comparative Inhalation Toxicity of Nickel Sulfate to F344/N Rats and B6C3F1 Mice Exposed for Twelve Days," *Fundam. Appl. Toxicol*., 1988, 10:164-178.

Benson, J.M., Carpenter, R.L., Hahn, F.F., et al., "Comparative Inhalation Toxicity of Nickel Subsulfide to F344/N Rats and B6C3F1 Mice Exposed for Twelve Days," *Fundam. Appl. Toxicol.,* 1987, 9:251-265.

Bernacki, E.J., Parsons, G.E., Roy, B.R., Mikac-Devic, M., Kennedy, C.D., Sunderman, F.W., "Urine nickel concentrations in nickel exposed workers," *Ann. Clin. Lab. Sci.,* 1978, 8:184-189.

Biedermann, K.A. and Landolph, J.R., "Induction of Anchorage Independence in Human Diploid Foreskin Fibroblasts by Carcinogenic Metal Salts," *Cancer Res*., 1987, 47:3815-3823.

Biggart, N.W. and Murphy, E. Jr., "Analysis of Metal-induced Mutations Altering the Expression or Structure of a Retroviral Gene in a Mammalian Cell Line," *Mutat. Res*., 1988, 198:115-130.

Biggart, N.W., Gallick, G.E. and Murphy E.C., Jr., "Nickel-induced Heritable Alterations in Retroviral Transforming Gene Expression," *J. Virol*., 1987, 61:2378-2388.

Biggart, N.W. and Costa, M., "Assessment of the Uptake and Mutagenicity of Nickel Chloride in Salmonella Tester Strains," *Mutat. Res*., 1986, 175:209-215.

Bingham, E., Barkley, W., Zerwas, M., et al., "Responses of Alveolar Macrophages to Metals. I. Inhalation of Lead and Nickel," *Arch. Environ. Health*, 1972, 25:406-414.

Calabrese, E.J., Kenyon E.M., *Air Toxics and Risk Assessment*, Chelsea, Lewis Publishers, Inc., 1991.

Centre d'Entude sur I'Evaluation de la Protection dans le Domaine Nucleaire (CEPN), "Risk Assessment Associated with the Nickel in the Ambient Air: Review of the European Situation," CEPN Report No. 249, December 1996.

Ciccarelli, R.B. and Wetterhahn, K.E., "Nickel Distribution and DNA Lesions Induced in Rat Tissues by the Carcinogen Nickel Carbonate," *Cancer Res*., 1982, 42:3544-3549.

Cohen, S.M. and Ellwein, L.B., "Cell Proliferation in Carcinogenesis," *Science*, 1990, 249:1007-1011.

Conway, K. and Costa, M., "Nonrandom Chromosomal Alterations in Nickel-transformed Chinese Hamster Embryo Cells," *Cancer Res*., 1989, 49:6032-6038.

Cornell R.G. and Landis J.R., "Mortality Patterns Among Nickel/Chromium Alloy Foundry Workers." In: Sunderman F.W., Jr., Aitio A., Berlin A., eds. *Nickel in the Human Environment*, IARC Scientific Publication No. 53, Lyon, IARC, 1984, pp. 87-94.

Costa, M., "Perspectives on the Mechanism of Nickel Carcinogenesis Gained From Models of *In Vitro* Carcinogenesis," *Environ. Health Perspect*., 1989, 81:73-76.

Costa, M. and Heck, J.D., "Specific Nickel Compounds as Carcinogens," *Trends Pharmacol. Sci.*, 1982, 3:408-410.

Costa, M., Heck, J.D. and Robinson, S.H., "Selective Phagocytosis of Crystallene Metal Sulfide Particles and DNA Strand Breaks as a Mechanism for the Induction of Cellular Transformation," *Cancer Res*., 1982, 42:2757-2763.

Costa, M. and Mollenhauser, H.H., "Carcinogenic Activity of Particulate Metal Compounds is Proportional to Their Cellular Uptake," *Science*, 1980, 209:515-517.

Cox, J.E., Doll, R., Scott, W.A., et al., "Mortality of Nickel Workers: Experience of Men Working with Metallic Nickel," *Br. Jr. Ind. Med*., 1981, 38:235-239.

Cragle, D.L., Hollis, D.R., Newport, T.H., et al., "A Retrospective Cohort Mortality Study Among Workers Occupationally Exposed to Metallic Nickel Dust at the Oak

Ridge Gaseous Diffusion Plant," In: Sunderman, F.W., Jr., Aitio, A., Berlin, A., eds. *Nickel in the Human Environment*, IARC Scientific Publication No. 53, Lyon, IARC, 1984, pp. 57-64.

Critical Reviews in Toxicology (CRC), "Toxicity and Carcinogenicity of Nickel Compounds", Volume 19, 1989, 341-384.

Curstedt, T., Casarett-Bruce, M., and Camner, P., "Changes in Glycerophosphatides and Their Ether Analogs in Lung Lavage of Rabbits Exposed to Nickel Dust", *Exp. Mol. Pathol.*, 1984, 41:226.

Deknudt, G.H. and Leonard, A., "Mutagenicity Tests With Nickel Salts in the Male Mouse," *Toxicology*, 1982, 25:289-292.

Deng, C.A., Lee, H.C.H., Xian, H.L., et al., "Chromosomal Aberrations and Sister Chromatid Exchanges of Peripheral Blood Lymphocytes in Chinese Electroplate Workers: Effect of Nickel and Chromium," *J. Trace Elements Exp. Med*., 1988, 1:57-62.

Deng C.A., Ou, B., Huang, J., et al., "Cytogenetic Effects of Electroplating Workers (Chin.)," *Acta. Sci. Circumst.*, 1983, 3:267-271.

DiPaolo, J.A. and Casto, B.C., "Quantitative Studies of *In Vitro* Morphological Transformation of Syrian Hamster Cells by Inorganic Metal Salts," *Cancer Res*., 1979, 39:3008-3013.

Dourson, M.L., Felter, S.P., and Robinson, D., "Evolution of Science-based Uncertainty Factors in Noncancer Risk Assessment," *Reg. Toxicol. Pharmacol*., 1996, 24:108-120.

Dourson, M.L. and Stara, J.F., "Regulatory History and Experimental Support of Uncertainty (Safety) Factors," *Reg. Toxicol. and Pharmacol*., 1983, 3:224-238.

Dunnick, J.K., Elwell, M.R., Benson, J.M., et al., "Lung Toxicity After 13-week Inhalation Exposure to Nickel Oxide, Nickel Subsulfide, or Nickel Sulfate Hexahydrate in F344/N Rats and B6C3F1 Mice," *Fundam. Appl. Toxicol*., 1989, 12:584-594.

