Canadian Environmental Protection Act

Priority Substances List
Assessment Report

Nickel and its Compounds

Government of Canada
Gouvernement du Canada

Environment Canada
Environnement Canada

Health Canada
Santé Canada

Canada

CANADA'S GREEN PLAN

Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

NICKEL AND ITS COMPOUNDS

Government of Canada
Environment Canada
Health Canada

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Synopsis

This assessment of "nickel and its compounds" focuses on the forms of nickel most likely to be present in the environment, i.e., several forms of inorganic nickel.

Nickel is a naturally occurring element that is ubiquitous in the environment principally in the divalent state. Approximately 197 000 tonnes (t) of nickel are currently produced per year in Canada, most of which is sold abroad. Nickel and its alloys are used in a wide variety of industrial applications for the automobile, shipbuilding, electrical, oil, food, and chemical industries. Nickel enters the Canadian freshwater and terrestrial (soil) environment as a result of natural weathering and erosion of geological materials, e.g., glacial overburden and bedrock. Nickel is also released into the environment in Canada as a result of human activities including mining, smelting, refining, alloy processing, scrap metal reprocessing, other metal operations, fuel combustion, and waste incineration.

The assessment of effects to the environment focused on aquatic biota and terrestrial plants since they are most likely to be affected by exposure to nickel in Canada. Comparison of reported effect levels to environmental concentrations indicates that dissolved and soluble forms of inorganic nickel likely cause harmful effects to sensitive pelagic organisms and terrestrial plants in the vicinity of major anthropogenic and natural sources.

Nickel occurs at low concentrations in suspended particulate material in the atmosphere, has an atmospheric residence time of 5 to 8 days, and does not absorb infrared radiation. The only significant gaseous nickel compound, nickel carbonyl, degrades in air with a half-life of less that one minute. Consequently, inorganic forms of nickel are not expected to contribute to global warming or to the depletion of stratospheric ozone.

Based on the estimation of the average daily intake of nickel (total) from air, drinking water, food, and soil for various age groups in the general population, food is likely the most significant source of human exposure in Canada.

There was no evidence that occupational exposure to metallic nickel was associated with cancer in humans, although there is some limited evidence that metallic nickel may be carcinogenic in experimental animals exposed by routes less relevant to assessment of effects in humans. Concentrations of total nickel in ambient air in Canada, of which metallic nickel is believed to comprise only a small proportion, are more than 5000 times less than the levels that induced minimal effects in experimental animals.

Based principally on the sufficient weight of evidence of carcinogenicity in occupationally exposed human populations for the groups of compounds examined in a recent extensive epidemiological analysis and some limited supporting data on individual compounds in experimental animals, each of the groups, "oxidic" (including nickel oxide, nickel-copper oxide, nickel silicate oxides, and complex oxides), "sulphidic" (including nickel subsulphide), and "soluble" (primarily nickel sulphate and nickel

chloride) nickel compounds has been classified as "Carcinogenic to Humans", i.e., substances for which there is believed to be some chance of adverse health effects at any level of exposure. Available data were inadequate to address individual compounds within these groups. For such groups, where data permit, estimated exposure is compared to quantitative estimates of cancer potency to characterize risk and provide guidance for further action, i.e., analysis of options to reduce exposure, under CEPA. For "oxidic", "sulphidic", and "soluble" nickel compounds (combined), such a comparison suggests that the priority for analysis of options to reduce exposure would be moderate to high. Available data also indicate that nickel (mostly "soluble" compounds) induces contact dermatitis in a proportion of the population. Moreover, a Tolerable Daily Intake (TDI) for non-carcinogenic effects developed for "soluble" nickel compounds would be less than the estimated total intake of nickel for the Canadian population through ingestion. A Tolerable Daily Intake is the intake to which it is believed that a person can be exposed over a lifetime without deleterious effect.

Based on these considerations, it has been concluded that dissolved and soluble* forms of inorganic nickel are entering or may enter the environment in a quantity or concentration or under conditions that are having or may have a harmful effect on the environment. It has been concluded that the substance "nickel and its compounds" does not or may not enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which human life depends. It has also been concluded that metallic nickel does not constitute a danger in Canada to human life or health, however, each of the groups, "oxidic" (including nickel oxide, nickel-copper oxide, nickel silicate oxides, and complex oxides), "sulphidic" (including nickel subsulphide), and "soluble" (primarily nickel sulphate and nickel chloride) nickel compounds as a whole, is entering the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human life or health.

* The term “soluble" includes water-soluble form of nickel (e.g., nickel sulphate and nickel chloride), as well as other more stable forms (e.g., nickel-bearing sulphide minerals and nickel oxide) that can dissolve under certain conditions of pH (e.g., acidic mine tailings) or redox potential (e.g., buried reducing sediment) in the environment.

1.0 Introduction

The *Canadian Environmental Protection Act* (CEPA) requires the Minister of the Environment and the Minister of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents, and wastes that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined under Section 11 of the Act which states:

> "...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions
>
> (a) having or that may have an immediate or long-term harmful effect on the environment;
>
> (b) constituting or that may constitute a danger to the environment on which human life depends; or
>
> (c) constituting or that may constitute a danger in Canada to human life or health."

Substances that are assessed as "toxic" as defined under Section 11 may be placed on the List of Toxic Substances (Schedule I of CEPA). Consideration can then be given to developing regulations, guidelines, or codes of practice to control any aspect of these substances' life cycle, from the research and development stage through manufacture, use, storage, transport, and ultimate disposal.

The substance "nickel and its compounds" is included on the Priority Substances List. The assessment of whether "nickel and its compounds" are "toxic", as defined under Section 11 of CEPA, was based on the determination of whether they **enter** or are likely to enter the Canadian environment in a concentration or quantities or under conditions that could lead to **exposure** of humans or other biota to levels that could cause adverse **effects**.

Based on the considerations that most of the nickel present in the environment occurs in inorganic form and the nature of the groups of nickel compounds considered in a recent extensive epidemiological study, assessment of "nickel and its compounds" under Paragraph 11(c) of CEPA focuses principally on metallic, "sulphidic" (including nickel subsulphide), "oxidic" (including nickel oxide, nickel-copper oxide, nickel silicate oxides, and complex oxides), and "soluble" (primarily nickel sulphate and nickel chloride) nickel compounds. Due to lack of relevant data, it has not been possible to assess individual nickel compounds within these groups. The term "nickel" in this report refers to total inorganic nickel, unless otherwise specified.

For the determination of whether the priority substance "nickel and its compounds" is "toxic" to the environment under Paragraph 11(a), this assessment focuses on inorganic forms of nickel (since most nickel present in and entering the

environment is inorganic), and particularly on dissolved forms, and those likely to be soluble over time under the range of pH and redox potential conditions that occur in the environment (since dissolved and soluble forms of nickel are expected to be most available for uptake by organisms). Although results of research on "nickel and its compounds" conducted outside Canada were considered, available Canadian data on sources, concentrations, fate, and effects on the environment were emphasized. Data relevant to the assessment of whether the priority substance, "nickel and its compounds", is "toxic" to the environment under CEPA were identified and obtained from original and review articles, books, and criteria documents published up to June 1993. These articles were obtained from searches of primary journals, as well as searches of the following abstracting services and data bases: CHEMICAL ABSTRACTS, BIOLOGICAL ABSTRACTS, POLLUTION ABSTRACTS, CURRENT CONTENTS, U.S. Environmental Protection Agency Toxic Releases Inventory, U.S. Agency for Toxic Substances and Disease Registry, MEDLINE, Canada Centre for Occupational Health and Safety-Access System (CCOHS), WAVES, AQUAREF, Aquatic Sciences and Fisheries Abstract (ASFA), AQUIRE (1978 to 1992), National Technical Information Service (NTIS), ENVIROLINE, and TOXLIT. Unpublished data were provided by the Canadian Wildlife Service, K. Winterhalder of Laurentian University in Sudbury, and P. Friske of the Geological Survey of Canada. From 1991 through 1993, background reports on the fate and concentrations of "nickel and its compounds" in the Canadian environment were prepared under contract to Environment Canada by O. Kulikovsky, H. Evans, P. Outridge, L. Evans, and M. Goss, and under contract to Natural Resources Canada by P. Doyle. Information was also obtained from the CEPA Domestic Substances List and from Statistics Canada.

For assessment of data other than those considered to be critical for determination of whether "nickel and its compounds" are "toxic" to human health under CEPA, evaluations of agencies such as the International Programme on Chemical Safety (IPCS, 1991), the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 1988; 1991), and the International Agency for Research on Cancer (IARC, 1990) have been consulted where available and considered appropriate. To identify toxicological data relevant to the preparation of the supporting documentation, a background review on the effects in experimental animals and humans was prepared under contract by BIBRA Toxicology International in 1992. Information therein was identified on the basis of a literature search of BIBRA's data sources. The following computerized data bases were also searched for relevant data in February, 1992: Hazardous Substances Data Bank (HSDB), Integrated Risk Information System (IRIS), CHEMID, Registry of Toxic Effects of Chemical Substances (RTECS), EMBASE, TOXLINE, and TOXLIT (all 1988 to 1992). Dr. G. Jenkins of the Ontario Ministry of the Environment provided monitoring data on levels of nickel in drinking water. Data relevant to assessment of whether "nickel and its compounds" are "toxic" to human health obtained after the completion of these sections of this report (i.e., August 1993) were not considered for inclusion.

Review articles were consulted where considered appropriate. However, all original studies that form the basis for the determination of "toxic" under CEPA have

been critically evaluated by the following Environment Canada staff (effects on the environment) and Health Canada staff (human exposure and effects on human health):

Environment Canada	Health Canada
Y.K. Chau	P.K.L. Chan
J.E. MacLatchy	K. Hughes
A.M. Scheuhammer	M.E. Meek
P. Doyle	L.J. Seed

Quantitative estimates of carcinogenic potency were provided by J. Shedden and S. Bartlett of Health Canada after consultation with Dr. H.J. Gibb of the U.S. Environmental Protection Agency.

In this report, a synopsis that will appear in the *Canada Gazette* is presented. In addition, an extended summary of the technical information that is critical to the assessment is presented in Section 2.0. The assessment of whether "nickel and its compounds" are "toxic" under CEPA is presented in Section 3.0. Supporting documentation in which the technical information is presented in greater detail has also been prepared and is available upon request.

As part of the review and approvals process established by Environment Canada, the environmental sections of this Assessment Report were reviewed by Prof. T.C. Hutchinson, (Trent University, Peterborough, Ontario) and Prof. E. Nieboer, (McMaster University, Hamilton, Ontario). Comments on the adequacy of coverage of the literature relevant to assessment of effects on human health in the supporting documentation were invited from Dr. J.S. Warner (INCO Ltd.), Dr. Albert Cecutti (Falconbridge Ltd.), Ms. D. Sivulka (NiPERA Inc.), and Mr. G. Crawford (Nickel Development Institute). Sections of the supporting documentation relevant to human exposure were forwarded to officials of the Mining Association of Canada for identification of additional pertinent data. Following external peer review of the draft health-related sections of the supporting documentation and Assessment Report by Dr. F.W. Sunderman (University of Connecticut Medical School), Dr. H.J. Gibb (U.S. Environmental Protection Agency), Dr. H. Shannon (McMaster University Medical Centre), Dr. L. Elinson (Ontario Workers Compensation Board), Dr. R.A. Goyer (a consulting toxicologist), Dr. S.H.H. Swierenga (Science Council of British Columbia), and staff of BIBRA Toxicology International (U.K.), these sections were approved by the Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The final Assessment Report was subsequently reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Copies of this Assessment Report and the unpublished supporting documentation are available upon request from:

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2.0 Summary of Information Critical to Assessment of "Toxic"

2.1 Identity, Properties, Production, and Uses

Nickel (Ni) is the twenty-fourth most abundant element in the earth's crust, occurring at an average concentration* of about 75 µg/g. Nickel has an atomic number of 28 and an atomic weight of 58.71. Although it has oxidation states of -1, 0, +1, +2, +3, and +4, the most common valence state in the environment is Ni^{2+} (Cotton and Wilkinson, 1988; Nieboer *et al.,* 1988). Nickel occurs in nature as a trace constituent in a wide variety of minerals, particularly those containing large amounts of iron and magnesium, such as olivine and pyroxenes (Avias, 1972; NRCC, 1981). In minerals in which it is an essential component, it occurs most frequently in combination with sulphur, arsenic, or antimony. Examples include millerite (NiS), red nickel ore [mainly niccolite (NiAs)], pentlandite $(Ni,Fe)_9S_8$, and deposits consisting primarily of NiSb, $NiAs_2$, NiAsS, or NiSbS. In Canada, the most important commercial deposits of nickel contain pentlandite. Other nickel minerals include annabergite $Ni_3(AsO_4)_2 \cdot 2H_2O$, bravoite $(Ni,Fe,Co)S_2$, skutterudite (Ni,Co)As, and heazlewoodite (or nickel subsulphide, Ni_3S_2) (Duke, 1980; NRCC, 1981). Although metallic nickel is not common in nature, it does occur (as the iron-nickel alloy, awaruite) in some iron and magnesium-enriched ultramafic rocks (Duke, 1980). In addition to metallic nickel, commercially important nickel compounds include nickel carbonate, nickel carbonyl, nickel chloride, nickel nitrate, nickel oxide, nickel sulphate, and nickel sulphide (Brecher *et al.,* 1989).

Nickel is a silver-white metal with typical metallic properties. It has high electrical and thermal conductivities, a melting point of 1452°C, and it can be drawn, rolled, forged, and polished. It is resistant to attack by air or water at ambient temperatures (-20°C to 30°C), and is therefore often electroplated as a protective coating. It is magnetic, but not as much as iron (Cotton and Wilkinson, 1988). Nickel commonly forms stable complexes with ligands containing oxygen, sulphur, phosphorus, or arsenic as donor atoms (NRCC, 1981). Nickel forms an extensive series of compounds in the divalent state, the only oxidation state of importance in the aqueous chemistry of nickel. The most water-soluble nickel compounds are nickel chloride hexahydrate (2500 g/L), nickel sulphate hexahydrate (660 g/L), nickel sulphate heptahydrate (760 g/L), and nickel nitrate hexahydrate (2400 g/L) (Lide, 1992). Less soluble nickel compounds include hexaammine nickel nitrate (45 g/L), nickel (II) hydroxide (0.13 g/L), and nickel carbonate (0.09 g/L) (Lide, 1992). Nickel subsulphide and nickel oxide are considered to be "insoluble" in water, but both are soluble in acids (Cotton and Wilkinson, 1980; IPCS, 1991).

Canada was ranked as the second largest producer of nickel in the world in 1990, with Ontario (Sudbury) and Manitoba (Thompson) producing 65% and 35% of the Canadian nickel, respectively (Mining Association of Canada, 1991). The average annual nickel production in Canada in 1988, 1989, and 1990 was about 197 000 tonnes (t). Nickel production is expected to increase marginally over the next several years

* In this report, concentrations are expressed as elemental nickel unless stated otherwise.

(Mining Association of Canada, 1991). Total exports and imports of nickel in 1990 were 187 000 t and 29 000 t, respectively (ISTC, 1992).

Metallic nickel is sold in the form of cathodes, pellets, powders, briquettes, rondelles, and coinage. Nickel is used in approximately 3000 alloys that have more than 250 000 applications (Mining Association of Canada, 1991). For example, nickel-containing stainless steel is used in the chemical and food processing industries and in the medical profession. Iron-nickel alloys are important materials for the electrical industry. Nickel-copper alloys are useful for shipbuilding. Nickel-chromium alloys are used for jet engine components, nuclear reactors, and turbine blades. Other important uses of nickel are in electronic equipment, motor vehicles, and oil and gas pipelines (IPCS, 1991).

Nickel compounds are also used in a variety of products and processes. For example, nickel carbonate hydroxide is used in plating, as a catalyst for the hardening of fats, and in colours and glazes for ceramics; nickel carbonate is used in electric components; anhydrous nickel chloride is used as an adsorbent for ammonia in gas masks and in nickel plating; nickel hydroxide is used as electrode material for secondary cells; nickel oxide is primarily used in metallurgical operations as an important raw material for smelting and alloy-producing processes, catalysts, and glass colours; nickel sulphate is used in catalysts, electrolyte solution, and jewellery; and nickel nitrate is used in nickel plating and nickel-cadmium batteries (IPCS, 1991).

2.2 Entry into the Environment

Nickel is released into the Canadian environment in various forms from natural sources and as a result of anthropogenic activities.

2.2.1 *Natural Sources*

Natural weathering and erosion of geological materials (e.g., glacial overburden and bedrock) release nickel into surface waters and soils in Canada. Natural sources of airborne nickel include soil dust, sea salt, volcanoes, forest fires, and particulate exudates from vegetation (Warren and Delavault, 1954; NRCC, 1981; Schmidt and Andren, 1980). During summertime in Canada, soil dust and vegetation are the predominant natural sources of nickel. Nickel is likely present in soil dust as a trace constituent of iron- and manganese-containing minerals (e.g., silicates and oxides) (NRCC, 1981). Sea spray may be a major contributor of atmospheric nickel in areas remote from anthropogenic sources during winter months (when soil dust sources are negligible), and in coastal areas at all times of the year. Forest fires can also be short-term, but intense, sources. At one location in Canada (Smoking Hills, NWT), the spontaneous burning of bituminous shales has resulted in the accumulation of large quantities of nickel and other metals in local surface waters (Havas and Hutchinson, 1983). In Canada, the estimated contribution of natural sources to airborne nickel in 1975 ranged from 595 to 11 200 t (soil dust, 480 to 2400 t; forest fires, 15 to 7500 t; vegetation, 100 to 1300 t) (NRCC, 1981).

2.2.2 *Anthropogenic Sources*

Although earlier summaries of emissions of nickel from all major anthropogenic sources in Canada are available (NRCC, 1981; Jaques, 1987), the only recent review identified was for primary base metal production. In 1988, mining, smelting, and refining of base metals were estimated to have released 1100 t of nickel as air emissions, and 64 t as effluents; approximately 1800 t of nickel were disposed of on land as sludges and solids, and 8700 t as slags (MacLatchy, 1992).

Air. The most important anthropogenic sources of nickel released into Canadian air are primary base metal production (accounting for approximately 65% of all releases in 1982), and fossil fuel combustion (Jaques, 1987). It is estimated that approximately 1100 t of nickel were released into the atmosphere in 1988 from Canadian base metal smelters and refineries, 700 t of which were released from nickel-copper smelting and refining operations in the Sudbury area, and about 320 t from similar operations at Thompson, Manitoba (MacLatchy, 1992). Estimated releases from nickel production operations in Sudbury in 1988 are similar to, or slightly higher than, earlier estimates of atmospheric emissions for the period 1973 to 1981 (Bolger and Buchanan, 1979; Chan and Lusis, 1986). Nickel released into the air in Canada as a result of smelting processes is likely in the form of nickel sulphate, nickel subsulphide, and nickel oxide (Gilman and Ruckerbauer, 1962). Warner (1984) reported a nickel content of 5 to 10% in flue dusts from a Canadian smelter; 10% of the nickel detected was water-soluble. However, analysis of stack dust from one of the nickel-copper smelters in the Sudbury area by Cox and Hutchinson (1981) indicated that 77% of the particulate nickel was in water-soluble forms.

Fuel combustion is the second most important anthropogenic source of airborne nickel in Canada. Combustion of petroleum releases more nickel than combustion of coal or coke (Taylor *et al.*, 1979; NRCC, 1981; Krishnan and Hellwig, 1982; Jaques, 1987). Of the 689 t of airborne nickel estimated to have been produced by fossil fuel combustion in Canada in 1975, 532 t were from the combustion of petroleum and 157 t were from the combustion of coal and coke (almost exclusively at the Alberta oil sands extraction site) (NRCC, 1981). Available data suggest that nickel released into the air in Canada as a result of fuel combustion is primarily in water-soluble forms (IPCS, 1991). For example, in one study, nickel sulphate was identified as the main constituent (comprising >77%) of fly ash from oil-fired utility boilers (the remainder was present as nickel oxide) (Henry and Knapp, 1980).

The alloy production industry and the scrap reprocessing industry are relatively minor sources of airborne nickel. Nickel emissions into the atmosphere can also occur from electroplating, grinding, polishing, and cutting operations performed on the finished product, and scrap metal (Radian Corporation, 1984). Currently, no nickel-cadmium batteries are manufactured in Canada (Capowski, 1993).

The incineration of municipal garbage and sewage sludge accounts for only a small fraction of nickel released to the atmosphere, primarily in "soluble" (39 to 58%), "sulphidic" (<10%), and "oxidic" (40 to 61%) forms (Steinsberger *et al.*, 1994). This

finding is consistent with earlier findings that 35 to 52% of the nickel in fly ash from incinerated sludge was in the form of soluble nickel chloride and sulphate, and the remainder was in the form of less soluble oxides and silicates (Henry *et al.,* 1982).

Other sources of atmospheric emissions of nickel include cement manufacturing, coke ovens, asbestos mining/milling, and cooling towers. During cement manufacturing, nickel is emitted either as a component of the clays, limestones, and shales (raw materials) or as an oxide formed in high-temperature process kilns. Nickel emitted to air from asbestos mining/milling is in the form of silicate minerals. Barbeau *et al.* (1985) reported that crude crysotile asbestos fibres from several mines in Quebec contained from about 60 to 390 µg/g of nickel, and that milled fibres contained up to about 2000 µg/g. The emissions from coke ovens are likely in the form of sulphides (Ni3S2 and NiS) and metallic nickel, owing to the highly reducing atmosphere of the coke ovens (IPCS, 1991).

Water. Nickel (in dissolved and particulate form) enters the aquatic environment in effluents and leachates, as well as through atmospheric deposition after release from anthropogenic sources.

Industrial effluents that contain a significant amount of nickel include those from nickel mining, smelting and refining, metal plating, gold mining, and iron and steel processing. Acid mine drainage resulting from the natural oxidation of iron sulphide minerals in ore, tailings, and waste rock piles, accounts for a substantial but unquantified portion of the nickel in effluents from the nickel-mining industry (MacLatchy, 1992).

In Ontario, the total nickel contained in wastewater discharges of the primary nickel sector was approximately 27 and 49 t 1988 and 1989, respectively. In Manitoba, wastewater discharges from the primary nickel sector were about 26 and 15 t in 1988 and 1990, respectively (Boyd, 1990; MacLatchy, 1992; 1993). During 1990, the wastewater treatment plant at Copper Cliff, Ontario, discharged an average of 59 kg/day of nickel. The estimated loading of nickel to water in Canada in both 1988 and 1990 from mining, smelting, and refinery operations was 64 t (Boyd, 1990; MacLatchy, 1992). Concentrations of nickel in these effluents ranged from 16 to 27 200 µg/L (Boyd, 1990; 1991; MacLatchy, 1992).

Concentrations of nickel in effluents of copper and lead-zinc mines are less than 50 µg/L, and the amounts contributed to the Canadian environment are insignificant compared to those from other mining operations (Environment Canada, 1992).

While most gold ores contain only traces of nickel, a few effluents from gold mines do contain significant amounts of nickel. The cyanidation process that leaches gold from the ore also leaches nickel and other metals. Concentrations of nickel in effluents from Ontario gold mines range from 50 to 500 µg/L; in other areas of Canada, the range is 21 to 277 µg/L. The estimated loading of nickel to water in Ontario in 1990 from gold-mining operations was 12.9 t (Boyd, 1992).

The use of sulphuric acid to extract uranium from its ore also results in minor amounts of nickel in effluents from uranium mines. For example, uranium mine effluent discharged to Key Lake in Saskatchewan in 1990 contained 180 µg/L nickel (Environment Canada, 1992). In 1990, uranium mines introduced an estimated 1.9 t of nickel to the aquatic environment in Canada (MacLatchy, 1992).

The use of nickel in stainless steel in the iron and steel industry results in significant amounts of nickel in some effluents. In Ontario, integrated steel mills and small specialty steel mills emitted totals of 26 kg/day and 2.6 kg/day in 1990, respectively (Boyd, 1991). In 1990, steel mills introduced an estimated 87 t of nickel to the Canadian aquatic environment (Boyd, 1991). Metal-plating operations may discharge substantial quantities of nickel into municipal sewers (Boyd, 1991; MacLatchy, 1992), but no quantitative data on loadings were identified.

Land. Mining operations generate ore that is milled, but also waste rock that is dumped near mining sites. Milling operations produce a slurry of solids that are settled in tailings ponds. Nickel may be leached from both waste rock and tailings. Nickel leached from poorly controlled tailings areas can contaminate local groundwater, vegetation, and other biota (Hawley, 1980). Slag, which is generated pyrometallurgically, is essentially dry and is disposed of on land. Sludge is generated through hydrometallurgical refining. The stability of the sludges and slags generated at nickel production facilities is unknown, but these wastes (particularly slags) are considered to be relatively stable (MacLatchy, 1993).

2.3 Exposure-related Information

2.3.1 *Fate*

Air. Most nickel enters the atmosphere in particulate form. Generally, nickel-containing particles from anthropogenic sources differ in composition and are smaller than particles of natural origin. Nickel particulates from anthropogenic sources have diameters in the range of 0.1 to 2 µm, while particulates in wind-blown dust, and from sea spray, volcanoes, and plant exudates, have diameters in the range of 2 to 10 µm. Although the particle size distribution of nickel is primarily a function of its sources, secondary processes, such as coagulation and condensation, may alter the size distribution somewhat as the aerosol ages (Schmidt and Andren, 1980).

Compared to large particulate matter (>10 µm), fine particulate matter (1 to 10 µm) has a longer residence time in air and is transported over longer distances (Beijer and Jernelov, 1986). Schmidt and Andren (1980) estimated an atmospheric residence time of 5 to 8 days for most nickel-containing particulates of natural and anthropogenic origin. Particles are removed by wet and dry deposition in nearly equal amounts. The persistence of gaseous nickel carbonyl in the atmosphere is low. For example, at 25^0C the half-life of ng/m^3 levels of nickel carbonyl is <1 minute (Stedman and Hikade, 1980; IPCS, 1991). Nickel compounds do not absorb infrared radiation (Lide, 1992).

Water and Sediment. Nickel is a relatively mobile heavy metal. In natural waters, nickel is transported in both particulate and dissolved forms. The pH, oxidation-reduction potential, ionic strength, type, and concentration of organic and inorganic ligands (in particular, humic and fulvic acids), and the presence of solid surfaces for adsorption (in particular, hydrous iron and manganese oxides) can all affect the transport, fate, and biological availability of nickel in fresh water and seawater (e.g., Semkin, 1975; Callahan *et al.*, 1979; Snodgrass, 1980). In some sediments under reducing conditions and in the presence of sulphur, relatively insoluble nickel sulphide is formed (Ankley *et al.*, 1991). Under aerobic conditions and pH <9, the compounds that nickel forms with hydroxide, carbonate, sulphate, and naturally occurring organic ligands are sufficiently soluble to maintain aqueous Ni^{2+} concentrations above 60 µg/L (Callahan *et al.*, 1979).

Most of the nickel in sediments and suspended solids is distributed among organic materials, precipitated and coprecipitated particle coatings, and crystalline particles.

Although Gibbs (1977) reported that more than 95% of the nickel transported in the Yukon River was in suspended particulate form, available data suggest that relatively little nickel is present in suspended solids in most Canadian lake waters. For example, Rossmann and Barnes (1988) reported that less than 10% of the nickel in samples of water (obtained between 1980 and 1985) from the Great Lakes, was in the particulate (>0.5 µm) fraction. Similarly, Nriagu *et al.* (1982) reported that more than 95% of the nickel in samples of water from lakes within a 20-km radius of Sudbury was in the dissolved (as opposed to particulate) phase.

Microbial activity or changes in some of the physical and chemical parameters described above (e.g., decreasing pH, or increasing concentrations of organic ligands) may result in desorption of nickel from suspended particulate material or sediment into the water column (DiToro *et al.*, 1986).

No data were identified on the potential for volatilization or photochemical reactions of nickel compounds in natural waters.

Soil. Nickel is present in detectable amounts in most types of rocks, and it may be mobilized in the surface environment during the chemical and mechanical weathering of rock to form soil. Kabata-Pendias and Pendias (1984) have documented the range of typical nickel content in rocks, from a low of 5 to 20 µg/g for granites, sandstones, and limestones, for example, to a high of about 2000 µg/g for ultramafic rocks (dunites, pyroxenites, and peridotites) in which the nickel is present in lattices of olivine and pyroxene minerals. Various authors have reported relatively high concentrations of nickel in soils and tills associated with mafic and ultramafic rock types in Canada (Roberts, 1980; Rencz and Shilts, 1980; Kaszycki and DiLabio, 1986; Klassen and Thompson, 1990; Shilts and Smith, 1989).

Nickel that is leached by rain water from surface A horizon soil can accumulate in the adjacent subsurface B horizons. Results of studies in various parts of Canada suggest

that, in areas remote from sources of pollution, nickel concentrations in A horizons are often lower (and higher in B horizons) than those in underlying, relatively unweathered, C horizons (Griffith *et al.*, 1984; McKeague *et al.*, 1979; McKeague and Wolynetz, 1980; Mills and Zwarich, 1975; Soon and Abboud, 1990; Wall and Marsh, 1988; Whitby *et al.*, 1978).

Nickel is preferentially adsorbed on iron and manganese oxides (which tend to accumulate in soil B horizons), and can substitute for magnesium in the lattice of soil clay minerals (NRCC, 1981). Less nickel will reach groundwater if removed from solution by these processes. Water solubility, and thus bioavailability to plants, are affected by soil pH, with decreases in pH below 6.5 generally mobilizing nickel (Sunderman and Oskarsson, 1988).

On the basis of nickel concentrations in soils and estimates of the loss of nickel from continents, the residence time of nickel in soils was estimated to be about 3500 years (Nriagu, 1980).

Aquatic Biota. In general, bioconcentration factors (BCFs, defined as the ratio of concentrations in dry tissue to concentrations in water) for nickel in aquatic organisms range from approximately 100 to 5000. For example, BCFs have been observed in the range of 120 to 550 for submerged lichens and 770 to 1500 for submerged mosses (Dietz, 1973); 2000 to 4500 for *Daphnia* species (Cowgill, 1976); 200 to 1000 for clams, zooplankton, and benthos (Mathis and Cummings, 1973; Hutchinson *et al.*, 1976); and 230 to 330 for fish (Hutchinson *et al.*, 1976), depending upon exposure concentration and age of the organism. Higher BCFs (>10 000) have been observed in some acid-tolerant and metal-tolerant flora (Hutchinson *et al.*, 1976; Mann *et al.*, 1988).

Some benthic organisms, such as unionid clams, periphyton, and crayfish, can accumulate higher concentrations of nickel than pelagic (i.e., water-column) organisms (Hutchinson *et al.*, 1976; Forester, 1980; Krantzberg, 1985). However, reported bioconcentration factors for sediment-associated biota (defined, in this case, as the ratio of concentrations in wet tissue to concentrations in dry sediment) are generally ≤ 1 (Hutchinson *et al.*, 1976; Wren *et al.*, 1983; Eriksen *et al.*, 1989).

Although there is potential for biomagnification because of high concentrations in algae and macrophytes, animals appear to be able to regulate the nickel content of their tissues, either by controlled uptake or by increased excretion (Stokes, 1988; Darmono, 1990). No data were identified in support of the biomagnification of nickel through fresh water food chains (Stokes, 1975; Moore and Ramamoorthy, 1984; Watras *et al.*, 1985). When algae and macrophytes die, the detritus produced is the major food source for fungi and bacteria and in this way nickel can re-enter the food chain (Mudroch, 1980; NRCC, 1981).

Bacteria can influence the chemistry and transfer of nickel through the aquatic food chain. For example, reducing conditions in water may lead to the microbial conversion of sulphate to sulphide, and the subsequent precipitation of insoluble nickel sulphide (Babich and Stotzky, 1983a;b).

Terrestrial Biota. In general, there is a good correlation between concentrations of nickel in a wide range of Canadian soils and those in plants that grow on these soils (Cataldo *et al.*, 1978; Aschmann and Zasoski, 1987; Warren and Delavault, 1954; Rencz and Shilts, 1980). Soil factors that influence the availability of nickel to plants and its subsequent uptake include pH, organic matter content, clay and hydrous iron and manganese oxide content, and cation exchange capacity (Halstead *et al.*, 1969; Haq *et al.*, 1980; Richter and Theis, 1980). Soil pH is of particular importance. At low pHs, acid-soluble nickel compounds [such as nickel-bearing sulphide, and to a lesser extent, silicate, minerals (Buckman and Brady, 1960; Rencz and Shilts, 1980)] are unstable, and the soil's capacity to remove nickel from pore water by adsorption (onto hydrous iron oxides, for example) is very low. Low pH ($\leq$6.0) therefore strongly favours bioavailability (Halstead *et al.*, 1969; Bisessar, 1989). Nickel that is complexed by organic ligands dissolved in soil pore waters is expected to be less available for uptake by plants than the free nickel ion (Kabata-Pendias and Pendias, 1992).

No data were identified indicating that biomagnification of nickel is important in terrestrial wildlife food chains. In studies comparing concentrations of nickel in wildlife and their food, concentrations of nickel were either similar in different trophic levels (Wren *et al.*, 1983; Scanlon, 1987; Beyer and Miller, 1990) or declined with increasing trophic level (Custer *et al.*, 1986; Szefer and Falandysz, 1987). For example, dietary items of ruffed grouse *(Bonasa umbellus)* near Sudbury, Ontario contained 32 to 95 µg/g dry weight (d.w.), whereas grouse body tissues typically had ten-fold lower concentrations of nickel (Rose and Parker, 1983).

2.3.2 *Concentrations in the Environment**

Common analytical methods used to measure inorganic nickel in environmental media include voltammetry, atomic absorption spectrophotometry, and atomic emission spectrometry. Over the past 15 to 20 years, the analysis of trace metals has been revolutionized by ultra-trace "clean lab" techniques, which greatly reduce sample contamination and yield more reliable analytical data (Nieboer, 1992). Most analytical methods do not distinguish between different oxidation states of nickel. However, it is reasonable to assume that inorganic nickel is present in the +2 oxidation state in the environment (Cotton and Wilkinson, 1988; Nieboer *et al.*, 1988). Detection limits for all nickel compounds depend on the analytical method, sample size, and matrix interferents.

Air. In general, there is a lack of data on speciation of nickel in ambient air and, therefore, most reported data refer to total concentrations of particulate nickel. In a survey conducted in 11 Canadian urban cities and one rural site from 1987 to 1990, the reported annual mean concentrations of nickel ranged from 1 to 20 ng/m^3 (maximum values ranged from 6 to 77 ng/m^3); the annual mean concentration at Walpole Island was

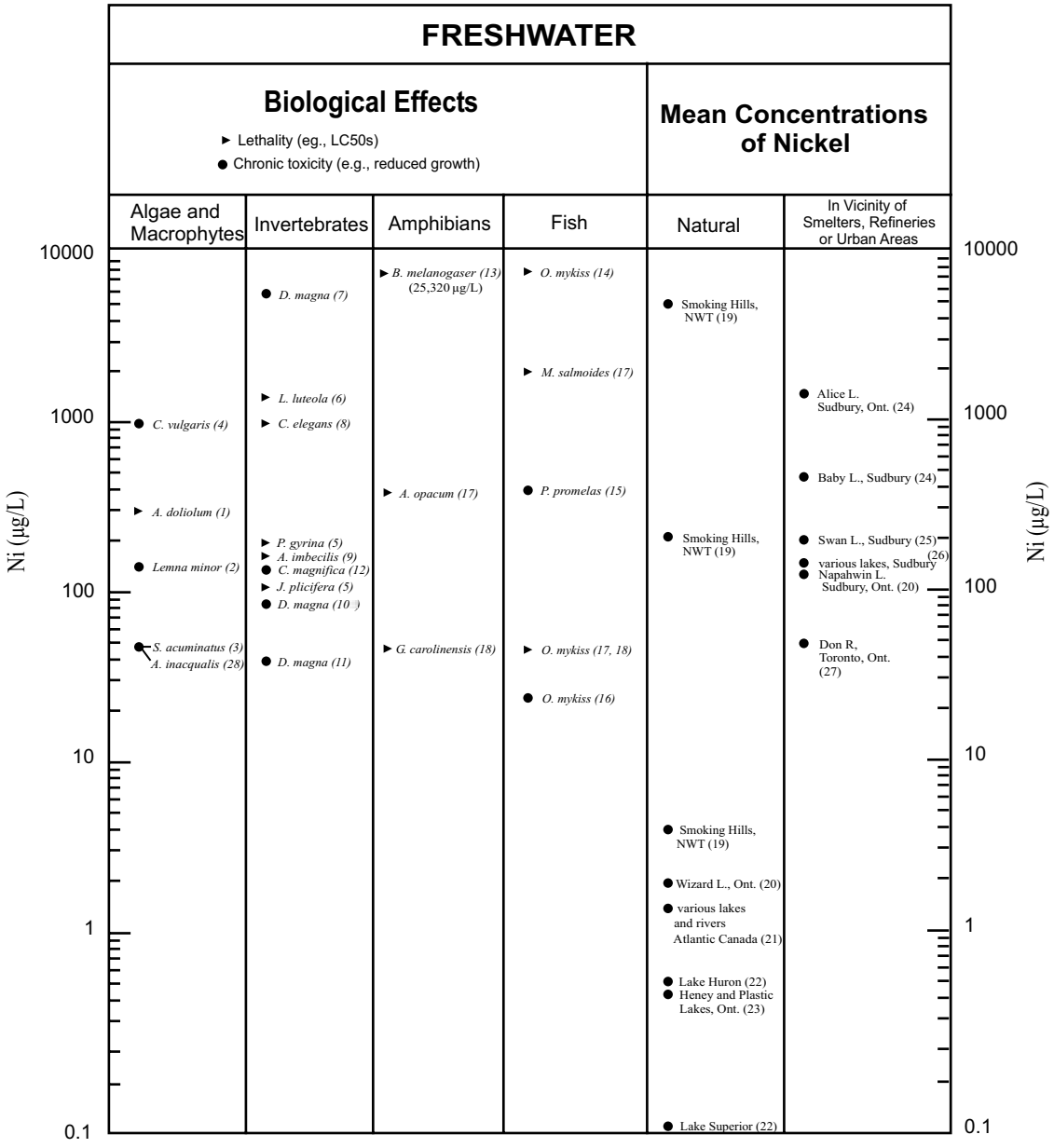
* Unless otherwise specified, the cited data on environmental levels of nickel refer to total nickel.

1 ng/m^3 (Dann, 1991a;b). The levels recorded for the same cities from 1984 to 1987 were similar, with annual mean values ranging from 1 to 26 ng/m^3 (Dann, 1990). Based on limited data, maximum values for concentrations of nickel in ambient air may be significantly elevated in the vicinity of industrial sources. For example, maximum concentrations that occurred near nickel production sites, such as Copper Cliff, Ontario, in 1980, 1986, and 1988 were 4400, 2300, and 6100 ng/m^3, respectively (Brecher *et al.*, 1989; Dobrin and Potvin, 1992; OME, 1992). Averages for the Sudbury-Copper Cliff area from 1978 to 1988 ranged from 100 to 250 ng/m^3 (Chan *et al.*, 1986; Dobrin and Potvin, 1992). In samples of ambient air taken from 1978 to 1980 in the Sudbury basin, concentrations of nickel ranged from 1 to 732 (mean 21) ng/m^3, while levels ranged from 10 to 124 ng/m^3 and 3 to 36 ng/m^3 at distances of 0 to 39 km and 0 to 37 km, respectively, from the INCO and Falconbridge smelters (Chan and Lusis, 1986). For remote locations, such as the Canadian Arctic, the annual mean concentration was 0.38 ng/m^3 in the early 1980s; maximum concentrations were not reported (Hoff and Barrie, 1986). The concentration of nickel in the stratosphere was below the detection limit of 1 ng/m^3 (Dann, 1991a;b).

Data on levels of nickel in Canadian indoor air in non-occupational settings have not been identified. In an indoor air quality study conducted in two New York State counties in 1986, the concentrations of nickel in week-long samples of fine particle mass collected in 394 homes ranged from 2 to 3 ng of Ni/m^3 (detection limit and levels in outdoor air near homes not reported) (Koutrakis *et al.*, 1992).

Drinking Water. The mean concentrations of nickel in drinking water in a survey of 96 plants across Ontario, with the exception of those for Sudbury, ranged from 0.2 to 7.2 µg/L (Jenkins, 1992) and are similar to those reported in earlier surveys conducted across Canada (Neri *et al.*, 1975; Méranger *et al.*, 1981). In surveys of drinking water supplies conducted between 1985 and 1988 in Northern Alberta and the Atlantic Provinces, the mean concentrations ranged from 2.1 to 2.3 µg/L (Moon *et al.*, 1988; Environment Canada, 1989a;b;c;d). Levels in drinking water in the Sudbury area sampled between 1972 and 1992 were markedly higher, with mean concentrations ranging from 26 to 300 µg/L (Flora and Nieboer, 1980; Hopfer *et al.*, 1989; Jenkins, 1992).