Dunnick, J.K., Benson, J.M., Hobbs, C.H., et al., “Comparative Toxicity of Nickel Oxide, Nickel Sulfate Hexahydrate, and Nickel Subsulfide after 12 Days of Inhalation Exposure to F344/N Rats and B6C3F1 Mice,” *Toxicology*, 1988, 50:145-156.

ECETOC, “Assessment factors in human health risk assessment”, Technical Report No. 68. Brussels, 1995.

Elias, Z., Muir, J.M., Pierre, F., et al., “Chromosome Aberrations in Peripheral Blood Lymphocytes of Welders and Characterization of Their Exposure by Biological Sample Analysis,” *J. Occup. Med*., 1989, 31:477-483.

Exxon Biomedical Sciences, Inc. (EBSI), "Determination of Air Quality Standard Bands for Benzene," Report prepared for CONCAWE, August 1994.

Gilman, J.P.W., "Metal Carcinogenesis II: A Study on the Carcinogenic Activity of Cobalt, Copper, Iron and Nickel Compounds," *Cancer Res*., 1962, 22:159-162.

Goldberg, M., Goldberg, P., Leclerc, A., et al., "Epidemiology of Respiratory Cancers Related to Nickel Mining and Refining in New Caldonia (1978-1984)," *Int. J. Cancer*, 1987, 40:300-304.

Graham, J.A., Miller, F.J., Daniels, M.J., et al., "Influence of Cadmium, Nickel and Chromium on Primary Immunity in Mice," *Environ. Res.*, 1978, 16:77-87.

Grandjean, P., Andersen, O., and Nielsen, G.D., "Carcinogenicity of Occupational Nickel Exposures: An Evaluation of the Epidemiological Evidence," *Am. J. Ind. Med.*, 1988, 13:193-209.

Grandjean, P., "Human Exposure to Nickel." In: Sunderman, F.W., Jr., ed*., Nickel in the Human Environment*, Proceedings of a joint symposium, IARC Scientific Publication No. 53, Lyon, IARC, 1984, pp. 469-485.

Green, M. and Bridges, P., "Use of Simplified Fluctuation Test to Detect Low Levels of Mutagens," *Mutat. Res.*, 1976, 38:33-42.

Haber, L.T., Allen, B.C., Kimmel, C.A., "Non-cancer risk assessment for nickel compounds: issues associated with dose-response modeling of inhalation and oral exposures," *Toxicol. Sci.*, 1998, 43:213-339.

Haley, P.J., Shopp, G.M., Benson, J.M., et al., "The Immunotoxicity of Three Nickel Compounds Following 13 week Inhalation Exposure in the Mouse," *Fundam. Appl. Toxicol*., 1990, 15:476-487.

Hamilton-Koch, W., Snyder, R.D. and Lavelle, J.M., "Metal-induced DNA Damage and Repair in Human Diploid Fibroblasts and Chinese Hamster Ovary Cells," *Chem. Biol. Interact*., 1986, 59:17-28.

Hansen, K. and Stern, R.M., "Toxicity and Transformation Potency of Nickel Compounds in BHK Cells *In Vitro*." In: Sunderman, F.W., Jr., Aitio, A., Berlin A., eds., *Nickel in the Human Environment*, IARC Scientific Publication No. 53., Lyon, IARC, 1984, pp. 193-200.

Hartwig, A. and Beyersmann, D., "Enhancement of UV-induced Mutagenesis and Sister-chromatid Exchanges by Nickel Ions in V79 Cells: Evidence for Inhibition of DNA Repair," *Mutat. Res*., 1989, 217:65-73.

Hattis, D, Erdich, L and Ballow, M. "Human Variability in Susceptibility to Toxic Chemicals - a Preliminary Analysis of Pharmacokinetic Data from Normal Volunteers." *Risk Analysis*, 1987, 7:415-426.

Health Council of the Netherlands, Committee on the evaluation of the carcinogenicity of chemical substances. Benzene. The Hague, 1997.

Health and Safety Executive (UK HSE), "EH40/95, Occupational Exposure Limits 1995", 1995.

Health and Safety Executive (UK HSE), "Toxicology Review 19, The Toxicity of Nickel and its Inorganic Compounds", 1988.

Hogetveit, A.C., Barton, R.T., Kostol, C.O., "Plasma nickel as a primary index of exposure in nickel refining," *Ann. Occup. Hyg.*, 1978; 21:113-120.

Horie, A., Tanaka, I., Haratake, J., et al., "Electron Microscopy of Pulmonary Lesions Including Carcinoma, Induced by Inhalation Exposure of Rats to Nickel-oxide Aerosol." In: Brown, S.S., Sunderman, F.W., Jr., eds., *Progress in Nickel Toxicology*, Proceedings of the 3rd International Congress on Nickel Metabolism and Toxicology, Oxford, UK, Blackwell, 1985, pp. 41-44.

Hsie, A.W., Johnson, N.P., Couch, D.B., et al, "Quantitative Mammalian Cell Mutagenesis and a Preliminary Study of the Mutagenic Potential of Metallic Compounds." In: Khararsch, N., ed., *Trace Metals in Health and Disease*, New York, Raven Press, 1979, pp. 55-69.

International Agency for Research on Cancer (IARC), "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 49, *Chromium Nickel and Welding*," Lyon, IARC, 1990, pp. 257-445.

Johansson, A. and Camner, P., "Adverse Effects of Metals on the Alveolar Part of the Lung," *Scanning Electron. Microsc*., 1986, 2:631-637.

Johansson, A., Curstedt, T., Robertson, B., et al., "Rabbit Lung After Inhalation of Soluble Nickel. II. Effects on Lung Tissue and Phospholipids," *Environ. Res.,* 1983, 31:399-412.

Johansson, A., Camner, P. and Robertson, B., "Effects of Long-term Nickel Dust Exposure on Rabbit Alveolar Epithelium," *Environ. Res*., 1981, 25:391-402.

Kanematsu, M., Hara, M. and Kada, T., 'Rec-assay and Mutagenicity Studies on Metal Compounds," *Mutat. Res.*, 1980, 77:109-116.

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

Kasprzak, K.S., Gabryel, P. and Jarczewska, K., "Carcinogenicity of Nickel (II) Hydroxides and Nickel (II) Sulfate in Wistar Rats and its Relation to the *In Vitro* Dissolution Rates," *Carcinogenesis*, 1983, 4:275-279.

Kiilunen, M., Utela, J., Rantanen, T., Norppa, H., Tossavainen, A., Koponen, M., Paakkulainen, H., Aitio, A., "Exposure to soluble nickel in electrolytic nickel refining," *Ann. Occup. Hyg.,* 1997, 41:167-188.

Klus, H. and Kuhn, H., "Distribution of Different Tobacco Smoke Constituents in Mainstream and Sidestream Smoke (A review)," *Beitr. Tabakforsch*., 1982, 11:229-265.