Surface Water and Sediment. As indicated in Figure 1, in general, concentrations of nickel in Canadian surface waters have been reported to range from 1 to 10 µg/L for relatively "uncontaminated" fresh waters. For example, Léger (1991) reported that nickel concentrations were typically less than 2 µg/L in several thousand samples from streams and lakes collected from 1973 to 1990 throughout Atlantic Canada. Much higher concentrations were detected (mean values of up to 6300 µg/L in filtered samples collected from 1975 to 1981) in pond waters near Smoking Hills, Northwest Territories, where the spontaneous burning of bituminous shales has resulted in the natural release of large quantities of nickel and other metals to local surface waters (Havas and Hutchinson, 1983). Elevated mean concentrations (50 to 1400 µg/L) have also been reported in lakes near Sudbury, Ontario (Hutchinson and Havas, 1986; Dixit *et al.*, 1991; Keller *et al.*, 1992). For example, Dixit *et al.* (1991) reported a mean of



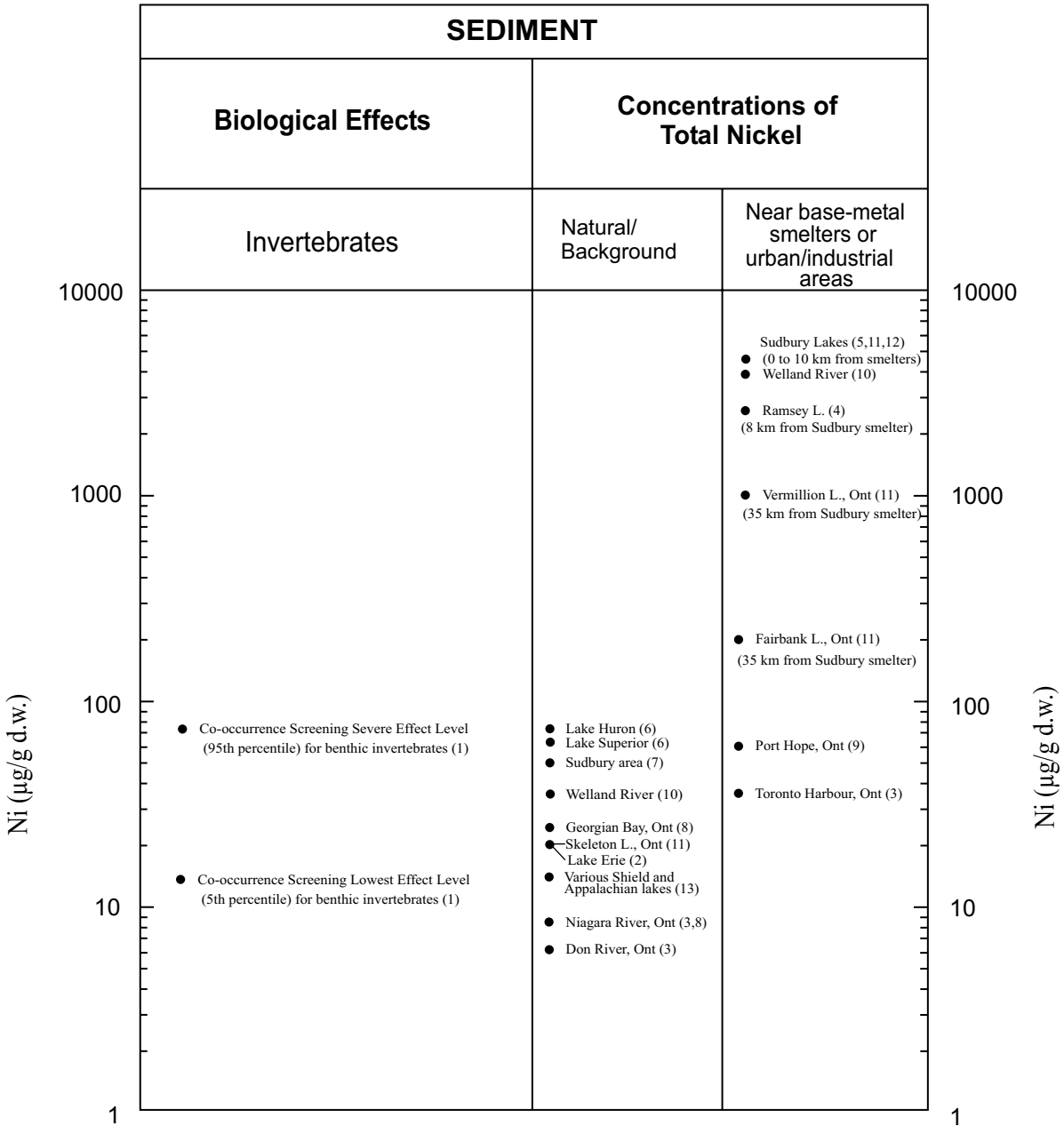
1. Mallick and Rai, 1990
2. Taraldsen and Norberg-King, 1990
3. Stokes, 1981
4. DenDooren deJong, 1965
5. Nebeker *et al.,* 1986
6. Khangarot and Ray, 1988
7. Khangarot and Ray, 1987b
8. Williams and Dusenbery, 1990
9. Keller and Zam, 1991
10. Kuhn *et al*., 1989
11. Münzinger, 1990
12. Nebeker *et al.,* 1984
13. Khangarot and Ray, 1987a
14. Nebeker *et al.,* 1985
15. Murty, 1986
16. Giattina *et al*., 1982
17. Birge *et al.,* 1978
18. Birge, 1978
19. Havas and Hutchinson, 1983
20. Alikhan *et al.,* 1990
21. Léger, 1991
22. Rossmann and Barnes, 1988
23. Jackson, 1988
24. Hutchinson and Havas, 1986
25. Keller *et al*., 1992
26. Dixit *et al*., 1991
27. Bodo, 1989
28. Stratton and Corke, 1979

Figure 1 Selected Mean Concentrations of Nickel (Total or Dissolved) in Canadian Surface Waters and Concentrations Causing Adverse Effects to Biota

131 µg/L of total nickel (maximum = 2000 µg/L) in unfiltered water samples collected in 1984 and 1987 from 72 lakes representing a range of pH conditions (4.0 to 8.0) located within 100 km of Sudbury. Keller *et al.* (1992) compared concentrations of total nickel in unfiltered water collected in 1981 and 1989 in 41 acidic lakes near Sudbury. They concluded that, although major reductions in emissions of trace metals to the atmosphere from the nickel-copper smelters in the 1970s led to significant decreases in concentrations of nickel in some lakes near Sudbury by the early 1980s, there was no evidence of a further decline since 1981. Concentrations were reported to have decreased exponentially with increasing distance from Sudbury; from 50 to 450 µg/L of total nickel were reported in lakes within a 20-km radius of Sudbury (Keller *et al.*, 1992). Recent estimates (based on diatom assemblages in buried sediments) of pre-industrial concentrations of nickel in lakes in the Sudbury area by Dixit *et al.* (1992), as well as decreases of over 80% in nickel concentrations in Sudbury lakes after atmospheric emissions from smelters were reduced in the early 1970s (Hutchinson and Havas, 1986), suggest that a significant fraction of the nickel in lakes closest to Sudbury was deposited from the atmosphere after being released from local smelters. Results of studies by Nriagu *et al.*, (1982) indicate that more than 95% of total concentrations of nickel in water from lakes in the Sudbury area is in the dissolved phase.

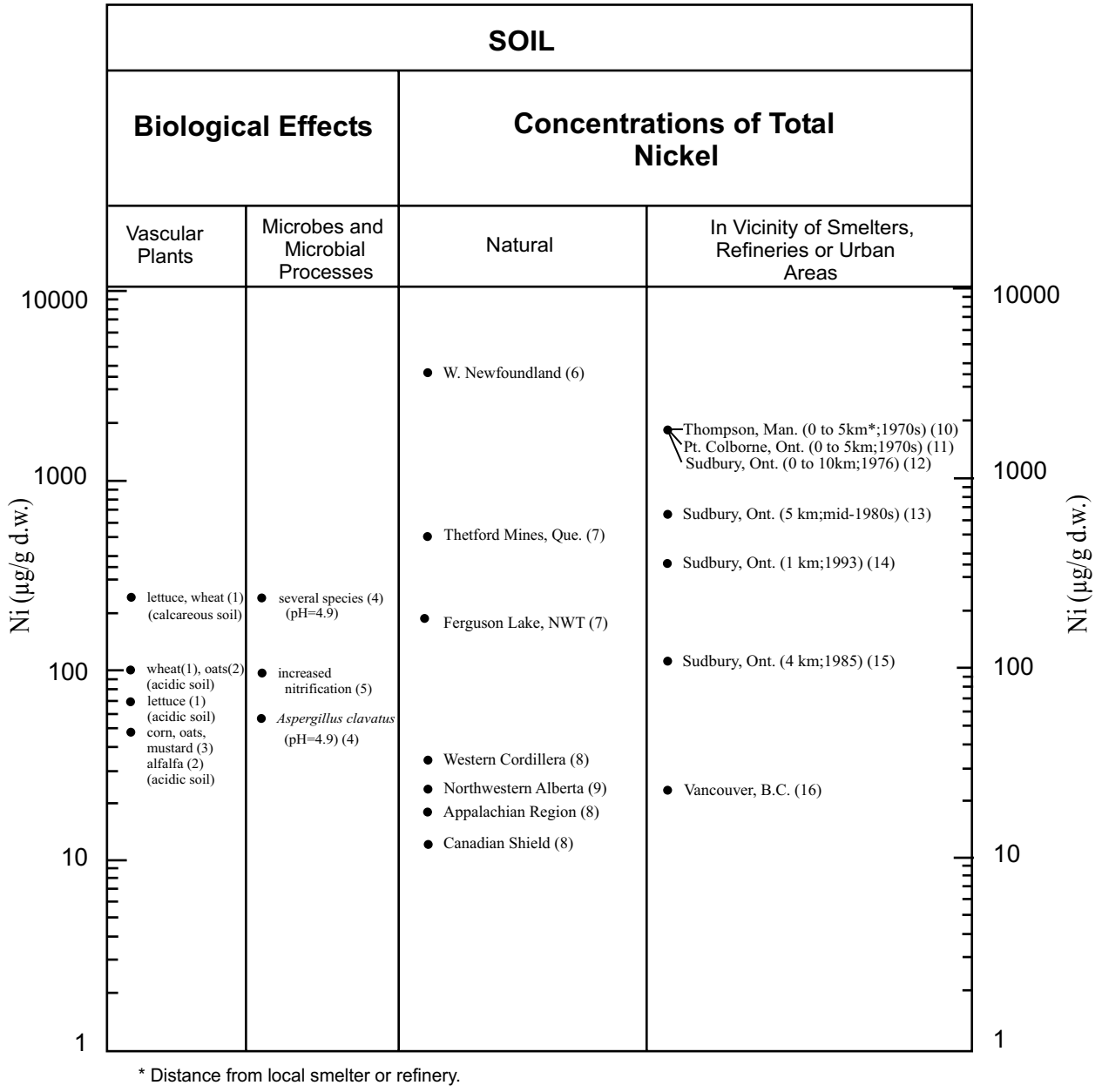
Selected data on total concentrations of nickel in Canadian sediments are presented in Figure 2. Concentrations of nickel in sediments from Canadian lakes varied from <10 µg/g (d.w.) in deeper or uncontaminated sediments (Bodo, 1989) to >4000 µg/g (d.w.) in contaminated surface or subsurface sediments (Bradley and Morris, 1986). Based on results of analysis of over 70 000 samples collected mainly in the Shield and Appalachian regions of Canada during the past 20 years, background concentrations of nickel in Canadian lake sediments typically range from about 5 to 50 µg/g (median value = 15 µg/g) (Friske, 1993). Concentrations of nickel well above normal background levels were reported in surface sediments in lakes within a radius of 40 km or more of the nickel-copper smelters at Sudbury, and in the Welland River, downstream from a steel manufacturing plant (Dillon and Smith, 1984; Palmer *et al.*, 1989; Dickman *et al.*, 1990).

Soil. Concentrations of total nickel in some Canadian soils are presented in Figure 3. Based on a survey of 288 samples collected in the early to late 1970s from 81 uncontaminated areas in Canada (McKeague *et al.*, 1979), the mean concentration of total nickel in Canadian soils is 22 µg/g (range = 1 to 67 µg/g). In more recent surveys of samples collected in five different locations in Alberta, the mean concentrations of total nickel at different sites ranged from 15 to 24.9 µg/g (Alberta Environment, 1991; CEA, 1985; Soon and Abboud, 1990; Spiers *et al.*, 1989). Given the distribution of nickel-enriched (mafic and ultramafic) bedrock in Canada, local areas of naturally nickel-enriched soil likely exist in most regions, with the possible exception of the St. Lawrence River lowlands and the southern plain regions of Alberta and Saskatchewan (Doyle, 1991). Rencz and Shilts (1980) reported concentrations of more than 200 µg/g of total nickel (and up to about 700 µg/g) in the silt- and clay-size fraction (<64 µm) of till, near an outcrop of ultramafic rock in the Thetford Mines area of Quebec, and 80 to 560 µg/g of total nickel in acidic soils associated with sulphide ore bodies near



1. Jaagumagi (1990)
2. Kauss (1983)
3. Bodo (1989)
4. Arafat and Nriagu (1986)
5. Dillon and Smith (1984)
6. Moore and Ramamoorthy (1984)
7. Nriagu *et al*. (1983)
8. Jackson (1988)
9. Hart *et al*. (1986)
10. Dickman *et al*. (1990)
11. Bradley and Morris (1986)
12. Palmer *et al*. (1989)
13. Friske (1993)

Figure 2 Selected Mean (or Median) Concentrations of Total Nickel in Canadian Sediment and Concentrations of Sediment-associated Nickel Causing Adverse Effects to Benthic Organisms



* Distance from local smelter or refinery.

1. Mitchell *et al.,* 1978
2. Halstead *et al.,* 1969
3. Webber, 1972
4. Babich and Stotzky, 1982
5. deCatanzaro and Hutchinson , 1985a,b
6. Roberts , 1980
7. Rencz and Shilts, 1980
8. McKeague *et al*., 1979
9. Soon and Abboud, 1990
10. Hutchinson *et al*., 1981
11. Temple and Bisessar, 1981
12. Freedman and Hutchinson, 1980
13. Roshon, 1988
14. Winterhalder, 1994
15. Skraba, 1989
16. Warren *et al.,* 1971

Figure 3 Selected Mean Concentrations of Total Nickel in Canadian Surface Soils and Concentrations in Soil Associated with Adverse Effects to Terrestrial Biota

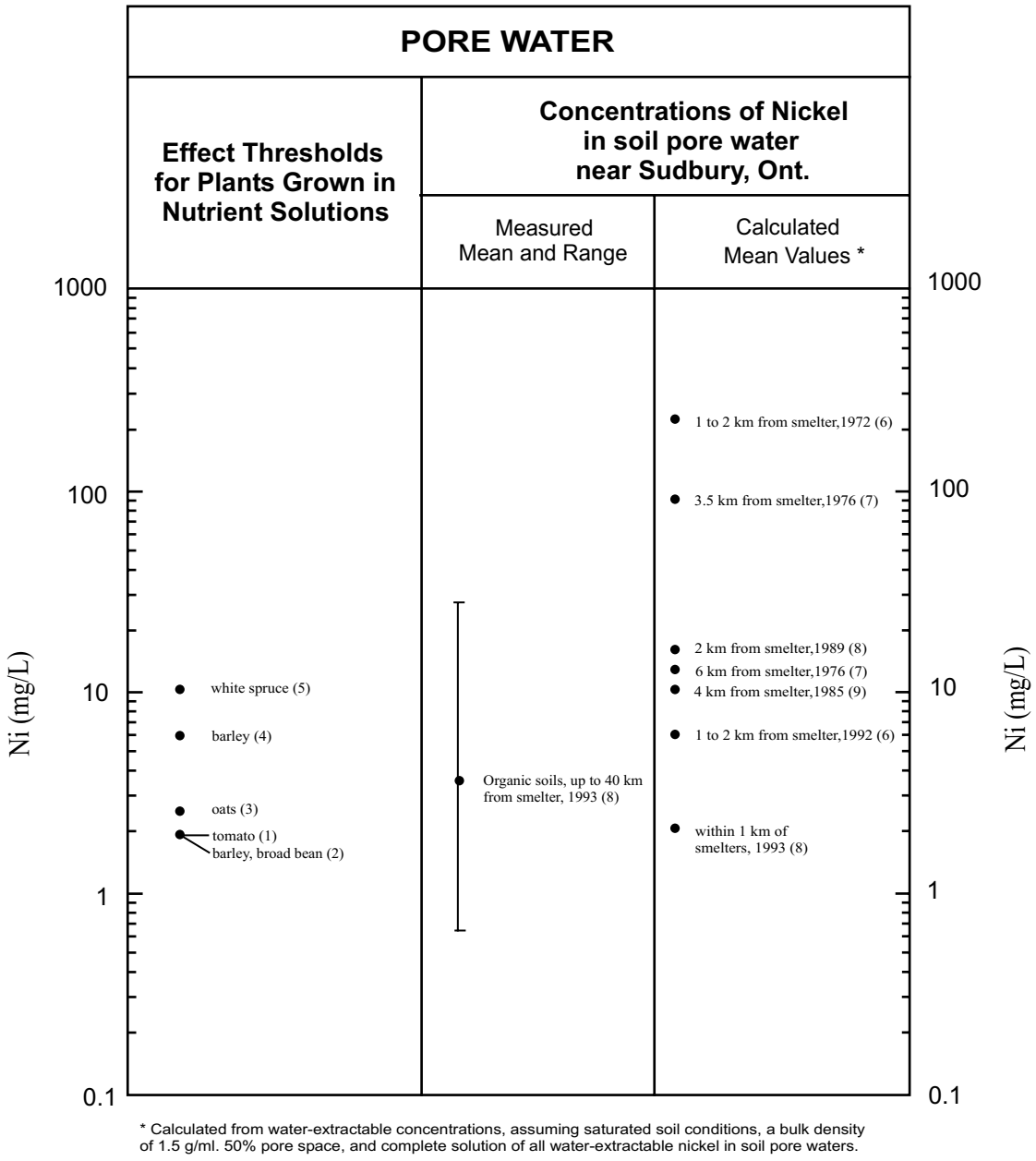
Ferguson Lake, NWT. Roberts (1980) reported even higher concentrations (mean = 3460 µg/g of total nickel) in neutral (pH 6.8 to 7.3) soils developed on ultramafic (serpentine) bedrock in western Newfoundland.

Although nickel levels in soils can be naturally elevated in certain areas, atmospheric deposition of anthropogenic nickel can also increase the nickel content of topsoils near major sources of emissions. Mean concentrations of 1800 to 1900 µg/g of total nickel were reported in surface soils collected in the 1970s within 10 km of nickel-copper smelters in Sudbury, Ontario and Thompson, Manitoba, and within 5 km of a nickel refinery in Port Colborne, Ontario (Freedman and Hutchinson, 1980; Hutchinson *et al.,* 1981; Temple and Bisessar, 1981). Reported concentrations typically decreased with increasing distance from these sources. This trend, along with the strong enrichment (up to an order of magnitude or more) of nickel in surface relative to subsurface horizons in the Sudbury and Port Colborne areas (Freedman and Hutchinson, 1980; Temple and Bisessar, 1981), suggest that most of the nickel in these surface soils was deposited from the atmosphere after release from local metal-processing facilities. Results of studies in the Sudbury area by Freedman and Hutchinson (1980) and the Ontario Ministry of the Environment (Pearson, 1991) indicate that, in the late 1970s and early 1980s, concentrations of nickel were elevated above background values (i.e., approximately 25 µg/g) within a radius of up to 100 km of Sudbury, and that the soils affected were typically acidic (pH 4.0 to 5.0). The pH of the organic soils near the refinery at Port Colborne was reported to be in the neutral range (Temple and Bisessar, 1981).

Nickel concentrations reported in samples of surface soils collected in the 1980s and early 1990s in the Sudbury area are somewhat lower than those reported in the 1970s, likely because of leaching and erosion processes (Hazlett *et al.,* 1984; Gundermann and Hutchinson, 1993). For example, average concentrations of total nickel in samples collected by K. Winterhalder and co-workers in the mid-1980s to early 1990s within approximately 5 km of the smelters ranged from about 100 to 725 µg/g (maximum = 1760 µg/g) (Archambault, 1991; Skraba, 1989; Roshon, 1988; Winterhalder, 1992; 1994). Maxwell (1991) reported that mean concentrations of total nickel in samples of soil collected from 1982 to 1984 from 6 sites located within 5 km of the smelters at Sudbury, ranged from 165 to 380 µg/g.

Concentrations of water-extractable nickel have also decreased in soils near Sudbury. For example, values of 4 to 74 µg/g of water-extractable nickel [equivalent to about 12 to 220 mg Ni/L in soil pore water* (Figure 4)] were reported in surface soils collected in the early to mid-1970s within a radius of 6 km of the smelters (Freedman and Hutchinson, 1980; Gundermann and Hutchinson, 1993), whereas samples collected from the same areas in the mid-1980s to early 1990s contained only from 0.7 to 4.9 µg/g of

* Calculated assuming a bulk soil density of 1.5 g/mL and 50% pore space (Buckman and Brady, 1960), water-saturated soil conditions, and complete solution of water-extractable nickel in soil pore waters.



* Calculated from water-extractable concentrations, assuming saturated soil conditions, a bulk density of 1.5 g/ml. 50% pore space, and complete solution of all water-extractable nickel in soil pore waters.

1. Whitby and Hutchinson, 1974
2. Brenchley, 1938
3. Vergnano and Hunter, 1952
4. Davis and Beckett, 1978
5. Lozano and Morrison, 1982
6. Gundermann and Hutchinson, 1993
7. Freedman and Hutchinson, 1980
8. Winterhalder, 1994
9. Skraba, 1989

Figure 4 Concentrations of Nickel (Measured or Calculated) in the Pore Waters of Soils Near Sudbury, Ontario and Concentrations in Nutrient Solutions Causing Adverse Effects to Selected Terrestrial Plants

water-extractable nickel (equivalent to 2 to 15 mg Ni/L in pore water*) (Gundermann and Hutchinson, 1993; Skraba, 1989; Winterhalder, 1994). As shown in Figure 4, the average concentration of nickel in 24 samples of organic-rich pore water from wetland soils collected within a radius of about 40 km of Sudbury was recently reported to be 3.5 mg/L (range of 0.6 to 22.6 mg/L) (Winterhalder, 1994). Based on data from other countries, nickel concentrations in pore waters of relatively uncontaminated soils are normally much lower (range of 0.003 to 0.15 mg/L) (Kabata-Pendias and Pendias, 1992).

Aquatic Biota. Few data were identified on concentrations of nickel in aquatic biota in Canada. As expected, such concentrations depend upon the organism and the location from which the sample was obtained. Concentrations were normally elevated in organisms in areas close to nickel smelters. In fish (whole body), invertebrates, and flora from "uncontaminated" Canadian waters, mean concentrations of nickel were 2 µg/g wet weight (w.w.), 4 to 29 µg/g (w.w.), and 1 µg/g (d.w.), respectively (Hutchinson *et al.*, 1976; Mudroch, 1980; Percy, 1983; Wren *et al.*, 1983; Johnson *et al.*, 1988; Krantzberg and Stokes, 1990). The mean concentration of nickel in insect larvae in 1984 in the Wanapitei region near Sudbury was 22.3 µg/g (d.w.) (Krantzberg, 1985). Concentrations of nickel in zooplankton from 6 of 7 lakes sampled near Sudbury were less than 25 µg/g (d.w.) (Yan and Mackie, 1989). The highest mean concentration of nickel in aquatic plants collected in the 1970s near Sudbury was 290 µg/g (d.w.) in aquatic weeds such as *Elodea canadensis* and *Potamogeton richardsonii* (Hutchinson *et al.*, 1976).

Concentrations of nickel in tissues of several species of fish from the French River in Ontario (which is slightly contaminated by nickel) were as high as 52 µg/g (w.w.) (Hutchinson *et al.*, 1976; Evans, 1991). Concentrations of nickel of up to 921 µg/g (d.w.) have been reported in the gut of crayfish *(Cambarus bartoni)* collected from Nepahwin and Ramsey Lakes in Sudbury (Bagatto and Alikhan, 1987).

Metal-tolerant green algae, consisting primarily of *Chlorococcales* and *Chlorophyta* species, isolated from Sudbury area lakes had concentrations of nickel of 4.5 µg/g (d.w.) (NRCC, 1981; Havas and Hutchinson, 1983). Algae from pristine locations contained about four times less nickel.

Terrestrial Biota. Information on concentrations of nickel in Canadian vegetation is presented in Figure 5. According to Hutchinson *et al.* (1981), concentrations of nickel in Canadian vegetation in areas remote from point sources are typically less than 10 µg/g (d.w.). McIlveen and Negusanti (in press) reported that mean concentrations in 65 plant species collected from 1990 to 1992 mostly in areas with no obvious nickel contamination were typically less than 6 µg/g (d.w.). Higher concentrations have been reported in Canadian vegetation in areas with naturally and anthropogenically nickel-enriched soils. Rencz and Shilts (1980) found mean values of 35 to 60 µg/g (d.w.) of nickel in leaf

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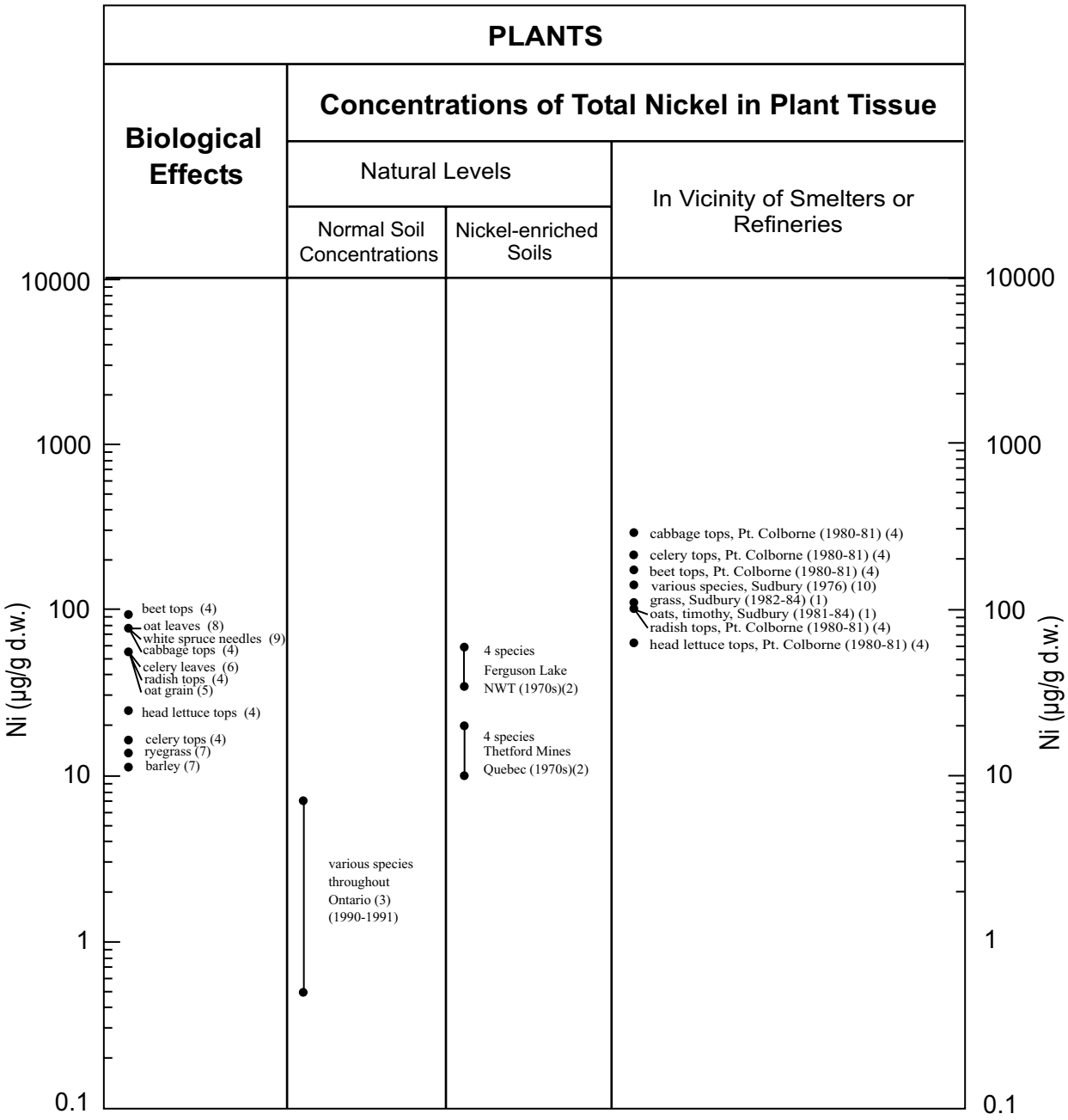
* Calculated assuming a bulk soil density of 1.5 g/mL and 50% pore space (Buckman and Brady, 1960), water-saturated soil conditions, and complete solution of water-extractable nickel in soil pore waters.



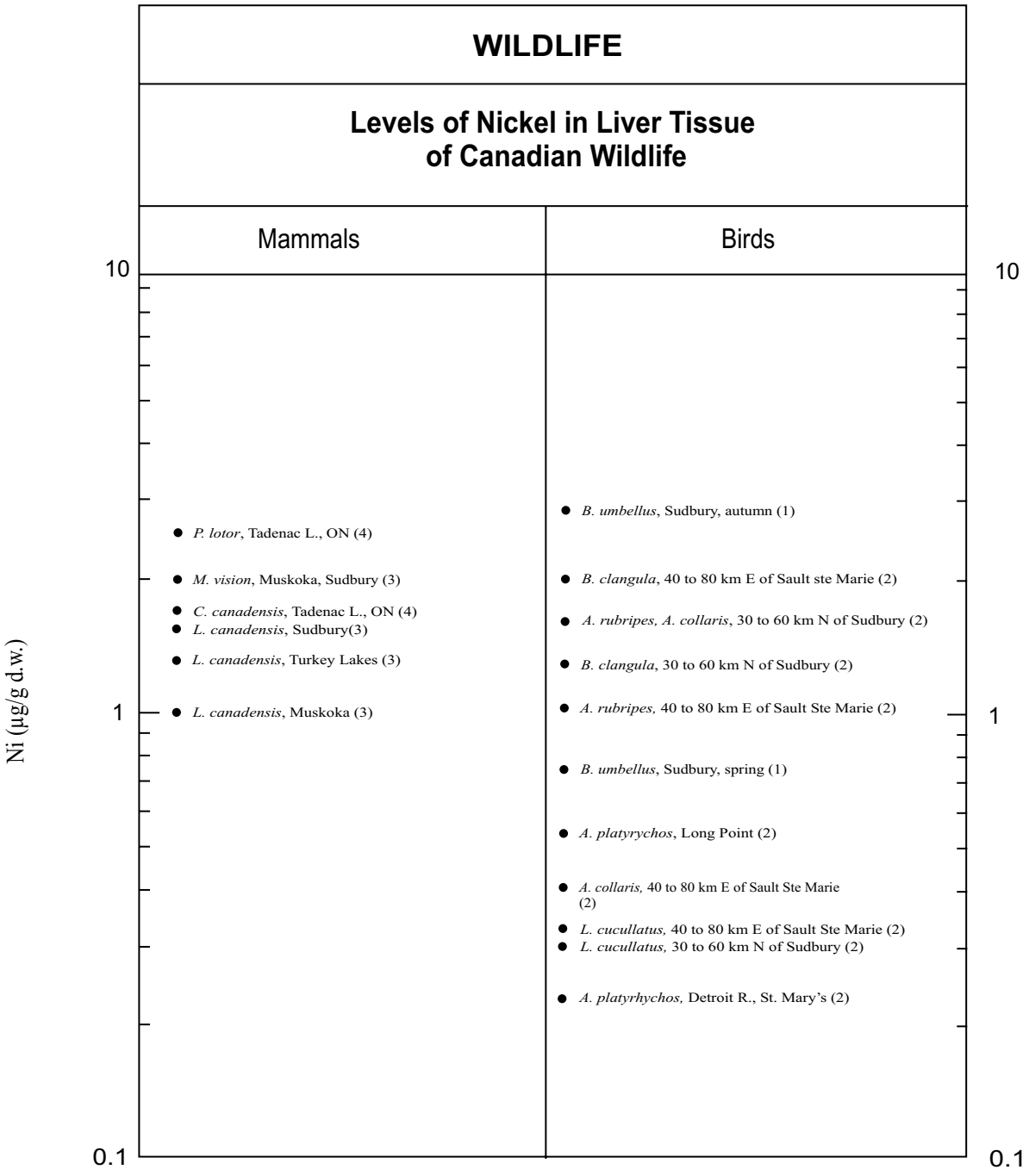
1. Negusanti and McIlveen, 1990
2. Rencz and Shilts, 1980
3. McIlveen and Negusanti, in press
4. Frank *et al*., 1982
5. Halstead *et al*., 1969
6. Temple and Bisessar, 1981
7. Davis and Beckett, 1978
8. Vergnano and Hunter, 1952
9. Lozano and Morrison, 1982
10. Freedman and Hutchinson, 1980

Figure 5 Selected Mean Nickel Concentrations in Canadian Vegetation and Nickel Concentrations in Plant Tissue Associated with Adverse Effects

tissue of four species of arctic plants growing in acidic soils near sulphide ore bodies near Ferguson Lake, NWT, and mean values of 10 to 20 µg/g (d.w.) [calculated as 0.05 x ash weight (Brooks, 1980)] in the leaves of four species of native trees near an exposure of ultramafic bedrock near Thetford Mines, Quebec. Elevated concentrations of nickel [mean = 140 µg/g (d.w.); maximum =460 µg/g (d.w.)] were also reported by Freedman and Hutchinson (1980) in samples of 17 terrestrial plant species collected in 1976 within 3.5 km of one of the smelters at Sudbury. Concentrations decreased with distance from the smelter, reaching a mean of approximately 12 µg/g (d.w.) at a distance of 60 km. Nickel levels in aspen *(Populus tremula)* leaves from the crops of ruffed grouse near Sudbury ranged from 61.7 µg/g (d.w.) in May 1980 to 136 µg/g (d.w.) in September 1980 (Rose and Parker, 1983). Samples of lawn grass, timothy, and oats exhibiting symptoms of nickel toxicity collected from 1981 to 1984 in the Sudbury area contained an average of about 100 µg/g (d.w.) of nickel [range = 80 to 150 µg/g (d.w.)] (Negusanti and McIlveen, 1990). Frank *et al.* (1982) also reported high concentrations of nickel [mean values from 40 to 290 µg/g, (d.w.)] in the top portions of vegetable crops (beet, cabbage, radish, celery, and head lettuce) grown in 1980 and 1981 in soils located about 1 km from the nickel refinery at Port Colborne, Ontario. All the plants analyzed by Frank *et al.* (1982) showed evidence of injury (e.g., reduced yield, stunted growth, chlorosis, and necrosis) which the authors attributed to exposure to high levels of nickel in local soils.

Tissues of wild mammals and birds from uncontaminated habitats in Canada and elsewhere contained < 0.1 to about 5 µg/g (d.w.), whereas in nickel-contaminated environments, mammalian and avian tissues accumulated about 0.5 to 10 µg/g (d.w.) (Outridge and Scheuhammer, 1992). The highest concentrations were usually associated with tissues directly exposed to the external environment (i.e., fur, feathers, and skin). Concentrations of nickel in the most commonly analyzed internal organs (liver and kidney) ranged from nondetectable to about 3 µg/g (d.w.), with higher concentrations in the kidney than in the liver. Few data were identified on concentrations of nickel in wildlife in Canada. Figure 6 summarizes concentrations of nickel found in the livers of mammals and birds in Canada. Concentrations of nickel in the kidneys of grouse *(Bonasa umbellus)* near Sudbury [3.0 µg/g (d.w.)] were about two- to four-fold higher than those in grouse 100 km away (Rose and Parker, 1983).

Food. Most foodstuffs consumed in Canada contain nickel. In a 1988 Canadian market basket survey of 112 different food types obtained from Montreal (NHW, 1992), nickel was detected in dairy products (from less than 0.002 µg/g in 2% B.F. milk to 0.323 µg/g in ice cream), meat and poultry (from less than 0.007 µg/g in eggs to 2.52 µg/g in cooked ground beef), fish (from 0.047 µg/g in cooked freshwater fish to 0.21 µg/g in cooked marine fish), soup (from 0.064 in dehydrated soups to 0.69 µg/g in canned soups), bakery goods and cereal products (from 0.012 in cooked pasta to 1.27 µg/g in cookies), vegetables (from 0.006 µg/g in cooked carrots to 0.98 µg/g in boiled potatoes), fruit and fruit juices (from 0.012 in canned apple juice to 0.42 µg/g in raw and canned cherries), cooking fats at 0.45 µg/g, peanut butter and peanuts at 1.47 µg/g, sugar



Note: Conversion from wet weight to dry weight was done by multipying the wet weight concentration by 3.5

1. Rose and Parker, 1983
2. Outridge and Scheuhammer, 1992
3. Wren *et al*., 1988
4. Wren, 1984

Figure 6 Selected Mean Total Nickel Concentrations in Canadian Wildlife

and candies (from less than 0.003 µg/g in sugar to 0.58 µg/g in chocolate candy), and beverages (from 0.001 µg/g in soft drinks to 0.052 µg/g in tea). The detection limits varied depending on the types of food and the reagent blank values. Based on data reported in earlier studies, the average concentrations of nickel were somewhat elevated in Canadian vegetable crops at locations close to smelters. At sites close to smelters, edible portions contained up to 166 µg/g (d.w.) (Frank *et al.*, 1982; McIlveen and Balsillie, 1977 in NRCC, 1981; Temple, 1978 in NRCC, 1981; Warren *et al.*, 1971). No data were identified on levels of nickel in breast milk in Canada.

Other Sources. Mainstream smoke produced by five samples each of five brands of Canadian cigarettes contained from 0.25 to 0.58 µg of nickel per cigarette (mean = 0.43 µg of Ni per cigarette). Levels of nickel present in sidestream smoke were similar, ranging from 0.25 to 0.53 µg (mean = 0.37 µg) per cigarette (Labstat Incorporated, 1991). Various household products also contain nickel. For example, Nava *et al.* (1987) reported that nickel was detected in 33 of 34 samples of different types of cleaning agents with mean concentrations ranging from 0.08 µg/g in bleaching agents to 19.17 µg/g in scouring powders. In a study of corrosion products from home cookware (Kuligowski and Halperin, 1992), nickel was detected in the leachates from seven different stainless steel utensils, at concentrations ranging from 0.01 to 0.21 µg/g.

2.4 Toxicokinetics and Essentiality

Nickel and nickel compounds are absorbed from the respiratory tract and to a lesser extent, from the gastrointestinal tract. In general, absorption of nickel increases with greater solubility of the compounds following both ingestion and inhalation (IPCS, 1991). Results of studies in humans indicate that approximately 35% of inhaled nickel is absorbed into the blood from the respiratory tract following inhalation (ATSDR, 1991), while only 1 to 10% of ingested nickel is absorbed, depending largely on the composition of the diet (IPCS, 1991). Following inhalation, absorbed insoluble particulate nickel (e.g., metallic nickel or nickel oxide dust) is very slowly removed with resulting accumulation over time. Distribution varies depending on the route of exposure (IPCS, 1991). Levels of nickel were much higher in the lungs than in the liver and kidneys following exposure by inhalation. After gastrointestinal absorption, however, nickel is present primarily in the kidneys, with substantial amounts in the liver, heart, lung, and fat, as well as in the peripheral nervous tissues and in the brain. The majority of absorbed nickel is excreted in the urine regardless of the route of exposure; however, most ingested nickel (i.e., unabsorbed) is excreted in the feces (ATSDR, 1991; IPCS, 1991). Nickel is transported in the blood, principally bound to albumin (IPCS, 1991). The results of several studies have indicated that transplacental transfer of nickel occurs in humans and animals (IPCS, 1991). Based on the results of various studies, which indicate that nickel may be an essential element in a number of experimental animal species, it has been postulated to be an essential element in humans. Nevertheless, nickel deficiency has not been unequivocally demonstrated in human beings (ATSDR, 1991; IPCS, 1991).

2.5 Effects-related Information

2.5.1 *Experimental Animals and* In Vitro

Available data indicate that the "soluble" nickel salts (e.g., nickel chloride, nickel sulphate, nickel nitrate, and nickel ammonium sulphate) are moderately to highly acutely toxic to rats [LD_{50}s of 42.5 to 112 mg of Ni/kg (b.w.)], while nickel powder and the insoluble nickel salts (green and black nickel oxides, nickel subsulphide, and amorphous nickel sulphide) are less acutely toxic [LD_{50}s of 3235 to 9000 mg of Ni/kg (b.w.)]. Most of the acute inhalation studies involved nickel carbonyl, with LC_{50} values of 100 mg/m^3 (20-minute exposure period) and 240 mg/m^3 (30 minutes) in rats and 67 mg/m^3 (30 minutes) in mice (BIBRA, 1992).

Minimal effects on the morphology and function of alveolar cells have been observed in rabbits exposed to concentrations of metallic nickel as low as 0.1 mg/m^3 in several short-term studies in which only respiratory effects were examined (Camner and Johansson, 1992; Camner *et al.*, 1978; Johansson and Camner, 1980; Lundborg and Camner, 1982). More severe effects on the respiratory system, but no systemic effects, have been observed in early limited or inadequate studies in rabbits (chronic inflammatory changes) exposed to 45 mg/m^3 for approximately 6 months (Friberg, 1950) and in rats (pleurisy, pneumonia, congestion, and edema) exposed to 15 mg/m^3 for up to 21 months (Hueper, 1958).

Adequate carcinogenicity bioassays in which experimental animals have been exposed to metallic nickel by inhalation have not been identified. No increase in lung tumours was observed in the only identified limited study in which mice were exposed to airborne metallic nickel powder (15 mg of Ni/m^3) for life (Hueper, 1958). In rats in which nickel powder (0.3 or 0.9 mg of Ni/week) was introduced directly by intratracheal instillation in saline for 10 to 20 weeks, however, there was a clear increase in the incidence of lung tumours (Pott *et al.*, 1987). In studies reviewed by the International Agency for Research on Cancer (IARC, 1990), in which animals have been administered metallic nickel via routes less relevant to assessment of effects of environmental exposure (e.g., intrapleural, subcutaneous, intramuscular, intraperitoneal, and intrarenal injection), increased incidences of tumours at the site of injection were observed.