Larramendy, M.L., Popescu, N.C. and DiPaolo, J.A., "Induction by Inorganic Metal Salts of Sister Chromatid Exchanges and Chromosome Aberrations in Human and Syrian Hamster Cell Strands," *Environ. Mutagen*., 1981, 3:597-606.

Lechner, J.F., Tokiwa, T., McClendon, I.A., et al., "Effects of Nickel Sulfate on Growth and Differentiation of Normal Human Bronchial Epithelial Cells," *Carcinogenesis,* 1984, 5:1697-1703.

Lewis, S.C., Lynch, J.R. and Nikiforov, A.I., "A New Approach to Deriving Community Exposure Guidelines from "No-Observed-Adverse-Effect-Levels"," *Reg. Toxicol. and Pharmacol.*, 1990, 11:314-330.

Lin, S., Fitzgerald, E., Munsie, J.P., "Residential exposure to nickel released from industrial facilities and childhood asthma hospitalizations (abstract)," *Am J Epidemiol* 1998, 147 (suppl):36.

Lumb, G. and Sunderman, F.W., Sr., "The Mechanism of Malignant Tumor Induction By Nickel Subsulfide," *Ann. Clin. Lab. Sci*., 1988, 18:353-366.

Mangus, K., Andersen, A., and Hogetveit, A.C., "Cancer of Respiratory Organs Among Workers at a Nickel Refinery in Norway," *Int. J. Cancer*, 1982, 30:681-685.

Marzin, D.R. and Phi, H.V., "Study of Mutagenicity of Metal Derivatives with *Salmonella Typhimurium* TA102," *Mutat. Res.,* 1985, 155:49-51.

Mathur, A.K., Datta, K.K., Tandon, S.K., et al., "Effect of Nickel Sulphate on Male Rats," *Bull. Environ. Contam. Toxicol.,* 1977, 17:241-248.

McGregor, D.B., Brown, A., Cattanch, P., et al., “Responses of the L5178Y TK+/TK- Mouse Lymphoma Cell Forward Mutation Assay, 3.72 Coded Chemicals," *Environ. Mol. Mutagen*., 1988, 12:85-154.

McMichael, A.J., "Standard Mortality Ratios and the `Healthy Worker Effect': Scratching Below the Surface," *J. Occup. Med.*, 1976, 18:165-168.

Melnick, R.L., Kohn, M.C., and Portier, C.J., "Implications for Risk Assessment of Suggested Nongenotoxic Mechanisms of Chemical Carcinogenesis." *Environ. Health Perspect.*, 1996, 104(Suppl 1):123-134.

Miura, T., Patierno, S.R. and Sakuramoto, T., "Morphological and Neoplastic Transformation of C3H/10tl/2C18 Mouse Embryo Cells by Insoluble Carcinogenic Nickel Compounds," *Environ. Mol. Mutagen.,* 1989, 14:65-78.

Miyaki, M., Akamatsu, N., Ono, T., et al., "Mutagenicity of Metal Cations in Cultured Cells from Chinese Hamster," *Mutat. Res.*, 1979, 68:259-263.

Moolenaar, R. J., "Carcinogen Risk Assessment: International Comparison," *Reg. Toxicol. Pharmacol.*, 1994, 20:302-336.

Muir, D.C.F., Julian, J.A., Jadon, N., et al., “Prevalence of Small Opacities in Chest Radiographs of Nickel Plant workers,” *Br. J. Ind. Med.*, 1993, 50:428-431.

Muhle, H., Bellmann, B., Takenaka, S., et al., "Chronic Effects of Intratracheally Instilled Nickel-containing Particles in Hamsters," In: E. Nieboer and J.O. Nriagu (eds.), *Nickel and Human Health: Current Perspectives*, New York: John Wiley and Sons, Inc., 1992, pp. 467-479.

National Institute of Occupational Safety and Health (NIOSH), "Criteria for a Recommended Standard for Occupational Exposure to Inorganic Nickel," NIOSH, Department of Health, Education, and Welfare, 1977.

National Air Toxics Information Clearinghouse (NATICH), "Report on State, Local and EPA Air Toxics Activities," 1996.

National Academy of Sciences (NAS), "Nickel," Washington DC, National Academy Press, 1975.

National Toxicology Program (NTP), Technical Report on the "Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313-99-1) in F344/N Rats and $B6C3F_1$ Mice (Inhalation Studies)," Technical Report Series Number 451, NIH Publication No. 96-3363, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, 1996a.

National Toxicology Program (NTP), Technical Report on the "Toxicology and Carcinogenesis Studies of Nickel Subsulfide (CAS No. 12035-72-2) in F344/N Rats and $B6C3F_1$ Mice (Inhalation Studies)," Technical Report Series Number 453, NIH Publication No. 96-3369, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, 1996b.

National Toxicology Program (NTP), Technical Report on the "Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate (CAS No. 10101-97-0) in F344/N Rats and $B6C3F_1$ Mice (Inhalation Studies)," Technical Report Series Number 454, NIH Publication No. 96-3370, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, 1996c.

New York State Department of Environmental Conservation (NYS DEC), "New York State Air Quality Report Ambient Air Monitoring System" (DAR-89-1). Division of Air Resources, NYS DEC, 1988.

New York State Department of Health (NYSDH), Bureau of Toxic Substance Assessment, "Ambient Air Criteria Document: Nickel," Albany, New York State Department of Health, Bureau of Toxic Substance Assessment, 1989.

NiPERA (in collaboration with Eurometaux), "Occupational Exposure Limits Criteria Document for Nickel and Nickel Compounds. Volume 1: Summary, Conclusions, and Recommendations." Report prepared for the European Commission, Directorate - General V, Public Health and Safety at Work Directorate, December 24, 1996.

Occupational Safety and Health Administration (OSHA), "Air Contaminants. Final Rule," *Fed. Reg.,* 1989, 54:2332-2983.

Occupational Safety and Health Administration (OSHA), "Air Contaminants, Table Z-1, Amended by Federal Regulation, 1993." *Fed. Reg.*, 1993, 58:35338-35351, corrected by *Fed. Reg.,* 1993, 58:40191.

Ohno, H., Hanaoka, F. and Yamada, M., "Inducibility of Sister Chromatid Exchanges by Heavy Metal Ions," *Mutat. Res*., 1982, 104:141-145.

Ontario Ministry of Environment and Energy (OMOEE), "Rationale Document for the Development of Ontario Air Standards for Nickel and its Compounds," Consultation Draft, October 1996.

Ottolenghi, A.D., Haseman,J.K., Payne, W.W., et al., "Inhalation Studies of Nickel Sulfide in Pulmonary Carcinogenesis of Rats," *J. Natl. Cancer Inst.*, 1974, 54:1165-1172.

Patierno, S.R. and Costa, M., "DNA-protein Cross-links Induced by Nickel Compounds in Intact Cultured Mammalian Cells," *Chem. Biol. Interact.,* 1985, 55:75-91.

Paustenbach, D.J., Jernigan, J.D., Finley, B.L., et al., "The Current Practice of Health Risk Assessment: Potential Impact on Standards for Toxic Air Contaminants," *J. Air Waste Manage. Assoc.*, 1990, 40:1620-1630.

Pikalek, P. and Necasek, J., "The Mutagenic Activity of Nickel in *Cornebacterium* sp. *folia*," *Microbiol.,* 1983, 26:17-21.

Pohl, H.R. and Abadin, H.G., "Utilizing Uncertainty Factors in Minimal Risk Levels Derivation," *Reg. Toxicol. Pharmacol.,* 1995, 22:180-188.

Polednak, A.P., "Mortality Among Welders, Including a Group Exposed to Nickel Oxides," *Arch. Environ. Health,* 1981, 36:235-242.

Pott, F., Ziem, U., Reiffer, F.J., et al., "Carcinogenicity Studies on Fibres, Metal Compounds, and Some Other Dusts in Rats," *Exp. Pathol.*, 1987, 32:129-152.

Rasmuson, A., "Mutagenic Effects of Some Water-soluble Metal Compounds in a Somatic Eye-color Test System in *Drosophila Melanogaster*," *Mutat. Res.,* 1985, 157:157-162.

Renwick, A.G., "Data Derived Safety Factors for the Evaluation of Food Additives and Environmental Contaminants," *Food Addit. Contam.,* 1993, 10:275-305.

Renwick, A.G., "Safety Factors and Establishment of Acceptable Daily Intakes," *Food Addit. and Contam.,* 1991, 8:135-150.

Report of the International Committee on Nickel Carcinogenesis in Man (RICNCM), Doll, R., Chair., *Scand. J. Work Environ. Health,* 1990, 16:1-84.

Robinson, S.H. and Costa, M., "The Induction of DNA Strand Breakage by Nickel Compounds in Cultured Chinese Hamster Ovary Cells," *Cancer Lett.,* 1982, 15:35-40.

Rodriquez-Amaiz, R. and Ramos, P., "Mutagenicity of Nickel Sulphate *in Drosophila Melanogaster*," *Mutat. Res.,* 1986, 170:115-117.

Sabbioni, E., Minoia, C., Pietra, R., Fortaner, S., Gallorini, M., Saltelli, A., "Trace element reference values in tissues from inhabitants in the European Community. II. Examples of strategy adopted and trace element analysis of blood, lymph nodes and cerebrospinal fluid of Italian subjects," *Sci. Total Environ.*, 1992, 120:39-62.

Saxholm, H.J.K., Reith, A. and Brogger, A., "Oncogenic Transformation and Cell Lysis in C3H/10T1/2 Cells and Increased Sister Chromatid Exchange in Human Lymphocytes by Nickel Subsulfide," *Cancer Res*., 1981, 41:4136-4139.

Sen, P., Conway, K. and Costa, M., "Comparison of the Localization of Chromosome Damage Induced by Calcium Chromate and Nickel Compounds," *Cancer Res.,* 1987, 47:2142-2147.

Sen, P. and Costa, M., "Incidence and Localization of Sister Chromatid Exchanges Induced by Nickel and Chromium Compounds," *Carcinogenesis,* 1986, 7:1527-1533.

Shen, H.M. and Zhang, Q.F., “Risk Assessment of Nickel Carcinogenicity and Occupational Lung Cancer,” *Environ. Health Perspect.*, 1994, Supp. 1:275-282.

Singh, I., "Induction of Gene Conversion and Reverse Mutation by Manganese Sulphate and Nickel Sulphate in *Saccharomyces Cerevisiae*," *Mutat. Res.*, 1984, 137:47-49.

Smialowicz, R.J., Rogers, R.R., Riddle, M.M., et al., "Immunologic Effects of Nickel. II. Suppression of Natural Killer Cell Activity," *Environ. Res.*, 1985, 36:56-66.

Sobti, R.C. and Gill, R.K., "Incidence of Micronuclei and Abnormalities in the Head of Spermatozoa Caused by the Salts of a Heavy Metal Nickel," *Cytolgia*., 1989, 54:249-254.

Spiegelberg, T., Koerdel, W. and Hochrainer, D., "Effect of NiO Inhalation on Alveolar Macrophages and Humoral Immune System of Rats," *Ecotoxicol. Environ. Safety,* 1984, 8:516-525.

Sunderman, F.W., Jr. and McCully, K.S., "Effects of Manganese Compounds on Carcinogenicity of Nickel Subsulfide in Rats," *Carcinogenesis,* 1983, 4:461-465.

Sunderman, F.W. and Sunderman, F.W., Jr., "Nickel Poisoning XI. Implication of Nickel as a Pulmonary Carcinogen in Tobacco Smoke," *Am. J. Clin. Pathol.,* 1961, 35:203-209.

Szadkowski, D., Schultze, H., Schaller, K.H., et al., "On the Ecological Significance of Heavy Metal Content of Cigarettes," *Arch. Hyg.,* 1969, 153:1-8.

Tanaka, I., Horie, A., Haratake, J., et al., "Lung Burden of Green Nickel Oxide Aerosol and Histopathological Findings in Rats After Continuous Inhalation," *Biol. Trace Elem. Res.*, 1988, 16:19-26.

Takenaka, S., Hochrainer, D. and Oldiges, H., "Alveolar Proteinosis Induced in Rats by Long-term Inhalation of Nickel Oxide." In: Brown, S.S., Sunderman, F.W., Jr., eds., *Progress in Nickel Toxicology*. Proceedings of the 3rd International Congress on Nickel Metabolism and toxicology, Oxford, U.K., Blackwell, 1985, pp. 89-92.

Tempelton, D.M., Sunderman, F.W., Herber, R.F.M., "Tentative reference values for nickel concentrations in human serum, plasma, blood, and urine: evaluation according to the TRACY protocol," *Sci. Total Environ.*, 1994, 148:243-251.

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

Tubiana, M., "The Carcinogenic Effect of Exposure to Low Doses of Carcinogens," *Br. J. Ind. Med.*, 1992, 49:601-605.

United States Environmental Protection Agency (U.S. EPA), “Arsenic, Inorganic (CAS #7440-38-2),” Integrated Risk Information System (on-line), Revision Date July 1, 1995.

United States Environmental Protection Agency (U.S. EPA), "Health Assessment Document for Nickel," Final Report, U.S. Environmental Protection Agency, 1986a.

United States Environmental Protection Agency (U.S. EPA), "Assessment of Nickel Subsulfide and Nickel Carbonyl as Potentially Toxic Air Pollutants," *Fed. Reg.*, 1986b, 51:34135-34139.

United States Environmental Protection Agency (U.S. EPA), "An Exposure and Risk Assessment for Nickel," Final Draft Report, U.S. Environmental Protection Agency, 1981.