Nickel powder did not induce chromosomal aberrations in human peripheral blood lymphocytes *in vitro* (Paton and Allison, 1972). However, there was a clear increase in the incidence of chromosomal aberrations in the bone marrow of female Wistar rats after repeated inhalation exposure to a metal aerosol derived from nickel refinery waste (Chorvatovicova and Kovacikova, 1992). No information was identified on the reproductive, developmental, immunotoxic, or neurological effects of metallic nickel in experimental animals.

For "oxidic" nickel, short-term inhalation studies have focused predominantly on the toxic effects on the lungs, although one group of investigators has conducted histopathological examination of an extensive range of tissues of rats and mice exposed for 12 days to nickel oxide (over a 16-day period) (Dunnick *et al.*, 1988). The

Lowest-Observed-Effect-Level (LOEL) in the identified studies was 0.1 mg of Ni/m^3; at this concentration, rats exposed to nickel oxide produced by decomposition of nickel acetate had increased numbers of macrophages with more than one nucleus (Spiegelberg *et al.,* 1984). In a subchronic study in which rats and mice were exposed to nickel oxide by inhalation at concentrations of from 0.4 to 7.9 mg of Ni/m^3 for 90 days, there was hyperplasia of the bronchial lymph nodes at 0.4 mg of Ni/m^3 and above in rats, and 0.9 mg of Ni/m^3 and above in mice. Hyperplasia of the alveolar macrophages was observed in both species at all concentrations, while chronic active inflammation (and, in some mice, focal interstitial fibrosis) was noted at higher concentrations (Dunnick *et al.,* 1989). Based on examination of body weight gain, clinical observations and histopathological changes, there were no effects other than those observed in the lungs in exposed rats and mice. The LOEL for both rats and mice was considered to be 0.4 mg of Ni/m^3. In rats exposed to nickel oxide (produced by decomposition of nickel acetate) at concentrations of 0.02 mg of Ni/m^3 and above for 4 months, there was a significant dose-related increase in the number of granulocytes and lymphocytes in the lungs, and an increase in the size of the macrophages and in the number of macrophages with more than one nucleus (Spiegelberg *et al.,* 1984). In chronic studies, lung damage (congestion, inflammation, fibrosis, edema) was reported in studies in which rats were exposed via continuous inhalation to 0.06 and 0.2 mg of Ni/m^3 as nickel oxide for 18 months (Glaser *et al.,* 1986; Takenaka *et al.,* 1985) or 0.9 mg of Ni/m^3 for 6 months (Haratake *et al*., 1992). However, only in the study by Haratake *et al.* (1992) was the extent of histopathological examination specified (it was restricted to the lungs, liver, pancreas, kidney, spleen, head, and neck).

In studies in which hamsters were exposed to nickel oxide by inhalation at concentrations of up to 42 mg of Ni/m^3 for life (Wehner *et al*., 1975), there was no evidence of nickel-induced carcinogenicity. In rats exposed to 5 or 15 mg of Ni as nickel oxide for 10 weeks by intratracheal instillation, there was a clear increase in the incidence of lung tumours (Pott *et al.,* 1987). "Oxidic" nickel compounds have also induced an increased incidence of tumours at the site of injection in experimental animals (IARC, 1990).

Nickel oxide induced cell transformation in cultured rodent cells and anchorage-independent growth in primary human diploid foreskin fibroblasts and inhibited progression through S phase in Chinese hamster ovary cells as measured by flow cytometry (IARC, 1990). However, it did not induce chromosomal aberrations in human peripheral blood lymphocytes *in vitro* (Paton and Allison, 1972). There were decreases in fetal body weights in rats continuously exposed to 1.6 and 3.2 mg of Ni/m^3 as nickel oxide (produced from decomposition of nickel acetate) for 21 days of pregnancy (Weischer *et al*., 1980). There were no exposure-related effects on testis weights or on sperm number, motility, or morphology in rats and mice exposed to 0.4 to 7.9 mg of Ni/m^3 as nickel oxide (Benson *et al*., 1990). No information was identified on the neurological effects of "oxidic" nickel in animal species.

Immunological effects, including increased antibody-forming cells in the lung-associated lymph nodes and decreased alveolar macrophage phagocytic activity,

were observed in mice exposed by inhalation to 0.47 mg of Ni/m^3 or greater as nickel oxide for 65 days (Haley *et al.,* 1990). Similarly, there was a decrease in the number of alveolar macrophages and in the humoral response in rats inhaling 0.025 mg of Ni/m^3 as nickel oxide (produced from decomposition of nickel acetate) for 4 months (Spiegelberg *et al,* 1984). Increased mortality due to viral infection was observed in mice following a single intratracheal instillation of 1 to 5 mg of nickel oxide [7 to 35 mg of Ni/kg (b.w.)] (Port *et al.,* 1975).

Short-term inhalation studies in experimental animals exposed to "sulphidic" nickel have also focused mainly on effects on the lungs. In one study in which extensive histopathological examination of a wide range of tissues was conducted in rats and mice exposed for 12 days (over a 16-day period) to nickel subsulphide (Benson *et al.,* 1987; Dunnick *et al.,* 1988), degeneration of the respiratory epithelium and atrophy of the olfactory epithelium occurred at concentrations as low as 0.4 mg of Ni/m^3 in the rats and 0.9 mg of Ni/m^3 in the mice. There was atrophy of lymphoid tissues (spleen, thymus, and bronchial lymph nodes) in both species exposed to 7.3 mg of Ni/m^3. Degeneration of the testicular germinal epithelium was also observed in mice and rats exposed to 3.6 or 7.3 mg of Ni/m^3. In a comprehensive study in which rats and mice were exposed to nickel subsulphide by inhalation at concentrations between 0.1 and 1.8 mg of Ni/m^3 for 90 days, alveolar macrophage hyperplasia was observed in rats at all concentrations and in mice at 0.2 mg of Ni/m^3 and above, while chronic active inflammation (and, in some mice, focal interstitial fibrosis) occurred at higher concentrations (Benson *et al.,* 1990; Dunnick *et al.,* 1989). There were biochemical changes in the lungs indicative of a cytotoxic and inflammatory response which correlated well with the degree of chronic active inflammation. Atrophy of the olfactory epithelium was observed at concentrations of 0.2 or 0.4 mg of Ni/m^3 in rats and mice, respectively. The LOEL was considered to be 0.1 mg of Ni/m^3 in rats, while this value was considered to be the NOEL in mice, based on minimal respiratory effects. Lung damage, consisting of congestion, inflammation, fibrosis, and edema, was reported in rats exposed via inhalation to 0.4 mg of Ni/m^3 as nickel subsulphide for 6 months, based on histopathological examination of the lungs, liver, pancreas, kidney, spleen, head, and neck (Haratake *et al.,* 1992).

Exposure to 0.97 mg/m^3 of nickel subsulphide dust (approximately 0.7 mg of Ni/m^3) for 78 weeks resulted in a statistically significant increase in the incidence of benign and malignant lung tumours in large groups of male and female Fischer 344 rats. There were 14 animals with malignant tumours and 15 with benign tumours in the 208 exposed rats examined compared with only one of each type in the 215 controls (Ottolenghi *et al.,* 1974). An increase in the incidence of lung tumours (2 tumours in 5 surviving exposed rats versus 0/47 in controls) was also reported in a secondary account of a limited Soviet study in which rats were exposed for 6 months to dust containing nickel subsulphide; however, data in the published account were inadequate for assessment (Saknyn and Blokhin, 1978). Rats exposed to 0.063, 0.125, or 0.25 mg of Ni/m^3 as nickel subsulphide by weekly intratracheal instillation for 15 weeks also had a clear increase in the incidence of lung tumours (Pott *et al.,* 1987). However, there was no increase in the incidence of tumours in mice exposed once to 0.04 or 0.12 mg of Ni/m^3 as nickel subsulphide every week, 2 weeks, or 3 weeks by intratracheal instillation

for 15 weeks (McNeill *et al.,* 1990). Local tumours have been induced in animals administered "sulphidic" nickel compounds by injection (IARC, 1990).

Nickel subsulphide induced gene mutations in mammalian cells in culture, including L5178Y mouse lymphoma cells (thymidine kinase locus), rat liver epithelial cells [hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus], and Chinese hamster V79 or ovary (CHO) cells (HGPRT locus), but not in human cells. Various "sulphidic" nickel compounds induced cell transformation, with the extent of transformation being greatest with crystalline nickel subsulphide and nickel sulphide, and negligible with amorphous nickel sulphide (IARC, 1990). Administration of nickel subsulphide by intraperitoneal injection induced an increased frequency of micronucleated polychromatic erythrocytes in mice (Arrouijal *et al.,* 1990).

Testicular degeneration was reported in rats exposed to nickel subsulphide at concentrations of 1.8 mg of Ni/m^3 and above, and in mice exposed to nickel subsulphide at concentrations of 3.6 mg of Ni/m^3 and above (Benson *et al.,* 1987; 1988). Immunological effects, including a decrease in the mixed lymphocyte response, alveolar macrophage phagocytic activity and spleen natural killer cell activity, and increased numbers of antibody-forming cells in lung-associated lymph nodes, have been observed in mice exposed to nickel subsulphide at concentrations of 0.45 mg of Ni/m^3 or greater (Haley *et al.,* 1990). No data on the developmental or neurological effects of "sulphidic" nickel were identified.

Only limited data are available on the short-term, subchronic, and chronic toxicity of "soluble" nickel compounds following inhalation. Ciliary activity of the upper respiratory tract was reduced in hamsters and mice exposed to a nickel chloride aerosol at concentrations as low as 0.1 mg of Ni/m^3 for 2 hours (Adalis *et al.,* 1978; Gardner, 1980). In one study in which extensive histopathological examination of a wide range of tissues was conducted in rats and mice exposed for 12 days (over a 16-day period), histopathological changes of the lungs were observed in both species exposed to nickel sulphate hexahydrate by inhalation at concentrations of 0.8 mg of Ni/m^3 and above (Benson *et al.,* 1987; Dunnick *et al.,* 1988). Respiratory effects included inflammation of the lungs, with necrotizing pneumonia and an increase in the number of alveolar macrophages in the mice, degeneration of the respiratory epithelium in rats, and atrophy of the olfactory epithelium in rats and mice. Testicular degeneration was reported in rats exposed to concentrations of 1.6 mg of Ni/m^3 and above. Exposure to 0.02 and 0.05 mg of Ni/m^3 (as nickel sulphate hexahydrate) by inhalation for 13 weeks resulted in lesions in the lung and nasal areas (alveolar macrophage hyperplasia and atrophy of the olfactory epithelium) in rats and mice, respectively (Dunnick *et al.,* 1989). Haley *et al.* (1990) also reported increased numbers of lung-associated lymph nodes, but not spleen nucleated cells in $B6C3F_1$ mice following inhalation of 0.11 or 0.45 mg of Ni/m^3 as nickel sulphate, 6 hours/day, 5 days per week for 65 days. There was no increase in the incidence of tumours in hamsters exposed for up to 20 months to fly ash enriched with nickel acetate, although histopathological examination was limited to only a few organs (Wehner *et al.,* 1981).

Short- and long-term studies of the effects of "soluble" nickel compounds have been acquired principally in studies in which these compounds were administered by the oral route. Decreased growth and levels of urea in serum, and increased levels of urinary urea and serum glucose, but no effects on hematological parameters (no other pathological or histopathological effects were examined) were observed in rats administered nickel chloride in the drinking water at concentrations equivalent to a dose of 0.15 mg of Ni/[kg(b.w.) · d] for 28 days (Weischer *et al.*, 1980). In subchronic studies, reversible hematological effects (reduced level of glucose in the plasma and an increased number of white blood cells) were observed in rats administered 1.2 mg of Ni/[kg (b.w.) · d] as nickel chloride by gavage for 90 days (American Biogenics Corporation, 1986), while the uptake of iodine by the thyroid was inhibited in rats exposed to 0.23 mg of Ni/[kg (b.w.) · d] or more as nickel chloride in the drinking water for 12 weeks (Lestrovoy *et al.*, 1974), although the biological significance of this latter observation is unclear.

No effects were observed in male or female Wistar rats exposed for 2 years to nickel sulphate hexahydrate at concentrations equivalent to doses of approximately 0, 5, 50, or 125 mg of Ni/[kg (b.w.) · d] in the diet, based on the histological examination of a wide range of tissues (Ambrose *et al.*, 1976). Administration of nickel sulphate in the drinking water at concentrations of 1 g/L (equivalent to a dose of 44 mg of Ni/[kg (b.w.) · d] or greater to female B6C3F_1 mice for a period of 6 months produced thymic and splenic atrophy and decreases in the number and the proliferative response of bone marrow cells in all exposed animals (Dieter *et al.*, 1988). There was no evidence of carcinogenicity in limited studies in which Long Evans rats were orally exposed to 0.3 mg of Ni/[kg (b.w.) · d] as an unspecified soluble salt for life (Schroeder *et al*, 1974 or in which CD mice were orally exposed to 1.25 Ni/[kg (b.w.) · d] as nickel acetate or nickel oxalate for life (Schroeder and Mitchener, 1975; Schroeder *et al.*, 1964); however, histopathological examination in these studies was limited to grossly visible tumours, and the heart, lungs, liver, spleen, and kidneys. The only non-neoplastic lesion noted was focal myocardial fibrosis in rats exposed to 0.3 mg of Ni/[kg (b.w.) · d]. An increased incidence of lung tumours was observed in mice administered hydrated nickel acetate by intraperitoneal injection (Poirier *et al.*, 1984; Stoner *et al.*, 1976); "soluble" nickel compounds have also induced tumours at the site of injection in animals (IARC, 1990).

"Soluble" nickel salts have been genotoxic in a range of *in vitro* test systems, but not in bacterial assays. Nickel sulphate induced chromosome aberrations and gene mutations in mammalian cells in culture, including L5178Y mouse lymphoma cells (thymidine kinase locus), rat liver epithelial cells [hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus], and Chinese hamster V79 or ovary (CHO) cells (HGPRT locus) (IPCS, 1991). DNA damage (strand breaks, crosslinks) and DNA binding have also been observed in mammalian cells exposed *in vitro* to a variety of "soluble" nickel salts (ATSDR, 1991; IPCS, 1991). The incidence of sperm head abnormalities and micronucleated polychromatic erythrocytes was increased significantly in mice exposed orally to nickel chloride [43 mg of Ni/kg (b.w.)], nickel sulphate [28 mg of Ni/kg (b.w.)], or nickel nitrate [23 mg of Ni/kg (b.w.)] in water; the effect was greatest with nickel

nitrate (Sobti and Gill, 1989). DNA damage, chromosomal aberrations, and micronucleated polychromatic erythrocytes have also been induced in rats, mice, or hamsters administered "soluble" nickel salts by intraperitoneal injection (Ciccarelli and Wetterhahn, 1982; Mohanty, 1987; Chorvatovicova, 1983; Arrouijal *et al.*, 1990; Dhir *et al.*, 1991). There was no evidence of genotoxicity in dominant lethal tests in rats and mice (Deknudt and Leonard, 1982; Jacquet and Mayence, 1982).

The administration of "soluble" nickel salts in the diet or drinking water to male and female rats for one or more generations produced fetotoxic effects, including reductions in fetal body weights and litter sizes, and increases in the numbers of runts and early pup deaths at doses of approximately 0.3 mg of Ni/[kg (b.w.) · d] or greater (Ambrose *et al.*, 1976; George *et al.*, 1989; Kimmel *et al.*, 1986; Schroeder and Mitchener, 1971, Smith *et al.*, 1993). In the most recent and well documented study (Smith *et al.*, 1993), female Long-Evans rats were administered 0, 10, 50, or 250 ppm of nickel chloride in the drinking water {approximately 0, 1.3,6.8, or 31.6 mg of Ni/[kg (b.w.) · d]} for 11 weeks before mating and then throughout two successive periods of mating, gestation (G1, G2), and lactation (L1, L2). There was a reduction in maternal weight gain during G1 in the mid- and high-exposure groups. The proportion of dead pups per litter was significantly elevated at the high dose in L1 and at 10 and 250 ppm, but not at 50 ppm in L2, with a dose-response in both periods {LOAEL = 1.3 mg/[kg (b.w.) · d]}.

An increased susceptibility to pulmonary bacterial or viral infection or to the development of transplanted tumours following exposure to "soluble" nickel compounds has been observed in mice after short-term administration of nickel sulphate in drinking water (3 g/L for 2 weeks or 0.08 g/L for 4 weeks before virus inoculation) (Gainer, 1977) and after acute (2-hour) inhalation exposure to nickel chloride (0.5 mg of Ni/m^3) or nickel sulphate (0.45 mg of Ni/m^3) (Adkins *et al.*, 1979; Gardner, 1980). There was a dose-related reduction in the weight of the thymus in mice administered nickel sulphate at concentrations equivalent to doses of 44 to 150 mg of Ni/[kg (b.w.) · d] for 180 days; no effects were noted on most of the several immunological parameters investigated (Dieter *et al.*, 1988).

Sensitivity has been induced in guinea pigs following topical application of nickel sulphate (Nilzen and Wikstrom, 1955), repeated intradermal injections and skin painting with nickel sulphate (Wahlberg, 1976), and single intracutaneous administration of nickel chloride (Duyeva, 1983). However, other groups of researchers were unable to induce sensitivity in experimental animals administered nickel compounds [Buhler, 1965; Hunziker, 1960; Samitz and Pomerantz, 1958; Samitz *et al.*, 1975 (all cited in IPCS, 1991)], although information presented in the secondary account of these studies (IPCS, 1991) was insufficient for review.

There were dose-related signs of neurotoxicity including lethargy, ataxia, and prostration in rats exposed to 8.7 mg of Ni/[kg (b.w.) · d] and above (as nickel chloride) for 90 days (American Biogenics Corporation, 1986).

2.5.2 *Humans*

The potential association between exposure to nickel and cancer has been investigated in numerous populations occupationally exposed to nickel predominantly as inorganic compounds or in the metallic form. In the most extensive analysis, which involved additional follow-up of the major cohorts, particular attention was focused on the levels and species of nickel to which the workers were exposed (Doll *et al.*, 1990).

Mortality due to lung cancer was significantly increased in sinter plant workers at three INCO mining, smelting, and refinery operations in Ontario (Port Colborne, Copper Cliff, and Coniston) who were exposed primarily to "oxidic" and "sulphidic" nickel [Standardized Mortality Ratio (SMRs) of 239, 307, and 292, respectively], while mortality due to nasal cancer was significantly elevated at the two larger facilities (Port Colborne and Copper Cliff) with SMRs of 776 and 3617, respectively. Mortality due to these causes also increased with duration of employment at the larger facilities. Mortality due to nasal cancer was also increased in electrolysis workers at the Port Colborne plant who were exposed primarily to "soluble" nickel (SMR of 2517). No information was presented on possible concomitant exposure of these workers to substances other than nickel (Doll *et al.*, 1990).

There were also significant increases in mortality due to lung and nasal cancer in a cohort of 3250 workers at the Falconbridge refineries in Kristiansand, Norway (SMRs of 262 and 453, respectively), with some indication of a relationship between mortality due to lung cancer and duration of employment as well as cumulative exposure (estimated based on information presented in the report). When specific work groups were considered, mortality due to lung cancer was elevated in electrolysis workers and roasting, smelting, and calcining workers, who were exposed primarily to "soluble" and oxidic" nickel, respectively. When analyzed by cumulative exposure to four types of nickel compounds (metallic, "oxidic", "sulphidic", and "soluble"), the increased mortality due to lung cancer was associated with exposure to "soluble" nickel, while exposure to "oxidic" nickel was related more to the increased mortality due to nasal cancer, and exposure to metallic nickel was not associated with either form of cancer. Some of these workers may also have been exposed to unspecified levels of arsenic, particularly in the earlier years of the study period (Doll *et al.*, 1990).

Mortality due to lung and nasal cancer was significantly increased (SMRs of 393 and 21120, respectively) in workers at the Clydach refinery in Wales who were first employed before control measures were introduced in 1930 (n = 1348). There was also a relationship between duration of employment and deaths due to these causes. Based on classification of workers by estimated cumulative exposure to the four types of nickel compounds, the authors concluded that the increase in lung cancer mortality was related to exposure to "sulphidic" nickel and possibly "oxidic" nickel, and that exposure to soluble" nickel accentuated the risks associated with these two forms of nickel. The increased mortality due to nasal cancer was strongly related to exposure to "sulphidic" nickel, as well as "soluble" nickel in conjunction with exposure to high levels of "oxidic" and "sulphidic" nickel. There was no evidence that exposure to metallic nickel was

associated with mortality due to cancer. There was a decrease in lung cancer mortality following a reduction in exposure to "soluble" and "sulphidic" nickel compounds as a result of an improvement in equipment and a reduction in the sulphur content in the feed. Workers in several departments were likely also exposed to arsenic (Doll *et al.,* 1990).