Waksvik, H., Boysen, M. and Hogetveit, A.C., "Increased Incidence of Chromosomal Aberrations in Peripheral Lymphocytes of Retired Nickel Workers," *Carcinogenesis,* 1984, 5:1525-1527.

Waksvik, H. and Boysen, M., "Cytogenetic Analyses of Lymphocytes from Workers in a Nickel Refinery," *Mutat. Res*., 1982, 103:185-190.

Wehner, A.P., "Health and Environmental Effects of Aerosols: Biological Effects and Fate of Inhaled Man-made and Natural Aerosols in Animals Models," *J. Aerosol Science*, 1986, 17:305-315.

Wehner, A.P., Stuart, B.O. and Sanders, C.L., "Inhalation Studies with Syrian Golden Hamsters," *Prog. Exp. Tumor Res.,* 1979, 24:177-198.

Wehner, A.P., Busch, R.H., Olson, R.J., et al., "Chronic Inhalation of Nickel Oxide and Cigarette Smoke by Hamsters," *Am. Ind. Hyg. Assoc. J.,* 1975, 36:801-809.

Weischer, C.H., Kordel, W. and Hochrainer, D., "Effects of NiCl2 and NiO in Wistar Rats After Oral Uptake and Inhalation Exposure, Respectively," *Zentral. Bakteriol. Mikrobiol. Hyg. (B)*, 1980, 171:336-351.

Wong, P.K., "Mutagenicity of Heavy Metals," *Bull. Environ. Contam. Toxicol.,* 1988, 40:597-603.

Wulf, H.C., "Sister Chromatid Exchanges in Human Lymphocytes Exposed to Nickel and Lead," *Dan. Med. Bull.,* 1980, 27:40-42.

World Health Organization (WHO), "Air Quality Guidelines for Europe," WHO Regional Publications, European Region, 1998 (in press).

Yarita, T. and Nettenheim, P., "Carcinogenicity of Nickel Subsulfide for Respiratory Tract Mucosa," *Cancer Res.*, 1978, 38:3140-3145.

APPENDIX 1

INHALATION ANIMAL STUDIES OF NICKEL EXPOSURES

INHALATION NICKEL EXPOSURES: ANIMAL

SPECIES	EXPOSURE DURATION/ FREQUENCY	SYSTEM	NOAEL (mg Ni/m^3)	LOAEL (EFFECT)		REFERENCE	COMPOUND
				LESS SERIOUS (mg Ni/m^3)	SERIOUS (mg Ni/m^3)		
ACUTE EXPOSURE							
Immunological							
Mouse	2 Hour		0.1	0.250 (immunosuppression)		Graham et al., 1978	Chloride
Mouse	2 Hour		-	0.455 (increased susceptibility to disease)		Adkins et al., 1979	Chloride/sulfate
INTERMEDIATE EXPOSURE							
Death							
Rat	16 day 5 days/week 6 hours/day		1.6		3.3 (10%)	Benson et al., 1988	Sulfate
Rat	16 days 5 days/week 6 hours/day		3.6		7.3 (20%)	Benson et al., 1987	Subsulfide
Mouse	16 days 5 days/week 6 hours/day		0.8		1.6 (100%)	Benson et al., 1988	Sulfate
Mouse	16 days 5 days/week 6 hours/day		3.6		7.3 (100%)	Benson et al., 1987	Subsulfide
Systemic							
Rat	21 days GD 1 - 21 7 days/week 24 hours/day	Hepatic Renal Other	3.2 3.2	0.8 (11% decreased in maternal body weight gains)		Weischer et al., 1980	Oxide
Rat	21 days 7 days/week 24 hours/day	Hepatic Renal Other	3.2	0.8 (decreased liver weight) 0.8 (36% decrease in body weight gain)		Weischer et al., 1980	Oxide

INHALATION NICKEL EXPOSURES: ANIMAL (cont'd)

SPECIES	EXPOSURE DURATION/ FREQUENCY	SYSTEM	NOAEL (mg Ni/m^3)	LOAEL (EFFECT)		REFERENCE	COMPOUND
				LESS SERIOUS (mg Ni/m^3)	SERIOUS (mg Ni/m^3)		
Rat	28 days 7 days/week 24 hours/day	Hepatic Renal Other	0.4 0.8 0.2	0.8 (decreased liver weight) 0.4 (30% decrease in body weight gain)		Weischer et al., 1980	Oxide
Rat	1 month 5 days/week 6 hours/day	Respiratory	-	0.5 (bronchial gland hyperplasia)		Horie et al., 1985	Oxide
Rat	16 days 5 days/week 6 hours/day	Other	-		0.8 (emaciation)	Benson et al., 1988	Sulfate
Rat	16 days 5 days/week 6 hours/day	Hepatic Other	1.8	1.8 (13% decrease in body weight gain)	3.6 (liver atrophy) 3.6 (emaciation)	Benson et al., 1987	Subsulfide
Rat	13 weeks 5 days/week 6 hours/day	Respiratory Hepatic Renal Other	0.05 0.4 0.4 0.4		0.1 (chronic active inflammation)	Dunnick et al., 1989	Sulfate
Rat	13 weeks 5 days/week 6 hours/day	Respiratory Hepatic Renal Other	1.8 1.8 1.8		0.11 (chronic active inflammation)	Dunnick et al., 1989	Subsulfide
Rat	13 weeks 5 days/week 6 hours/day	Respiratory	-		2.0 (chronic inflammation)	Benson et al., 1989 Dunnick et al., 1989	Oxide
Rat	13 weeks 5 days/week	Hepatic Renal Other	7.9 7.9 7.9			Dunnick et al., 1989	Oxide
Rat	12 months 5 days/week 7 hours/day	Respiratory	-		0.2 (pneumonia)	Tanaka et al., 1988	Oxide

INHALATION NICKEL EXPOSURES: ANIMAL (cont'd)

SPECIES	EXPOSURE DURATION/ FREQUENCY	SYSTEM	NOAEL (mgNi/m^3)	LOAEL (EFFECT)		REFERENCE	COMPOUND
				LESS SERIOUS (mg Ni/m^3)	SERIOUS (mg Ni/m^3)		
Rabbit	1 - 8 months 5 days/week 6 hours/day	Respiratory	-	0.2 (impaired macrophage function)		Johansson and Camner, 1986	Chloride
Rabbit	3 - 6 months 5 days/week 6 hours/day	Respiratory	-	1.0 (impaired macrophage function)		Johansson et al., 1981	Metallic
Mouse	16 days 5 days/week 6 hours/day	Hepatic Other	-		3.6 (liver atrophy) 3.6 (emaciation)	Benson et al., 1987	Subsulfide
Mouse	13 weeks 5 days/week 6 hours/day	Respiratory Hepatic Renal Other	0.2 0.4 0.4 0.4		0.4 (chronic active inflammation; fibrosis)	Dunnick et al., 1989	Sulfate
Mouse	13 weeks 5 days/week 6 hours/days	Respiratory Hepatic Renal Other	0.1 1.8 1.8 1.8		0.9 (chronic active inflammation; fibrosis)	Dunnick et al., 1989	Subsulfide
Mouse	13 weeks 5 days/week 6 hours/day	Respiratory	-		2.0 (chronic active inflammation)	Benson et al., 1989	Oxide
Mouse	13 weeks 5 days/week 6 hours/day	Hepatic Renal	7.9 7.9			Dunnick et al., 1989	Oxide
Immunological							
Rat	16 days 5 days/week 6 hours/day	Immune	-	0.8 (lymphoid hyperplasia in lymph nodes)	6.7 (lymphocyte depletion - spleen)	Benson et al., 1988	Sulfate
Rat	16 days 5 days/week 6 hours/day	Immune	1.8		3.6 (spleen, lymph node atrophy)	Benson et al., 1987	Subsulfide

INHALATION NICKEL EXPOSURES: ANIMAL (cont'd)

SPECIES	EXPOSURE DURATION/ FREQUENCY	SYSTEM	NOAEL (mg Ni/m^3)	LOAEL (EFFECT)		REFERENCE	COMPOUND
				LESS SERIOUS (mg Ni/m^3)	SERIOUS (mg Ni/m^3)		
Rat	16 days 5 days/week 6 hours/day	Immune	7.9		23.6 (thymus atrophy)	Dunnick et al., 1988	Oxide
Rat	4 weeks or 4 months 7 days/week 24 hours/day	Immune	-	0.025 (decreased macrophages)		Spiegelberg et al., 1984	Oxide
Mouse	16 days 5 days/week 6 hours/day	Immune	0.8		1.6 (spleen atrophy)	Benson et al., 1988	Sulfate
Mouse	16 days 5 days/week 6 hours/day	Immune	1.8		3.6 (spleen atrophy)	Benson et al., 1987	Subsulfide
Mouse	16 days 5 days/week 6 hours/day	Immune	7.9		23.6 (thymus atrophy)	Dunnick et al., 1988	Oxide
Mouse	65 days 5 days/week 6 hours/day	Immune	0.11	0.45 (decreased alveolar macrophage activity)		Haley et al., 1990	Sulfate
Mouse	65 days 5 days/week 6 hours/day	Immune	0.11	0.45 (decreased alveolar macrophage activity)		Haley et al., 1990	Subsulfide
Mouse	65 days 5 days/week 6 hours/day	Immune	-	0.47 (decreased alveolar macrophage activity)		Haley et al., 1990	Oxide
Developmental							
Rat	21 days GD 1 - 21 7 days/week 24 hours/day	General	0.8	1.6 (9% decrease in fetal body weight)		Weischer et al., 1980	Oxide

INHALATION NICKEL EXPOSURES: ANIMAL (cont'd)

SPECIES	EXPOSURE DURATION/ FREQUENCY	SYSTEM	NOAEL (mg Ni/m^3)	LOAEL (EFFECT)		REFERENCE	COMPOUND
				LESS SERIOUS (mg Ni/m^3)	SERIOUS (mg Ni/m^3)		
Reproductive							
Rat	16 days 5 days/week 6 hours/day	Reproductive	0.8		1.6 (testicular degeneration)	Benson et al., 1988	Sulfate
Rat	16 days 5 days/week 6 hours/day	Reproductive	0.9		1.8 (testicular degeneration)	Benson et al., 1987	Subsulfide
Rat	13 weeks 5 days/week 6 hours/day		0.4			Dunnick et al., 1989	Sulfate
Rat	13 weeks 5 days/week 6 hours/day		1.8			Dunnick et al., 1989	Subsulfide
Rat	13 weeks 5 days/week 6 hours/day		7.9			Dunnick et al., 1989	Oxide
Mouse	16 days 5 days/week 6 hours/day	Reproductive	0.8		1.6 (testicular degeneration)	Benson et al., 1988	Sulfate
Mouse	16 days 5 days/week 6 hours/day	Reproductive	1.8		3.6 (testicular degeneration)	Benson et al., 1987	Subsulfide
Mouse	13 weeks 5 days/week 6 hours/day		0.4			Dunnick et al., 1989	Sulfate
Mouse	13 weeks 5 days/week 6 hours/day		1.8			Dunnick et al., 1989	Subsulfide
Mouse	13 weeks 5 days/week 6 hours/day		7.9			Dunnick et al., 1989	Oxide

INHALATION NICKEL EXPOSURES: ANIMAL (cont'd)

SPECIES	EXPOSURE DURATION/ FREQUENCY	SYSTEM	NOAEL (mg Ni/m^3)	LOAEL (EFFECT)		REFERENCE	COMPOUND
				LESS SERIOUS (mg Ni/m^3)	SERIOUS (mg Ni/m^3)		
CHRONIC EXPOSURE							
Death							
Rat	78 weeks 5 days/week 6 hours/day		-		0.7 (30% higher mortality)	Ottolenghi et al., 1974	Subsulfide
Rat	Life 7 days/week 23 hours/day		-		0.06 (23% lower survival time)	Takenaka et al., 1985	Oxide
Systemic							
Rat	78 weeks 5 days/week 6 hours/day	Respiratory	-		0.07 (pneumonitis)	Ottolenghi et al., 1974	Subsulfide
Rat	Life 7 days/week 23 hours/day	Respiratory Other	-	0.06 (weight loss)	0.06 (alveolar proteinosis)	Takenaka et al., 1985	Oxide
Hamster	Life 5 days/week 7 hours/day	Respiratory Other	42		42 (pneumoconiosis)	Wehner et al., 1975, 1979; Wehner 1986	Oxide
Cancer							
Rat	78 weeks 5 days/week 6 hours/day		-		0.7 (lung adenoma, adenocarcinoma, and squamous cell carcinoma)	Ottolenghi et al., 1974	Subsulfide

GD = Gestation Day
LOAEL = Lowest-Observed-Adverse-Effect-Level
Ni = Nickel
NOAEL = No-Observed-Adverse-Effect-Level
Other = Body weight changes and histological changes of other organs