Excess deaths due to lung cancer were also noted in 11 594 miners and smelter workers at the Falconbridge operations in Sudbury, Ontario who were primarily exposed to low levels of predominantly "sulphidic" nickel (SMRs of 158 and 163, respectively). However, the authors noted that the increased lung cancer mortality in smelter workers could also be due to exposure to arsenic (although this hypothesis was not further investigated), while the mortality due to this cause in the miners was similar to that reported for other groups of miners not exposed to nickel (Doll *et al.,* 1990).

Some evidence of an increase in lung cancer mortality was noted in a cohort of 1155 workers exposed to "soluble" nickel at the Outokumptu Oy refinery in Finland and in 1855 workers exposed to "sulphidic" nickel before 1947 at the Huntingdon Alloy facility in West Virginia. Although mortality due to lung cancer was elevated in 1510 workers at the Hanna mining and smelting operations in Oregon, the increase could not be confidently associated with exposure to nickel, as the greatest increase was observed in workers with less than one year of employment. In a nested case-referent study of workers (79 cases and 223 referents) at the Societé le Nickel mining and smelting operations in New Caledonia, cases did not have greater cumulative exposure to nickel (although a greater proportion of cases were exposed to very low levels of "sulphidic" nickel). Both of these study populations (Oregon and New Caledonia) were exposed primarily to much lower levels of "oxidic" nickel than those previously discussed. Similarly, deaths due to lung cancer were not increased in 1907 men exposed to low levels of "oxidic" or metallic nickel at the Henry Wiggin Alloy plant in England. Mortality due to lung or nasal cancer was not elevated in two small cohorts of workers (n = 716 and 813) exposed to metallic nickel at the Sherritt Gordon hydrometallurgical nickel refinery in Fort Saskatchewan, Alberta, or the Oak Ridge gaseous diffusion plant in Tennessee, although it should be noted that the number of expected cases in the former study was very small (n = 3) (Egedahl *et al.,* 1991; Doll *et al.,* 1990).

Doll *et al.* (1990) concluded that exposure to high concentrations of any of three forms of nickel ("soluble", "oxidic", or "sulphidic") resulted in increases in mortality due to lung and nasal cancer. There was no evidence that elevated mortality due to cancer was associated with exposure to metallic nickel. There was no consistent or convincing evidence to suggest that occupational exposure to nickel or any of its compounds was associated with cancers at sites other than the lung or nose. However, it should be noted that most workers studied were still alive at the time of the investigation and that the period of follow-up for some was relatively short. In addition, the estimates of exposure of these workers were based largely on information on process and on very few actual measurements of airborne concentrations, which varied among the cohorts. Although smoking was not taken into account in any of these investigations, it was unlikely to explain the relatively large observed excesses in lung cancer (Blair *et al.,* 1985; Siemiatycki *et al.,* 1988). Similarly, there was little information on the exposure to other

compounds of workers involved in these industrial processes, and the limited information that was available (as previously noted) was not taken into account in the analyses.

On the basis of their analyses, Doll *et al.* (1990) concluded 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." They further speculated that "with excess risks being confined to these high levels of exposure and the absence of any evidence of hazard from metallic nickel, it can be concluded that the risk to the general population from exposure to the extremely small concentrations (less than 1 µg of Ni/m^3) to which it is exposed is minute, if indeed there is any risk at all." Clearly, however, conjecture about absolute risks associated with exposure to substances in the general environment on the basis of empirical observations of the lack of effects at poorly characterized levels of exposure in epidemiological studies of limited power is fraught with uncertainty; indeed, speculation of this nature in the absence of data on mechanisms must be interpreted extremely cautiously. Moreover, specification of "de minimis" levels of risk was clearly outside the scope of this epidemiological investigation.

Occupational exposure to nickel occurs in a wide range of other industries, including the manufacture of nickel/cadmium batteries, foundry work, the welding, grinding and polishing of metals, the manufacture and use of nickel alloys and stainless steel, and nickel plating (IARC, 1990). Although an increased level of morbidity or mortality due to cancer has frequently been associated with these occupational activities (e.g., Acheson *et al.*, 1981; Becker *et al.*, 1991; Kjellstrom *et al.*, 1979; Langard and Stern, 1984), the role of nickel in the development of cancer cannot be assessed with confidence, as most of these employees were also exposed to a number of other substances.

Mixed results have been obtained concerning an association between exposure to nickel and laryngeal cancer in case-control studies in patients in Denmark and Ontario, investigations of inherently weaker design than the cohort studies discussed above (Olsen and Sabroe, 1984; Burch *et al.*, 1981). The odds ratio for developing stomach cancer was non-significantly elevated in those exposed to metal dusts in a case-control study of patients in Los Angeles, California (Wu-Williams *et al.*, 1990). There was no evidence of an association between exposure to nickel and nasal or sinonasal cancer in case-control studies in Connecticut, North Carolina, and Europe (Brinton *et al.*, 1984; Hernberg *et al.*, 1983; Roush *et al.*, 1980). In a large case-control study in Montreal, Quebec, there was a significant association between occupational exposure to nickel and lung cancer, although these individuals had also been exposed to chromium (Germ *et al.*, 1984); however, no association was apparent in a smaller study of workers manufacturing aircraft from nickel-containing metals (Bernacki *et al.*, 1978). In some of these studies, occupational exposure was based on the subject's recall and not verified through examination of employment records. With the exception of the study by Germ *et al.* (1984), the power of all of the case-control studies was quite limited.

Mortality due to bladder and lung cancer was greater in a population whose drinking water contained elevated levels of nickel (up to 1.3 µg/L, form unspecified) compared to the statewide population-based cancer incidence in an ecological study of residents of towns (population of 1000 to 10 000) in Iowa whose drinking water supply was from a single stable ground source. The authors suggested that, while no conclusion can be drawn concerning an association between ingestion of nickel in drinking water and cancer, due to the inherent limitations of studies of this design, the incidence of cancer may be elevated in populations consuming water from wells subject to anthropogenic contamination (Isacson *et al.,* 1985).

The frequencies of chromosomal aberrations and sister chromatid exchanges (SCEs) in the peripheral lymphocytes of workers occupationally exposed to nickel have been investigated in several studies (Decheng *et al.,* 1987; Deng *et al.,* 1988; Elias *et al.,* 1989; Popp *et al.,* 1991; Senft *et al.,* 1992; Waksvik and Boysen, 1982; Waksvik *et al.,* 1984). Although an increased incidence of chromosome aberrations or of SCEs has been associated with occupational exposure in the majority of the studies, the specific role of nickel is difficult to assess. Most of these studies involved a small number of workers (maximum exposed number of 39) who were generally also exposed to a number of other metals (e.g., iron, manganese, and chromium during welding, chromium in an electroplating refinery, copper and other metals in a nickel refinery).

Data on the non-neoplastic effects of nickel in humans are limited. Increases in mortality due to non-malignant respiratory disease have been reported in earlier investigations of some of the cohorts discussed above (the more recent analyses were focused exclusively on cancer), although it is not possible to determine the role of nickel in the development of such effects. For example, mortality due to pneumoconiosis at the Falconbridge mining and smelting operations in Ontario was significantly increased; however, this increase was ascribed to exposure to silica in the mines (Shannon *et al.,* 1991). Although asthma has been reported in a number of studies in nickel-plating workers and metal polishers exposed to nickel and other metals (Block and Yeung, 1982; Cirla *et al.,* 1985; Lavaud *et al.,* 1990; Malo *et al.,* 1982; McConnell *et al.,* 1973; Novey *et al.,* 1983; Shirakawa *et al.,* 1990), insufficient information was presented on other substances to which these workers may have been exposed to draw any conclusions about the specific role of nickel in the induction of asthma. An increased or "high" frequency of nasal disorders and damage to the nasal epithelium have also been observed in cross-sectional studies in groups occupationally exposed to nickel (Kucharin, 1970; Suschenko and Rafikova, 1972; Tatarskaya, 1960; Boysen *et al.,* 1982; 1984; Torjussen *et al.,* 1979a;b).

Although there was a two-fold increase in deaths due to cerebrovascular disease in Clydach workers first employed before 1925 (Peto *et al.,* 1984), and an increase in mortality due to heart disease other than ischaemic heart disease in a small number of workers (total number of deaths due to all causes was 27, compared to more than 45 expected) at the Sherrit Gordon nickel refinery in Fort Saskatchewan, Alberta (Egedahl *et al.,* 1991), such an association has not been confirmed in other analytical epidemiological studies in exposed populations. With the exception of some indirect

indication of kidney disease reported in a single study in a small number of nickel refinery workers, (Sunderman and Horak, 1981), no evidence of renal effects has been recorded in the various mortality studies of nickel-exposed workers discussed here, although such effects have not been extensively investigated. With respect to the effects of nickel on reproduction in humans, the only relevant study identified (i.e., Lindbohm *et al.,* 1991) is inadequate to serve as a basis for conclusions. Sunderman *et al.* (1989) reported that only one out of ten volunteers acutely exposed to 0.05 mg of Ni/kg (b.w.) developed transient neurological effects.

"Soluble" nickel compounds have induced skin irritancy following dermal application in several clinical studies (Kalimo and Lammintausta, 1984; Mendelow *et al.,* 1985; Storrs *et al.,* 1989; Frosch and Kligman, 1976; Wahlberg, 1990; Wall and Calnan, 1980; Vandenberg and Epstein, 1963; Fullerton *et al.,* 1989); nickel chloride appears to be a more severe irritant, based on a much higher response in 390 patients to a 2.5% aqueous solution of the chloride than to 5% nickel sulphate in petrolatum (Kalimo and Lammintausta, 1984). Skin sensitization has also been induced in numerous studies in volunteers, with nickel chloride being a more potent sensitizer than nickel sulphate (Kalimo and Lammintausta, 1984; Wall and Calnan, 1980). Skin sensitization has also been reported in a number of studies in occupationally exposed workers (Fischer, 1989; Lunder, 1988; Meding and Swanbeck, 1990; Nethercott and Holness, 1990; Peltonen, 1979) and in persons exposed to nickel in medical and dental devices (Kieffer, 1979; Hensten-Pettersen, 1989; Wilkinson, 1989), as well as other common articles (such as jewellery, wrist watches, etc.) (Meding and Swanbeck, 1990; Menné *et al.,* 1982; Peltonen, 1979; Prystowsky *et al.,* 1979; Seidenari *et al.,* 1990). In studies in the general population conducted in Denmark, Finland, Sweden, Italy, and the United States, the prevalence of nickel sensitivity ranged from 8 to 21.9% in women and 0.3 to 2.8% in men. Prystowsky *et al.* (1979) determined that the higher prevalence of sensitivity to nickel in women was due to the higher frequency of ear piercing.

In studies conducted in Toronto (n = 1076) and Saskatoon (n = 542), 16.7% and 23.1% of all female dermatitis patients responded to nickel sulphate in patch tests; the corresponding response rates in males were 5.1% and 8.5% (Hogan *et al.,* 1988; Nethercott and Holness, 1990). The results of a number of studies in dermatitis patients indicate that a significant proportion of those sensitized respond to concentrations of nickel on the skin in the range of 1 to 100 ppm (Allenby and Goodwin, 1983; Emmett *et al.,* 1988; Fisher *et al,* 1984), and to single or multiple oral doses of 2 to 2.5 mg (Bedello *et al.,* 1985, in Veien, 1991; Roduner *et al.,* 1987; Sertoli *et al.,* 1985, in Veien, 1991; Veien *et al.,* 1987).

2.5.3 *Ecotoxicology*

Aquatic Biota. There are significant differences in susceptibility to nickel among taxa. Observed acute and chronic non-lethal effects in fish and invertebrates include tissue damage, genotoxicity, and decreased growth (EIFAC, 1984; IPCS, 1991). Some fungi, microorganisms, and invertebrates (e.g., chironomids) are relatively tolerant of nickel; invertebrates that are relatively sensitive include molluscs, crustaceans, and

Daphnia. Despite being sensitive, *Daphnia magna* may be able to regulate nickel uptake, excretion, or both (Hall, 1978). Tolerant biota have been isolated from naturally mineralized and anthropogenically contaminated habitats. For example, the alga *Euglena mutabilis* isolated from strongly acidic ponds near Smoking Hills, Northwest Territories, and the alga *Chlorella saccharophila* isolated from roots of hairgrass *(Deschampsia cespitosa)* from contaminated Sudbury area soils, have been shown to grow well in their respective environments (NRCC, 1981; Nakatsu and Hutchinson, 1988).

Representative data on the range of concentrations of nickel in fresh water producing acute or chronic toxicity in algae and aquatic macrophytes, invertebrates, amphibians and fish are presented in Figure 1. Acute or chronic toxicity to freshwater organisms results from exposure to concentrations of nickel in the range of 24 to 10 000 µg/L. The most sensitive freshwater organisms in short-term acute toxicity tests were the mussel *Anodonta imbecilis* and the snail *Juga plicifera*. The 96-h LC50 for these organisms was 190 µg/L (soft water) and 102 µg/L (very soft water), respectively (Keller and Zam, 1991; Nebeker *et al.,* 1986). Sensitive freshwater organisms in chronic toxicity tests included: rainbow trout, *Oncorhynchus mykiss,* with an avoidance threshold of 24 µg of Ni/L (Giattina *et al.,* 1982); the cladoceran, *Daphnia magna,* for which tests over seven generations showed that nickel concentrations of 40 µg/L and above decreased the mean life span (Münzinger, 1990); the alga *Scenedesmus acuminatus,* for which cell numbers were reduced by 50% on exposure to 50 µg of Ni/L (Stokes, 1981); the alga *Anabaena inaequalis,* for which growth was inhibited at 50 µg of Ni/L (Stratton and Corke, 1979); rainbow trout embryo/larval stages, with a 28-day LC50 of 50 µg of Ni/L (Birge, 1978; Birge *et al.,* 1978); and the narrow-mouthed toad, *Gastrophryne carolinensis,* embryo/larval stages, with a seven-day LC50 of 50 µg/L (Birge, 1978). In each of the studies cited above, NiC12 · 6H20 was used for testing.

In Figure 2, available data for the toxicity of nickel to freshwater benthic invertebrates are presented. No spiked-sediment bioassay data on the effects of nickel to freshwater benthic invertebrates were identified. However, a field co-occurrence study of 422 locations in and adjacent to the Great Lakes region indicated 5% of the known sensitive benthic invertebrate species were absent from sediments with nickel concentrations of $\underline{\geq}$16 µg/g (d.w.) (Jaagumagi, 1990). Additionally, 95% of known invertebrate species were absent from sediments with nickel concentrations of $\geq$75 µg/g (d.w.) (Jaagumagi, 1990).

Terrestrial Biota. In Figure 3, selected information on concentrations of nickel in soil that produce adverse effects in microorganisms and microbially mediated soil processes is summarized. Addition to soil of 100 lag of Ni/g soil (as NiSO4) disrupted the nitrogen cycle by stimulating nitrification and nitrogen mineralization, which resulted in a loss of soil nitrogen through leaching. Since nitrogen is probably the most limiting nutrient in boreal forest ecosystems, this loss could have adverse ecological effects (deCatanzaro and Hutchinson, 1985a;b). Growth of the filamentous fungus, *Aspergillus clavatus,* was reduced by 36% when 50 µg of Ni/g were added (as NiC12 · 6H20) to an acidic soil (pH 4.9) already containing 20 µg of Ni/g soil (Babich and Stotzky, 1982).

The growth and survival of several species of microorganisms *(Agrobacterium radiobacter, Bacillus megaterium, Cryptococcus terreus,* and *Torulopsis glabrata)* were significantly reduced after a seven-day exposure when 250 µg of Ni/g (the lowest exposure concentration tested) were added to this soil (Babich and Stotzky, 1982). By contrast, the growth and survival of microorganisms were not affected when 1000 µg of Ni/g (the highest exposure concentration tested) were added to an alkaline soil (pH 7.7) already containing 17 µg of Ni/g (Babich and Stotzky, 1982).

Although nickel is essential for plant growth (Brown *et al.,* 1987a;b; Ferago and Cole, 1988; Hutchinson, 1992), relatively high concentrations of nickel, such as those occurring in nickel-enriched ultramafic (serpentine) soils, can have adverse effects to plants (Kabata-Pendias and Pendias, 1992). General signs of nickel toxicity are reduced growth of roots and shoots, poor branching, deformation of various plant parts, decreased dry matter production, leaf spotting, abnormal flower shape, mitotic root tip disturbance, germination inhibition, and chlorosis that can lead to foliar necrosis (Mishra and Kar, 1974; Rauser, 1978; McIlveen and Negusanti, in press). Although effects have been reported in tolerant plants containing up to 1000 µg/g (d.w.), based on available data, effect thresholds are normally below about 80 µg/g (d.w.) of plant tissue (Kabata-Pendias and Pendias, 1984; Aller *et al.,* 1990; McIlveen and Negusanti, in press; Hogan and Rauser, 1979; Cox and Hutchinson, 1980). The most sensitive plants in chronic tests were barley *(Hordeum vulgare)* and ryegrass *(Lolium perenne),* for which respective effect (reduced yield) thresholds were 12 and 14 µg of Ni/g (d.w.) in plant tissue (administered in nutrient solutions as $NiCl_2$ for 14 and 36 days, respectively) (Davis and Beckett, 1978). Frank *et al.* (1982) reported symptoms of injury including stunted roots and tops, chlorosis, necrosis, and discoloured roots, as well as reduced yields in celery, lettuce, radish, cabbage, and beets containing as little as 15, 25, 56, 76, and 94 µg of Ni/g (d.w.) in plant tops, respectively. Although the tests were carried out in organic soils contaminated with both nickel and copper from a nickel refinery, copper concentrations were not considered to be high enough to cause crop damage (Frank *et al.,* 1982). Lozano and Morrison (1982) reported that growth was reduced in white spruce *[Picea glauca* (Moench) Voss] seedlings when concentrations in needles were approximately 80 µg of Ni/g (d.w.) (administered in nutrient solutions as $NiSO_4$ for 12 weeks). In tests using nutrient solutions spiked with $NiSO_4$, necrosis and chlorosis were reported in leaves of oat seedlings after exposure to nickel for 33 days; nickel concentrations in the affected oat *(Avena sativa)* leaves were about 80 µg/g (d.w.) (Vergnano and Hunter, 1952).

As indicated in Figure 4, study of the effects of dissolved nickel on plants grown in nutrient or sand cultures indicates that effect thresholds are typically in the range of 2 to 15 mg/L. For example, Brenchley (1938) reported reduced growth (measured over two growing seasons) in both barley and broad beans grown in water cultures containing 2 mg of Ni/L as either $NiC1_2$ or $NiSO_4$. Whitby and Hutchinson (1974) reported that nickel inhibited the elongation of tomato *(Lycopersicum esculentum)* roots when present in nutrient solutions at 2 mg/L as $Ni(N0_3)_2$ after exposure for 9 days. In tests using sand

cultures, chlorosis was reported in leaves of oat *(Avena sativa)* seedlings exposed for 33 days to 2.5 mg of Ni/L as $NiSO_4$ (Vergnano and Hunter, 1952).

Data on effects of nickel, added to soil in water-soluble forms, on various types of agricultural plants, are summarized in Figure 3. Yields of oats, *Avena sativa,* and mustard, *Brassica* sp., decreased by 16% and 31%, respectively, when grown in soils containing added nickel (from $NiSO_4$) concentrations of 50 µg/g soil at a pH of 5.7 (Webber, 1972). With an added nickel concentration of 100 µg/g, the yields of oats and mustard, decreased by 71% and 97%, respectively. At a pH of 6.4, nickel had a much smaller effect on yields of both oats and mustard (Webber, 1972). For lettuce, *Lactuca longifolia,* a yield reduction of 25% was reported when approximately 75 and 270 µg of Ni/g were added (as NiSO4) to an acid and a calcareous soil, respectively (Mitchell *et al.,* 1978). For wheat, *Triticum aestivum,* a 25% reduction in yield occurred when approximately 110 and 250 µg of Ni/g were added to the acid and calcareous soil, respectively (Mitchell *et al.,* 1978).

No reports on the toxicity of nickel to wild mammals were identified. Results of laboratory studies in experimental animals are described in Subsection 2.5.1.

In adult mallards *(Anas platyrhynchos)* ingesting diets containing 0, 12.5, 50, 200, or 800 µg/g (d.w.) of nickel (as $NiSO_4$) for 90 days, there were no effects on the following endpoints: body weight, histological changes in the liver or kidney, tissue damage, and changes in blood chemistry. Egg laying, hatchability, and survival of hatchlings to 14 days of age were likewise unaffected at these dose levels (Eastin and O'Shea, 1981). However, when newly-hatched mallard ducklings were exposed to 0, 200,800, or 1200 µg/g (d.w.) of dietary nickel (as $NiSO_4$) for up to 90 days, significant effects were observed at 800 µg/g. The ducklings developed tremors and ataxia by 28 days, and began to die at 60 days (Cain and Pafford, 1981). The effects were similar, but more severe, at 1200 µg/g, while no signs of toxicity were seen at 200 µg/g. Newly-hatched chickens *(Gallinus domesticus)* maintained for 3 weeks on diets containing 0, 300, 500, 700, 900, or 1100 µg/g (d.w.) of dietary nickel had significantly slower growth rates at the 300 µg/g level and above (Ling and Leach, 1979). Mortality was also noted at the 500 µg/g level and above, becoming severe (50%) at the 900 µg/g level.