APPENDIX 2

IN VITRO AND *IN VIVO* GENOTOXICITY STUDIES OF NICKEL

GENOTOXICITY OF NICKEL *IN VITRO*

SPECIES (TEST SYSTEM)	END POINT	RESULT[a]	REFERENCE	COMPOUND
PROKARYOTIC ORGANISMS				
Salmonella typhimurium	Gene Mutation	-	Wong 1988; Arlauskas et al., 1985; Biggart and Costa 1986; Marzin and Phi 1985	Nickel Chloride, Nickel Nitrate, Nickel Sulfate
Escherichia coli *Cornebacterium sp.* *Bacillus subtilis*	Gene Mutation Gene Mutation DNA Damage	- + -	Green and Bridges, 1976 Pikalek and Necasek, 1983 Kanematsu et al., 1980	Nickel Chloride Nickel Chloride Nickel Chloride and Trioxide
EUKARYOTIC ORGANISMS				
Fungi				
Saccharomyces cerevisiae	Gene Mutation	-	Singh, 1984	Nickel Sulfate
Mammalian Cells				
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
Mouse Lymphoma Cells	Gene Mutation	+	Amacher, 1980; McGregor et al., 1988	Nickel Chloride, Nickel Sulfate
Chinese Hamster V79 Cells	Gene Mutation	+	Miyaki et al., 1979; Hartwig and Beyersmann, 1989	Nickel Chloride
CHO Cells	DNA Damage	+	Patierno and Costa, 1985; Hamilton-Koch et al., 1986	Crystalline Nickel Sulfate Nickel Chloride
Human Diploid Fibroblasts	DNA Damage	-	Hamilton-Koch et al., 1986	Nickel Chloride
Hamster Cells	Sister Chromatid Exchange	+	Ohno et al., 1982; Larramendy et al., 1981; Sen and Costa 1986	Nickel Sulfate, Nickel Chloride, Crystalline Nickel Sulfate
Human Lymphocytes	Sister Chromatid Exchange	+ +	Wulf, 1980; Larramendy et al., 1981; Andersen, 1983; Saxholm et al., 1981	Nickel Sulfate, Nickel Sulfide

GENOTOXICITY OF NICKEL *IN VITRO* (cont'd)

SPECIES (TEST SYSTEM)	END POINT	RESULT[a]	REFERENCE	COMPOUND
Hamster Cells	Chromosome Aberration	+	Sen and Costa 1986; Larramendy et al., 1981; Conway and Costa, 1989; Sen et al., 1987	Nickel Sulfate, Nickel Chloride, Nickel Monosulfide
Human Lymphocytes	Chromosome Aberration	+	Larramendy et al., 1981	Nickel Sulfate
Human Bronchial Epithelial Cells	Chromosome Aberration	+	Lechner et al., 1984	Nickel Sulfate
Hamster Cells and C3H/1OT1/2 Cells	Cell Transformation	+	Dipaolo and Casto, 1979; Costa et al., 1982; Hansen and Stern 1984; Saxholm et al., 1981; Conway and Costa 1989; Costa and Heck 1982; Costa and Mollenhauser, 1980	Nickel Monosulfide, Nickel Subsulfide, Nickel Chloride, Nickel, Nickel Oxide or Trioxide
Mouse Embryo Fibroblasts	Cell Transformation	-	Miura et al., 1989	Nickel Sulfate, Nickel Chloride
Mouse Embryo Fibroblasts	Cell Transformation	+	Miura et al., 1989	Nickel Subsulfide, Nickel Monosulfide, Nickel Oxide
Human Foreskin Cells	Cell Transformation	+	Biedermann and Landolph, 1987	Nickel Subsulfide, Nickel Oxide, Nickel Sulfate, Nickel Acetate

[a] Metabolic activation is not an issue for nickel compounds

CHO = Chinese Hamster Ovary
DNA = Deoxyribonucleic Acid
- = Negative Result
+ = Positive Result

GENOTOXICITY OF NICKEL *IN VIVO* ANIMAL STUDIES

SPECIES (TEST SYSTEM)	END POINT	RESULT[a]	REFERENCE	COMPOUND
Drosophila melanogaster	Gene Mutation	-	Rasmuson, 1985	Nickel Nitrate or Chloride
D. melanogaster	Recessive Lethal	+	Rodriguez-Amaiz and Ramos 1986	Nickel Sulfate
Mammalian Cells				
Rat Bone Marrow and Spermatogonial Cells	Chromosome Aberrations	-	Mathur et al., 1977	Nickel Sulfate
Mouse Bone Marrow Cells	Micronucleus Test (oral)	+	Sobti and Gill 1989	Nickel chloride, Nickel Sulfate, Nickel Nitrate
Mouse Bone Marrow Cells	Micronucleus Test (ip)	-	Deknudt and Leonard 1982	Nickel Chloride
Mouse	Dominant Lethal (ip)	-	Deknudt and Leonard 1982	Nickel Acetate

[a] Metabolic activation is not an issue for nickel compounds

ip = Intraperitoneal
\- = Negative Result
\+ = Positive Result

APPENDIX 3

REVIEW OF FINNISH COPPER / NICKEL SMELTER AND NICKEL REFINERY WORKER STUDY (ANTTILA ET AL., 1998)

Anttila et al. (1998) examined cancer incidence among 1388 workers employed at least 3 months at the Harjavalta Works (Outokumpu Oy) copper/nickel smelter and nickel refinery in Finland. Cancer incidence was determined for the cohort from 1960 when nickel production began, up to 1995. An earlier study of this cohort examined cancer incidence from 1960 to 1987 (Karjalainen et al., 1992).

There were 1155 workers exposed to nickel in the study period in the smelter (n=566), repair shop (n=239), or refinery (n=418). Workers in the smelter were exposed to low levels of various species of nickel (nickel matte, nickel subsulfide, and nickel sulfides) and other metals (Cu, Cd, Pb, Co, As), sulfur, and possibly asbestos. Industrial hygiene measurements taken in 1983 indicated mean personal levels of exposure between 0.02 and 0.2 mg/m^3 (one value measured 0.7 mg/m^3) in the smelter. In the nickel refinery, measurements from stationary sampling in 1973 showed nickel concentrations of 0.2-0.4 mg/m^3 in grinding and 0.06-0.20 mg/m^3 in leaching. Short term exposures could reach 2 mg/m^3. Exposures in the electrolysis hall were reported to be stable from 1966-1988 and ranged from 0.2-0.8 mg/m^3, as measured by stationary samplers (Karjalainen et al., 1992; Kiilunen et al., 1997). The highest exposure level measured by the samplers in the electrowinning hall was 1.2 mg/m^3. Yearly personal mean exposure levels were estimated at approximately 0.25 mg/m^3 (Kiilunen et al., 1977).

The results indicated that overall cancer incidence was as expected. Smelter workers exposed to insoluble nickel with at least 20 years latency had a statistically significant increased incidence of lung cancer (standardized incidence ratio [SIR]=2.0; 95% confidence interval [CI]=1.07-3.42, n=13 cases). There was, however, no association between duration of employment and lung cancer risk in smelter workers. Among nickel refinery workers, overall cancer incidence was elevated but not statistically significant (SIR=1.36; 95% CI=0.84-2.08). Stomach cancer (SIR=4.98; 95% CI=1.62-11.6, n=5 cases), nasal cancer (SIR=41.1; 95% CI=4.97-148, n=2 cases) and lung cancer (SIR=2.61; 95% CI=0.96-5.67, n=6 cases) were elevated among the refinery workers, although lung cancer was not statistically significantly increased. Analyses by duration of employment showed a trend of increasing risk with increasing duration of employment for all cancers combined, stomach cancer and nasal cancer, but not lung cancer. The authors conclude that, since elevated nasal and lung cancer risks were confined to the refinery, where the primary exposure was to nickel sulfate at levels below 0.5 mg/m^3, it is likely that nickel sulfate is mainly responsible for the elevated respiratory cancer risk.