3.0 Assessment of "Toxic" Under CEPA

3.1 CEPA 11(a) Environment

Nickel is a naturally occurring element that is present in the environment principally in the divalent state. Annual production and imports of nickel in 1990 were 197 000 t and 29 000 t, respectively, of which 187 000 t were exported. Metallic nickel, nickel alloys, and various nickel compounds are widely used in the transportation, electrical, chemical, and other industrial sectors.

Nickel (in various, mainly inorganic forms) enters the atmospheric, aquatic, and terrestrial (soil) environment naturally, and as a result of anthropogenic activities. Natural sources of nickel include the weathering and erosion of bedrock (particularly nickel-enriched ultramafic or sulphide-bearing types), and at one location (Smoking Hills, NWT), the spontaneous combustion of nickel-bearing bituminous shales. As a result, concentrations of nickel are naturally elevated (relative to normal background values) in soils and surface waters in some parts of Canada.

Anthropogenic sources, which release nickel in both dissolved and particulate forms to Canadian surface waters, include mining and milling of nickel, gold and uranium ores, and iron and steel processing. The main anthropogenic sources of nickel released into the Canadian atmosphere are nickel smelting and refining operations (Sudbury, Ontario and Thompson, Manitoba), and to a lesser extent, fossil fuel combustion. Based on examination of flue dusts, nickel released from Canadian base metal smelting operations is likely in the form of nickel sulphate, nickel subsulphide, and nickel oxide. From 10 to 77% of the nickel in the flue dusts of Canadian smelters was reported to be water-soluble. Releases of nickel (particularly to the atmosphere) from nickel mining, smelting, and refining operations have resulted in accumulations of nickel at concentrations above normal background values in surface waters, lake sediments, and soils near Sudbury, Ontario, and (based on results of older studies) in surface soils near Port Colborne, Ontario and Thompson, Manitoba.

Adverse effects have been reported in acute and chronic toxicity tests with a variety of aquatic organisms exposed to dissolved nickel at concentrations in the 24 to 50 µg/L range, and higher (Figure 1). For example, an avoidance threshold of 24 µg of Ni/L was reported for rainbow trout *(Oncorhynchus mykiss),* and life span was reduced in the cladoceran *(Daphnia magna)* at nickel concentrations of 40 µg/L. In addition, growth and cell numbers were reduced in two species of alga *(Scenedesmus acuminatus* and *Anabaena inaequalis),* and acute lethality was reported in the embryonic and larval stages of rainbow trout *(Oncorhynchus mykiss)* and narrow-mouthed toad *(Gastrophryne carolinensis)* at a concentration of 50 µg/L. Mean concentrations above these effect levels (that is in the 50 to several thousand µg/L range) have been reported recently (mid- to late-1980s) in both filtered and unfiltered samples of water from lakes within a radius of 20 km or more of Sudbury that have been affected by inputs of airborne nickel from local smelters, and in filtered pond waters near Smoking Hills, NWT (Figure 1). Results

of studies in the Sudbury area indicate that most (95%) of the nickel in lake waters is in dissolved and hence bioavailable forms.

Although relatively high mean concentrations of total nickel (>4,000 µg/g) have been found in sediments from some Canadian lakes and rivers (Figure 2), spiked-sediment bioassays reporting dose-response relationships for nickel were not identified, and consequently, effect thresholds for sensitive freshwater benthic organisms could not be estimated. In a field co-occurrence study in the Great Lakes region, however, 95% of known invertebrate species were absent from sediments with nickel concentrations of $\geq$ 75 µg/g (d.w.) (Figure 2).

Adverse effects have been reported in terrestrial plants and microorganisms exposed to nickel in soil. Reduced yields occurred in several types of agricultural plants (lettuce, oats, wheat, mustard, and alfalfa) grown in acidic soils containing from 50 to about 100 µg/g of nickel added in soluble form ($NiC1_2$ or $NiSO_4$) (Figure 3). Furthermore, microbially mediated processes (nitrification and nitrogen mineralization), and growth and survival of several species of soil microorganisms (including *Agrobacter radiobacter, Bacillus megaterium, Cryptococcus terreus,* and *Torulopsis glabrata)* were adversely affected when 50 to 250 µg/g of nickel were added as $NiC1_2$ or $NiSO_4$ to acidic soils. As indicated in Figure 3, concentrations of total nickel equal to or greater than these effect levels have been reported near nickel smelting and/or refining operations at Sudbury and Port Colborne, Ontario and Thompson, Manitoba, as well as in naturally nickel-enriched soils in western Newfoundland, and near Thetford Mines, Quebec, and Ferguson Lake, Northwest Territories.

The bioavailability of nickel in soils varies, depending in particular upon the forms of nickel present and the soil pH. Nickel that is bound in the lattice of naturally occurring silicate minerals (e.g., olivine or pyroxenes) is relatively unavailable for uptake by plants compared to water-soluble forms, such as nickel sulphate, which may be deposited on surface soils from the atmosphere. In general, bioavailability increases with decreasing soil pH. In acidic soils, nickel-bearing sulphide and, to a lesser extent, silicate minerals (and possibly nickel oxide) can dissolve over time, and relatively little nickel is removed from soil pore waters by adsorption processes. Nickel complexed by organic ligands dissolved in soil pore waters is expected to be less bioavailable than free nickel ions.

Because of the low pHs ($\leq$ 5.0) in nickel-enriched soils near the smelters at Sudbury, concentrations of bioavailable nickel (i.e., soluble forms of nickel and dissolved nickel in soil pore waters) in these soils are expected to be relatively high. In one recent study, the concentration of nickel in samples of organic-rich pore water from wetland soils collected within a radius of about 40 km of Sudbury ranged from 0.6 to 22.6 mg/L; the mean value was 3.5 mg/L (Figure 4). These measured values are within the range of values calculated (based on recent data on mean water-extractable nickel levels) for some mineral soils near smelters at Sudbury (i.e., 2.0 to 15 mg of Ni/L). The bioavailability of nickel in the pore waters of the wetland soils may be reduced relative to the mineral soils, however, because of complexation with dissolved organic ligands.

Both the measured and calculated pore water concentrations are similar to concentrations (i.e., 2.0 mg of Ni/L and higher) that have been reported to cause adverse effects (e.g., chlorosis, reduced yields, and reduced root growth) in sensitive plants (including tomato, broad bean, barley, and oats) grown in nutrient solutions (Figure 4).

Concentrations of nickel in plant tissues also provide an indication of the concentrations of bioavailable forms of nickel in the soils in which they are growing. Elevated concentrations of nickel have been reported in vegetables (lettuce, cabbage, celery, beets, and radish) grown in the early 1980s in organic soils near Port Colborne, Ontario [mean value of 64 to 290 µg/g (d.w.)]; in lawn grass, timothy, and oats collected in the early 1980s near Sudbury, Ontario [mean values of about 100 µg/g (d.w.)]; in various arctic plants growing in soil near sulphide ore bodies at Ferguson Lake, NWT [mean values from 35 to 60 µg/g (d.w.)]; and in leaves of native trees near an outcrop of ultramafic bedrock near Thetford Mines, Quebec [mean values from 10 to 20 µg/g (d.w.)] (Figure 5). All vegetables grown in soils near Port Colborne, and the lawn grass, timothy, and oats near Sudbury showed evidence of injury (e.g., reduced yield, stunted growth, chlorosis, and necrosis), which was attributed to exposure to high concentrations of nickel in soil. Furthermore, concentrations of nickel in native vegetation growing in naturally nickel-enriched soils were within the range reported to cause harm (including reduced growth) to various types of agricultural plants (Figure 5).

Recent data that would permit estimation of exposure of wild mammals to nickel were not identified. However, worst-case exposure scenarios were developed for aquatic and terrestrial avian species using maximum concentrations from early studies near Sudbury, Ontario (which may be one or two orders of magnitude higher than current levels).

The model aquatic avian species that was chosen for consideration is the mallard duck *(Anas platyrhynchos).* Prefledged mallard ducklings consume primarily invertebrates, while older ducklings and adults (with the exception of laying females) have a diet consisting primarily of plant material such as grass, bulrush *(Scirpus)* seeds, and seeds and tubers of pondweed *(Potamogeton)* (Chura, 1961). The mean concentration of nickel in insect larvae in 1984 in the Wanapitei region near Sudbury was 22.3 µg/g (d.w.) (Krantzberg, 1985). Similarly, concentrations of nickel in zooplankton from 6 of 7 lakes sampled near Sudbury were less than 25 µg/g (d.w.) (Yan and Mackie, 1989). These levels are more than an order of magnitude lower than the lowest level causing effects in ducklings [i.e., 300 µg/g (d.w.) for 3 weeks caused a decreased growth rate]. The highest mean concentration of nickel in aquatic plants near Sudbury in the 1970s was 290 µg/g (d.w.) in aquatic weeds such as *Elodea canadensis* and *Potamogeton richardsonii* (Hutchinson *et al.*, 1976). Although effect levels for free-living birds have not been established, no effects were observed in a laboratory study with adult mallards fed a diet containing nickel at 800 µg/g (d.w.) for 90 days. Thus, levels of nickel in aquatic plants are not expected to be harmful to mallard ducks.

Similarly, for terrestrial birds, dietary exposure of ruffed grouse *(Bonasa umbellus)* can be estimated. Levels in aspen *(Populus tremula)* leaves from the crops of ruffed

grouse near Sudbury ranged from 61.7 µg/g (d.w.) in May 1980 to 136 µg/g (d.w.) in September 1980 (Rose and Parker, 1983). Although feeding studies in this species have not been identified, based on the mallard feeding study, no effects on ruffed grouse are expected at levels present in aspen.

In conclusion, although nickel concentrations in the food of Canadian aquatic and terrestrial birds are likely not high enough (based on worst-case scenarios) to cause harmful effects, concentrations of dissolved inorganic nickel in Canadian surface waters are within the range that may have harmful effects on sensitive pelagic (i.e., water-column) organisms near nickel smelting and refining operations and near natural sources. Furthermore, concentrations of dissolved and soluble forms of inorganic nickel in surface soils contaminated by nickel smelting and refining, and in some areas where soils are naturally nickel-enriched, are within the range that may cause harmful effects to sensitive terrestrial plants as well as soil microbial populations in Canada. Therefore, on the basis of the available data, dissolved and soluble* forms of inorganic nickel are entering or may enter the environment in a quantity or concentration or under conditions that are having or may have a harmful effect on the environment.

3.2 CEPA 11(b) Environment on Which Human Life Depends

Nickel occurs at low concentrations in suspended particulate material in the atmosphere (typically about 5 ng/m^3), has an atmospheric residence time of 5 to 8 days, and does not absorb infrared radiation. The only significant gaseous nickel compound, nickel carbonyl, degrades in air with a half-life of less than 1 minute. Consequently, "nickel and its compounds" are not expected to contribute to global warming or the depletion of stratospheric ozone.

Therefore, on the basis of available data, the substance "nickel and its compounds" does not enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which human life depends.

3.3 CEPA 11(c) Human Life or Health

Exposure. Estimates of the average daily intake of nickel (on a per body weight basis) for the general population in Canada are presented in Table 1. Due to the lack of

* The term "soluble" includes water-soluble forms of nickel (e.g., nickel sulphate and nickel chloride), as well as other more stable forms (e.g., nickel-hearing sulphide minerals and nickel oxide) that can dissolve under certain conditions of pH (e.g., acidic mine tailings) or redox potential (e.g., buried reducing sediment) in the environment.

Table 1 Estimated Average Daily Intake of Nickel for the General Population in Canada

Medium[a]	Estimated Daily Intake {µg/[kg(b.w.) · d]}				
	0 to 0.5 yr[b]	0.5 to 4 yr[c]	5 to 11 yr[d]	12 to 19 yr[e]	20 to 70 yr[f]
Ambient Air	0.0003 to 0.006	0.0004 to 0.008	0.0004 to 0.009	0.0004 to 0.007	0.0003 to 0.007
Water	0.02 to 0.77	0.01 to 0.44	0.007 to 0.24	0.005 to 0.16	0.004 to 0.15
Food	22	16	10	5.7	4.4
Soil	0.04 to 0.25	0.03 to 0.19	0.01 to 0.06	0.003 to 0.018	0.002 to 0.014
Tobacco Smoking[g]	—	—	—	0.15	0.12

a Mean concentrations in ambient air based on a survey of Canadian cities were 0.001 to 0.02 µg/m^3 (Dann, 1991a;b). Mean concentrations in drinking water were 0.2 to 7.2 µg/L based on a range of mean concentrations of nickel reported in Ontario (Jenkins, 1992) which are similar to those reported elsewhere in Canada (Environment Canada, 1989a;b;c;d; Mineraux Noranda Inc., 1992; Moon *et al.*, 1988). Intake in food was estimated based on concentrations of nickel in the various food types (NHW, 1992) multiplied by the age-specific food intakes from the Nutrition Canada Survey (EHD, 1992). No suitable data were identified to estimate intake of nickel by infants through breast milk. Mean concentrations of nickel in the soil in uncontaminated regions were 8 to 50 µg/g dry weight (see supporting documentation).

b Weighs 7 kg, breathes 2 m^3 of air, drinks 0.75 L of water, and ingests 35 mg of soil daily (EHD, 1992).

c Weighs 13 kg, breathes 5 m^3 of air, drinks 0.8 L of water, and ingests 50 mg of soil daily (EHD, 1992).

d Weighs 27 kg, breathes 12 m^3 of air, drinks 0.9 L of water, and ingests 35 mg of soil daily (EHD, 1992).

e Weighs 57 kg, breathes 21 m^3 of air, drinks 1.3 L of water, and ingests 20 mg of soil daily (EHD, 1992).

f Weighs 70 kg, breathes 23 m^3 of air, drinks 1.5 L of water, and ingests 20 mg of soil daily (EHD, 1992).

g Based on estimated mean nickel content of mainstream cigarette smoke of 0.43 µg per Canadian cigarette (Labstat Incorporated, 1991) and 20 cigarettes smoked per day (Kaiserman, 1992).

identified data on the speciation of nickel in various environmental media, it was not possible to estimate the exposure of the general population to individual nickel compounds. Therefore, estimated values refer to total nickel. Based on these estimates, the principal route of nickel intake for all age groups is from ingestion of food, followed by drinking water, soil (particularly in infants and young children), and inhalation in air, though it should be noted that absorption following inhalation is greater than that for ingestion. Inhalation of cigarette smoke may increase total daily intake by 0.12 and 0.15 µg/[kg (b.w.) · d). Exposure to nickel may also occur from household products (Kuligowski and Halperin, 1992; Nava *et al.*, 1987); however, available information is considered insufficient to permit quantification of exposure to nickel from such sources.

People residing in the vicinity of point sources may be exposed to higher levels of nickel in food, air, soil, and water than the general population. Based on comparison of the limited available data on concentrations of nickel in foodstuffs in the vicinity of point sources (Frank *et al.*, 1982; McIlveen and Balsillie, 1977, in NRCC, 1981; Temple, 1978, in NRCC, 1981; Warren *et al.*, 1971) with those determined in the total diet survey (NHW, 1992), it is possible that intake from food may be elevated for populations residing in the vicinity of industrial sources. Available data were considered insufficient, however, to quantitatively estimate intake in food for populations under such conditions. For purposes of estimation of exposure, therefore, it was considered to be similar to that of the general population. Based on the mean values reported in a limited early study of ambient air in the vicinity of point sources, the estimated intake in air was similar to that in the general population; however, based on maximum recorded values in this survey, intake in air in the vicinity of point sources may be considerably greater than that for the general population. Estimated mean intakes in such areas may range from 0.05 to 1.9 µg/[kg (b.w.) · d] in soil and from 0.6 to 12 µg/[kg (b.w.) · d] in water, with the greatest intake being in young children (Table 2).

Effects. In epidemiological studies in exposed human populations and in toxicological studies in experimental animals, the respiratory system appears to be the critical target for adverse effects following exposure by inhalation to nickel. In view of the serious nature of the adverse health impact of cancer, carcinogenicity is considered to be one of the most critical endpoints for assessment of whether "nickel and its compounds" (specifically metallic, "oxidic", "sulphidic", and "soluble" nickel) are "toxic" under Paragraph 11(c) of CEPA. The weight of evidence for the carcinogenicity of these forms of nickel has been assessed, therefore, based on the criteria developed for the "Determination of 'Toxic' under Paragraph 11(c) of the Canadian Environmental Protection Act" (EHD, 1992).

In the following assessment of the weight of evidence for carcinogenicity, the studies considered most relevant to the assessment of hazard and risk to the general population are those in epidemiological studies of human populations. Toxicological studies in animal species considered most relevant to the assessment are those in which routes of exposure were similar to those by which humans are exposed in the general environment (i.e., inhalation and ingestion). Results of investigations in which animals have been exposed intratracheally (which bypasses natural defence mechanisms of the

Table 2 Estimated Average Daily Intake of Nickel by Canadians Living Near Point Sources

Medium[a]	Estimated Daily Intake {µg/[kg(b.w.) · d]}				
	0 to 0.5 yr[b]	0.5 to 4 yr[c]	5 to 11 yr[d]	12 to 19 yr[e]	20 to 70 yr[f]
Ambient Air	0.006	0.008	0.009	0.008	0.007
Water	2.8 to 12	1.6 to 6.7	0.87 to 3.6	0.60 to 2.5	0.56 to 2.3
Food	22	16	10	5.7	4.4
Soil	0.83 to 1.9	0.63 to 1.5	0.21 to 0.49	0.06 to 0.13	0.05 to 0.11

a Mean concentrations in various media were those reported in the vicinity of Sudbury: 0.021 µg/m^3 in ambient air based on an early study covering the period from 1978 to 1980 (Chan and Lusis, 1986); 26.2 to 108.3 µg/L in drinking water at two water treatment plants (Jenkins, 1992); 165 to 380 mg/kg dry weight in soil (Maxwell, 1991). Intake in food was considered to be the same as that for the general population (Table 1).

b Weighs 7 kg, breathes 2 m^3 of air, drinks 0.75 L of water, and ingests 35 mg of soil daily (EHD, 1992).

c Weighs 13 kg, breathes 5 m^3 of air, drinks 0.8 L of water, and ingests 50 mg of soil daily (EHD, 1992).

d Weighs 27 kg, breathes 12 m^3 of air, drinks 0.9 L of water, and ingests 35 mg of soil daily (EHD, 1992).

e Weighs 57 kg, breathes 21 m^3 of air, drinks 1.3 L of water, and ingests 20 mg of soil daily (EHD, 1992).

f Weighs 70 kg, breathes 23 m^3 of air, drinks 1.5 L of water, and ingests 20 mg of soil daily (EHD, 1992).

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lung), intraperitoneally or intrapleurally, or by direct injection into specific tissues are considered as supporting data only.

Based on an extensive analysis of recent follow-ups of the principal exposed cohorts, mortality due to lung cancer was significantly increased in sinter plant workers at three INCO facilities in Ontario who were exposed primarily to "oxidic" and "sulphidic" nickel, while mortality due to nasal cancer was significantly elevated at the two larger of the three facilities (Copper Cliff and Port Colborne). Mortality due to these causes increased with duration of employment in these two larger plants, and with estimates of cumulative exposure derived from data presented in the published report. In

addition, nasal cancer mortality was increased in electrolysis workers at the Port Colborne plant who were exposed primarily to "soluble" nickel (Doll *et al.*, 1990).

Mortality due to lung and nasal cancer was also significantly increased in workers at the Falconbridge nickel refinery in Kristiansand, Norway. Lung cancer mortality increased with duration of employment and with cumulative exposure. When the data were analyzed by various species of nickel compounds, the elevated mortality due to lung cancer was associated with exposure to "soluble" nickel, while excess nasal cancer mortality was related to exposure to "oxidic" nickel (Doll *et al.*, 1990).

Similarly, in the cohort of the Mond/INCO refinery at Clydach, mortality due to lung and nasal cancer increased both with duration of employment and estimated cumulative exposure in the subgroup of workers exposed to high concentrations of "oxidic", "sulphidic", metallic, and "soluble" nickel. However, based on the cross-classification by cumulative exposure to various forms of nickel, increased mortality due to lung or nasal cancer was most strongly associated with exposure to "sulphidic" nickel or a combination of "sulphidic", "oxidic", or "soluble" nickel, but not metallic nickel. In addition, there was a decrease in lung cancer mortality following a reduction in exposure to "soluble" and "sulphidic" nickel compounds. (Doll *et al.*, 1990).