The results of Anttila et al. (1998) are based on small numbers of workers and cancer cases (e.g. the findings for nasal cancer among nickel refinery workers is based on only 2 nasal cancer cases). Consequently, the risk ratios are very imprecise, i.e. the 95% confidence interval for the SIR for nasal cancer among refinery workers ranges from 4.97 to 148. Further, the results are not internally consistent. Among nickel refinery workers, nasal cancer risk increases with increasing duration of employment, but the same trend is not observed for lung cancer. Further, there is an unusual trend of increasing risk with increasing duration of employment for all cancers combined and stomach cancer; these results are not consistent with the much larger, more detailed assessment of nickel workers conducted by Doll et al. (RICNCM, 1990).

Another important consideration in interpreting the Anttila et al. (1998) study is the quality of the exposure data, as the findings suggest increased respiratory cancer risks at exposure levels below those found to be associated with respiratory cancer in the Doll et al. (RICNCM, 1990) study. The most detailed exposure data available for the Outokumpu Oy refinery are from recent time periods (i.e., late 1980's forward) (Kiilunen et al., 1997), which is problematic for interpreting cancer epidemiology findings where the relevant exposures are likely those that occurred at least 20 years before respiratory cancer diagnosis.

The Outokumpu Oy work force reportedly currently uses respiratory protective equipment (RPE) for control of exposures in high exposure tasks (Kiilunen et al., 1997). Recent air exposure sampling

data reflects the reduction of exposure by use of respiratory protection, with air samples being taken from within the facepieces of the respiratory protective devices. Anttila et al. (1998) comments that yearly mean exposures were approximately 0.25 mg Ni/m^3. However, this value likely reflects the use of RPE. Thus, these current personal exposure data are not likely representative of historical exposures which are most relevant for interpreting the cancer incidence findings. In particular, past exposures, when RPE was not used as extensively, were likely higher.

Kiilunen et al. (1997) provide historic area sampling data from 1966 to 1993. The authors comment that modifications made at the nickel refinery in 1991 reduced exposures. Calculating averages for the pre 1991 and post 1991 area data for tank house one shows 0.475 mg/m^3 and 0.141 mg/m^3 respectively. There is not enough information provided to understand how these area samples relate to personal exposure. However, area concentrations were 0.475/0.141, or 3.4 times higher pre 1991 in tank house one. For tank houses two and three, the differences between 1983 (their start) to 1991 and post 1991 are less remarkable (2.1 and 1.2 respectively.) If these ratios represent the change in personal exposure, then the pre-1991 exposures may have been in the range 0.5 to 1.5 mg/m^3, which is essentially consistent with the findings of Doll et al. (RICNCM, 1990).

The Kiilunen et al. (1997) data show that in recent biological sampling, electrolytic refining workers have lower urinary nickel concentrations than shown in other reports. The attached table compares urinary nickel levels among the Outokumpu Oy workers with other nickel refining and smelter workers. Lower urinary values among the Outokumpu Oy workers would be expected if the workers used respiratory protection more than workers in other groups, even if other exposure factors were otherwise the same. However, Karjalainen et al. (1992) summarizes worker urinary nickel concentrations in electrowinning as 1.2 to 2 micromoles/liter (90 to 120 micrograms/liter.) These values indicate higher exposure (circa 1991 and prior), and are comparable to other electrolytic refining worker nickel urine data.

The various reports on the Outokumpu Oy workforce and exposures do not state when the rigorous use of RPE started. However, Kiilunen (1997) comments “During the early years apparently the use of masks was not insisted upon, and even more recently it was difficult to convince the workers of the importance of the masks.” Further comments imply that this did not change until after 1981. If the use is relatively recent, the recent exposure data may not represent historic exposures adequately. Thus, taken as a whole, the results of Anttila et al. (1998) should not be the basis for deriving an AQS for nickel at the exclusion of the much larger and significantly more detailed assessment of nickel exposures in relation to respiratory cancer performed by Doll et al. (RICNCM, 1990)

COMPARISON OF URINARY NICKEL LEVELS FOR NICKEL REFINERY AND SMELTER WORKERS

REFERENCE	WORK GROUP DESCRIPTION	NUMBER EVALUATED	URINE :G NI/LITER	COMMENTS
Kiilunen et al., 1997 (Finland)	Controls (not exposed)	52	1.6	
Kiilunen et al., 1997 (Finland)	All workers who used respiratory protection	Not stated	39	Many high exposure tasks are controlled via respiratory protection. Air 0.25 mg Ni/m^3 mean (0.1 to 0.5 range)
Kiilunen et al., 1997 (Finland)	All workers who did not use respiratory protection	Not stated	45	Many high exposure tasks are controlled via respiratory protection. Air 0.25 mg Ni/m^3 mean (0.1 to 0.5 range)
Karjalainen et al., 1992 (Finland)	Electrowinning workers, 1991 and prior	Not stated	90 to 120	Converted from 1.5 to 2.0 :mol/liter. Historic breathing zone data 0.16 to 0.23 mg Ni/m^3
Torjussen and Andersen 1979 (Norway - Falconbridge)	Roasting/smelting	97	34 +/- 35	Air 0.5 mg Ni/m^3
Torjussen and Andersen 1979 (Norway - Falconbridge)	Electrolytic refining	144	73 +/- 85	Air 0.2 mg Ni/m^3
Torjussen and Andersen 1979 (Norway - Falconbridge)	Retired, (6 months to 10 years)	15	11 +/1 13	
Torjussen and Andersen 1979 (Norway - Falconbridge)	Controls (not exposed)	57	4.9 +/- 4.2	
Hogetveit et al., 1978 (Norway-Falconbridge)	Electrolytic refining	90	129 +/- 106	Air 0.23 +/- 1.42 mg Ni/m^3
Hogetveit et al., 1978 (Norway-Falconbridge	Roasting/smelting	24	65 +/- 58	Air 0.86 +/- 1.2 mg Ni/m^3
Bernacki 1978 (North America)	Non-exposed industrial workers	19	3.2 +/- 2.6	
Bernacki et al., 1978 (North America)	Electrolytic refining	15	222 +/- 226	Air 0.49 +/- 0.56 mg Ni/m^3
Templeton et al., 1994 (North America)	Reference levels, background	Not stated	< 2 to 6	