There was also elevated mortality from lung cancer in workers exposed mainly to "sulphidic" nickel and to low levels of mineral-based nickel, iron-" sulphidic" nickel, "oxidic" nickel, and "soluble" nickel at the Falconbridge mining and smelting operations in Sudbury (Doll *et al.*, 1990), although the increase could not be unequivocally attributed to nickel. Some evidence of increased lung cancer risk was noted in workers exposed to "soluble" nickel and "sulphidic" nickel, respectively, at the Outokumptu Oy refinery in Finland and the Huntingdon Alloy facility in West Virginia (Doll *et al.*, 1990). However, in studies in small numbers of workers at mining and smelting operations in Oregon and New Caledonia, who were mainly exposed to "oxidic" nickel at levels much lower than those reported in other facilities in which increased mortality due to lung and nasal cancer was observed, there was little convincing evidence of increased mortality due to lung or nasal cancer (Doll *et al.*, 1990). Similarly, exposure to low levels of "oxidic" or metallic nickel resulted in no increase in the number of lung or nasal cancer deaths in a group of workers at the Henry Wiggin Alloy plant in England (Doll *et al.* 1990). Mortality due to lung or nasal cancer was not elevated in two small cohorts of workers exposed to metallic nickel at the Oak Ridge Gaseous Diffusion plant in Tennessee and the Sherritt Gordon hydrometallurgical nickel refinery in Fort Saskatchewan, Alberta, although it should be noted that the number of expected cases in the former cohort was very small (n = 3) (Doll *et al.*, 1990; Egedahl *et al.*, 1991).

All of the available epidemiological studies are limited. There are few data on cumulative exposure (or limited documentation to serve as a basis for estimation of cumulative exposure) and little information on exposure to other substances, which was not taken into account in the analyses. Moreover, information on the smoking habits of the subjects was not presented in any of these investigations. Nevertheless, variations in smoking habits are unlikely to explain the large observed excesses in respiratory cancer

(Blair *et al.,* 1985; Siemiatycki *et al.,* 1988). Furthermore, the total number of deaths recorded in most of these studies is still only a small proportion of those included in the cohort. Despite the limitations of these studies, many of which would have contributed to the obfuscation of an association between exposure to nickel and the development of cancer, there is sufficient weight of evidence in several studies (i.e., the most sensitive) for an association between exposure to "oxidic", "sulphidic", and "soluble" nickel and respiratory and nasal cancer. In addition, there was evidence of exposure-response relationships for all three forms and some indication that a reduction in occupational exposure to "sulphidic" and "soluble" nickel resulted in a decrease in mortality due to lung cancer. However, there is no convincing evidence that occupational exposure to metallic nickel was associated with cancer. Although not as well documented, there is no consistent evidence that cancers at sites other than the lung and nose may be associated with occupational exposure to nickel (Doll *et al.,* 1990).

Available epidemiological data on the potential association of ingested nickel and cancer are inconclusive, and do not contribute to assessment of the weight of evidence for carcinogenicity.

An increased frequency of chromosomal aberrations has been observed in the peripheral lymphocytes of chemical plant workers exposed to "soluble" nickel and nickel refinery workers exposed to "oxidic", "soluble", and "sulphidic" nickel (combined) (Senft *et al.,* 1992; Waksvik *et al.,* 1984; Waksvik and Boysen, 1982), with some indication of a dose response in the study of Senft *et al.* (1992). An elevated frequency of chromosomal aberrations and sister chromatid exchanges was also reported in electroplaters (form of nickel unknown) (Deng *et al.,* 1988). Mixed results have been obtained in two studies in welders (form of nickel not specified) (Popp *et al.,* 1991; Elias *et al.,* 1989). Most of these studies, however, involved small numbers of workers (maximum number of exposed individuals was 39) who were generally also exposed to a number of other metals (e.g., iron, manganese, and chromium during welding, chromium in an electroplating refinery, copper and other metals in a nickel refinery).

Although there was a clear increase in the incidence of lung tumours in rats administered metallic nickel powder by intratracheal instillation (Pott *et al.,* 1987), the carcinogenicity of this form of nickel has not been investigated in adequate, more relevant, inhalation studies. Increased incidences of tumours have also been induced at the site of administration in limited studies in experimental animals exposed to metallic nickel via routes less relevant to environmental exposure (e.g., intrapleural, subcutaneous, intratesticular, intramuscular, intraperitoneal, and intrarenal injection) (IARC, 1990).

Chromosomal aberrations in the bone marrow were induced by a metallic nickel aerosol derived from nickel refinery waste (repeated inhalation exposure) in rats (Chorvatovicova and Kovacikova, 1992). Metallic nickel did not induce chromosomal aberrations in cultured human cells but it transformed animal cells *in vitro* (IARC, 1990).

Nickel subsulphide induced an increased incidence of lung tumours in rats exposed by inhalation for approximately 80 weeks (Ottolenghi *et al.,* 1974) and there was some

weak evidence of a similar increase in the incidence of lung tumours reported in rats exposed to a "sulphidic" nickel-containing dust for 6 months in a limited study for which the published account was inadequate for assessment (Saknyn and Blokhin, 1978). Following intratracheal administration, there was a clear increase in the incidence of lung tumours in rats administered nickel subsulphide in one study (Pott *et al.,* 1987), but not in mice in two other investigations exposed to lower doses (Fisher *et al.,* 1986; McNeill *et al.,* 1990). In addition, local tumours were observed in animals administered "sulphidic" nickel by routes other than ingestion or inhalation (IARC, 1990).

Nickel subsulphide administered by intraperitoneal injection produced chromosomal damage (micronuclei) in mice (Arrouijal *et al.,* 1990). "Sulphidic" nickel compounds produced chromosome aberrations, sister chromatid exchanges, and cell transformation in numerous *in vitro* systems (IARC, 1990; IPCS, 1991).

There was an increase in the incidence of lung tumours in rats administered nickel oxide by intratracheal instillation (Pott *et al.,* 1987); however, no evidence of cancer was observed in a limited study in hamsters exposed by inhalation (Wehner *et al.,* 1975). "Oxidic" nickel compounds have also induced tumours at the site of injection in rats and mice (IARC, 1990).

"Oxidic" nickel induced cell transformation in cultured rodent cells. However, it did not induce chromosomal aberrations in a study in cultured human cells (IARC, 1990).

There was no evidence of cancer in studies in hamsters exposed to nickel acetate-enriched fly ash by inhalation (Wehner *et al.,* 1981). In studies in which rats and mice were administered nickel sulphate or other "soluble" nickel salts in the diet or drinking water, there have been no increases in tumour incidence; however, all of these studies are considered to be inadequate for an assessment of carcinogenicity, due to small group sizes, limited examination of tissues and/or poor documentation of the results (Ambrose *et al.,* 1976; Dieter *et al.,* 1988; Schroeder and Mitchener, 1975; Schroeder *et al.,* 1964; 1974). Hydrated nickel acetate induced lung tumours in mice following repeated intraperitoneal injection (Poirier *et al.,* 1984; Stoner *et al.,* 1976). There is some limited evidence that "soluble" nickel compounds induced local tumours following administration by routes less relevant to environmental exposure (IARC, 1990).

Although the weight of evidence indicates that various "soluble" nickel salts were not mutagenic in a range of bacterial assays, "soluble" nickel salts produced chromosome aberrations, sister chromatid exchanges, and cell transformation in numerous *in vitro* systems (IARC, 1990). In addition, chromosomal aberrations in the bone marrow were induced by nickel chloride (single intraperitoneal injection) in mice (Dhir *et al.,* 1991; Mohanty, 1987) and hamsters (Chorvatovicova, 1983). There was also an increased frequency of micronucleated polychromatic erythrocytes in mice following oral administration (Sobti and Gill, 1989) and intraperitoneal injection (Deknudt and Leonard, 1982; Dhir *et al.,* 1991) of nickel chloride, nickel sulphate, or nickel nitrate and induction of DNA damage in the kidneys and lungs of rats administered nickel carbonate intraperitoneally (Ciccarelli and Wetterhahn, 1982). There was no convincing evidence of activity of nickel chloride and nickel nitrate administered by intraperitoneal injection

in dominant lethal mutation assays in mice (Deknudt and Leonard, 1982; Jacquet and Mayence, 1982).

In summary, there was no evidence that exposure to metallic nickel was associated with increased mortality due to lung or nasal cancer in two small cohorts of workers exposed primarily to this form of nickel (Doll *et al.*, 1990) and in cross-classification analyses in two larger cohorts (Doll *et al.*, 1990). While there is some evidence that metallic nickel may be carcinogenic in experimental animals exposed by direct intratracheal instillation (Pott *et al.*, 1987), the carcinogenicity of this form of nickel has not been investigated in adequate inhalation studies for which exposure conditions are more relevant to assessment of effects in humans. Due to the limited sensitivity of available epidemiological studies in which the association between exposure to metallic nickel and cancer in occupationally exposed populations has been investigated, and the lack of identified adequate carcinogenicity bioassays in which experimental animals have been exposed to metallic nickel by inhalation, metallic nickel is classified in Group VI ("Unclassifiable with Respect to Carcinogenicity in Humans") of the classification scheme developed for the determination of "toxic" under Paragraph 11(c) of CEPA (EHD, 1992). For compounds classified in Group VI, a tolerable daily intake or concentration to which it is believed that a person can be exposed daily over a lifetime without deleterious effect is generally developed by division of a relevant No-Observed-(Adverse)-Effect Level [NO(A)EL] or Lowest-Observed-(Adverse)-Effect Level [LO(A)EL] for non-neoplastic effects in animal species by an uncertainty factor. Minimal effects on the morphology and function of alveolar cells have been observed in rabbits exposed to concentrations of metallic nickel as low as 0.1 mg/m^3 (Camner and Johansson, 1992; Curstedt *et al.*, 1983; Johansson *et al.*, 1983; Lundborg and Camner, 1982). Concentrations of total nickel in ambient air in Canada are more than 5000 times less than this value. Moreover, metallic nickel is believed to comprise only a small proportion of the total nickel present in ambient air in Canada (MacLatchy, 1992), although quantitative information on speciation in the general environment was not identified.

Therefore, metallic nickel is not considered to be entering the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human life or health.

There is sufficient and consistent evidence of the carcinogenicity of "oxidic", "sulphidic", and "soluble" nickel in adequate epidemiological studies in different types of exposed workers and some weak evidence of genotoxicity in limited epidemiological studies. Although there may have been concomitant exposure to other compounds in these studies, the common predisposing factors in the various groups of workers examined appear to be these groups of nickel compounds. In addition, there is some supportive evidence of carcinogenicity and genotoxicity of these forms of nickel in principally limited studies in animal species. Therefore, each of "oxidic", "sulphidic",

and "soluble" nickel* has been included in Group I ("Carcinogenic to Humans") of the classification scheme developed for the determination of "toxic" under Paragraph 11(c) of CEPA (EHD, 1992).

For such substances, where data permit, the estimated exposure in relevant environmental media is compared to quantitative estimates of cancer potency, expressed as the concentration or dose that induces a 5% increase in the incidence of or mortality due to relevant tumours ($TD_{0.05}$) (i.e., exposure/potency indices), to characterize risk and provide guidance for further action (i.e., analysis of options to reduce exposure) under CEPA (EHD, 1992).

The data considered most relevant to the quantification of the cancer potency associated with exposure to inorganic nickel compounds in the general environment are those obtained in epidemiological studies in occupationally exposed populations, since the weight of evidence of such an association in these studies is convincing. This approach also obviates the need for interspecies extrapolation.

The epidemiological studies that provide sufficient information to serve as a basis for quantitative estimation of the carcinogenic potency of inhaled inorganic nickel are those of large cohorts (n = 3250 to 54509) of exposed workers at two nickel refineries for whom the most extensive information on exposure is available: the INCO mining, smelting, and refinery operations in Ontario, and the Falconbridge refineries in Kristiansand, Norway (Doll *et al.*, 1990). Estimates of the carcinogenic potency of "oxidic", "sulphidic", and "soluble" nickel (combined), based on results at the INCO mining, smelting, and refinery operations in Ontario were considered the most relevant and reliable for several reasons: the cohorts were relatively large (e.g., total expected numbers of deaths of Copper Cliff sinter plant workers with 15 or more years since first exposure due to lung cancer was approximately 20); there was clear evidence of increased lung and nasal cancer mortality with increasing duration of exposure in the sinter workers, and there was no exposure to metallic nickel (i.e., the estimates of total concentrations of nickel did not include a form of nickel for which there is no convincing evidence of carcinogenicity). Although the potency of the various species may vary considerably, the $TD_{0.05}$s estimated on the basis of the INCO cohort are based on "oxidic", "sulphidic", and "soluble" nickel (combined) since available data do not permit separate estimates for each of the groups of compounds. This is justified on the basis that all three forms are likely to be present in the general environment.

The Kristiansand cohort consisted of two clearly defined working groups, i.e., electrolysis workers with no employment in other high exposure departments and those employed in the roasting, smelting, and calcining department. There was little exposure to metallic nickel in both groups. Based on the data presented for these workers, $TD_{0.05}$s may be developed for "oxidic", "sulphidic", and "soluble" nickel (combined), and "soluble" nickel (specifically).

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* Based on the nature of the available data, this classification is considered to apply to the groups of "oxidic", "sulphidic", and "soluble" nickel compounds rather than to any specific compound within these groups.

A detailed description of the mathematical derivation of the constant concentration that corresponded to a 5% increase in mortality due to lung or nasal cancer ($TD_{0.05}$), based on the data reported by Doll *et al.* (1990), is presented in the Appendix of the supporting documentation. The age-specific death rate for lung cancer observed in the cohorts of the Copper Cliff sinter plant and Coniston sinter plant was assumed to be a linear function of the cumulative exposure to total nickel, whereas the age-specific death rate for lung cancer reported in the cohorts of Port Colborne nickel refinery and Kristiansand nickel refinery workers was assumed to be an exponential function of the cumulative exposure to total nickel. The age-specific death rate was also assumed to be multiplicative to the death rate for the general population. The increase in probability of death due to a constant lifetime exposure to nickel has been determined, based on the assumption that there are no competing causes of death and a constant exposure for a period equal to the median survival time of 75 years. The estimates of the $TD_{0.05}$ for inhaled "oxidic", "sulphidic", and "soluble" nickel (combined) for lung cancer mortality ranged from 0.04 to 1.0 mg/m^3. It should be noted that the $TD_{0.05}$s based on data for workers in the Clydach refinery (although the numbers of workers in each occupational group were small) would not be substantially different. The $TD_{0.05}$ for lung cancer mortality for "soluble" nickel, estimated based on data for the Kristiansand cohort, was also within this range of values (i.e., 0.07 mg/m^3).

Corresponding calculated exposure/potency indices (EPIs) for the range of mean concentrations of total inorganic nickel reported in ambient air in several cities across Canada [0.001 to 0.02 µg/m^3 (Dann, 1991a;b)] range from 1.0×10^{-6} to 5.0×10^{-4}. Calculated EPIs, based on the $TD_{0.05}$s derived for nasal cancer for the Copper Cliff and Port Colborne cohorts, are less than those derived for lung cancer (i.e., 3.8×10^{-7} to 7.6×10^{-6} and 6.8×10^{-7} to 1.4×10^{-5}, respectively). Based solely on considerations of potential health effects, therefore, the priority for further action (i.e, analysis of options to reduce exposure) would be considered to be moderate to high. Values calculated for populations residing in the vicinity of point sources based on early, limited available monitoring data are within the same range [i.e., the priority for further action is considered to be moderate to high based on a concentration of total inorganic nickel in ambient air of 0.021 µg/m^3 determined in an early survey in Sudbury (Chan and Lusis, 1986)].

It should be noted, however, that there are several limitations of the EPIs that should be considered in their interpretation. For example, the estimated concentrations of total airborne nickel at the INCO mining, smelting, and refinery operations were based on only a few industrial hygiene samples of the occupational environment taken in the later period of employment of study subjects. In addition, concomitant exposure to other compounds and smoking were not taken into account in the analyses. It should also be noted that there were few data on atmospheric concentrations of nickel in the Kristiansand plant before the early 1970s (the estimated concentrations of total airborne nickel for earlier periods were based largely on the subjective judgements of retired personnel) and expected numbers of deaths from lung and nasal cancer in this cohort were very small, i.e., the cohort was small (e.g., expected numbers of deaths from lung cancer in electrolysis workers with 15 or more years since first exposure ranged from 0.8

to 3.8). As well, only a small proportion of the cohorts studied had died at the time of the follow-up. Furthermore, although it is recognized that the potencies of the various forms of nickel are likely to vary, most of the available data were inadequate to permit calculation of separate potencies for each of the compounds, and no data are available on the speciation of nickel present in ambient air in Canada [although these three forms of nickel are likely present (IPCS, 1991)].

Based principally on the sufficient weight of evidence of carcinogenicity in occupationally exposed populations for the groups of compounds examined in a recent extensive epidemiological analysis and some limited supporting data on individual compounds in experimental animals, each of the groups * "oxidic" (including nickel oxide, nickel-copper oxide, nickel silicate oxides, and complex oxides), "sulphidic" (including nickel subsulphide), and "soluble" (primarily nickel sulphate and nickel chloride) nickel compounds has been classified as "Carcinogenic to Humans" (i.e., groups for which there is considered to be some probability of harm for the critical effect at any level of exposure). Each of these groups is, therefore, considered to be entering the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human life or health.

This approach is consistent with the objective that exposure to substances for which one of the critical effects is considered not to have a threshold should be reduced wherever possible and obviates the need to establish an arbitrary "de minimis" level of risk for the determination of "toxic" under the Act.

In addition to the documented carcinogenicity of "oxidic", "sulphidic", and "soluble" nickel in occupationally exposed human populations, nickel (mostly "soluble" compounds) induces allergic contact dermatitis in a proportion of the general population. Contact hypersensitivity following dermal application has also been induced in experimental animals (IPCS, 1991). No information has been identified on the proportion of the Canadian general population that is sensitized towards nickel. In a number of studies of the general population of other countries of similar economic and social character, however, the prevalence was 8 to 21.9% in females and 0.3 to 2.8% in males (Meding and Swanbeck, 1990; Menné *et al.*, 1982; Peltonen, 1979; Prystowsky *et al.*, 1979; Seidenari *et al.*, 1990). The major cause of the sensitized state in the general population is believed to be contact with low quality jewellery, particularly earrings and other items, such as watch-straps.

The available epidemiological data on effects other than cancer and dermatological sensitivity for "oxidic", "sulphidic", and "soluble" nickel compounds are insufficient to

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* Based on the nature of available data, this assessment of these forms of nickel under Paragraph 11(c) of CEPA is considered to apply to the groups of "oxdic", "sulphidic", and "soluble" nickel compounds, rather than to any specific compound within these groups.

serve as a basis for establishment of effect levels. However, Tolerable Daily Intakes (TDIs) or Concentrations (TDCs) developed on the basis of the somewhat limited data on non-neoplastic effects in animal species would, for some of these forms of nickel, be similar to the mean exposure of some subgroups in the population. For example, the Lowest-Observed-Adverse-Effect-Level {i.e., 1.3 mg of Ni/[kg(b.w.) · d] for an increased proportion of dead pups per litter} in a suitable study in animals ingesting "soluble" inorganic nickel compounds (Smith *et al.*, 1993), is 36 to 260 times greater than estimated total intakes through ingestion for populations residing in the vicinity of point sources (i.e., less than the magnitude of an uncertainty factor that might be used in the derivation of a TDI). The lowest LOEL (0.02 mg/m^3) for minimal respiratory effects in animals exposed to nickel oxide (Spiegelberg *et al.*, 1984) or nickel sulphate (Dunnick *et al.*, 1989) is less than 1000 times greater than concentrations of nickel in ambient air at some locations.

3.4 Conclusions

Based on these considerations, it has been concluded that dissolved and soluble* forms of inorganic nickel are entering or may enter the environment in a quantity or concentration or under conditions that are having or that may have a harmful effect on the environment. It has been concluded that the substance "nickel and its compounds" does not or may not enter the environment in a quantity or concentration or under conditions that constitute or that may constitute a danger to the environment on which human life depends. It has also been concluded that metallic nickel does not constitute a danger in Canada to human life or health, however each of the groups, "oxidic" (including nickel oxide, nickel-copper oxide, nickel silicate oxides, and complex oxides), "sulphidic" (including nickel subsulphide), and "soluble" (primarily nickel sulphate and nickel chloride) nickel compounds, as a whole, is entering the environment in a quantity or concentration or under conditions that may constitute a danger in Canada to human life or health.

* The term "soluble" includes water-soluble forms of nickel (e.g., nickel sulphate and nickel chloride), as well as other more stable forms (e.g., nickel-bearing sulphide minerals and nickel oxide) that can dissolve under certain conditions of pH (e.g., acidic mine tailings) or redox potential (e.g., buried reducing sediment) in the environment.

4.0 Recommendations for Research and Evaluation

Acquisition of data in the following areas would permit a more complete assessment of the effects of nickel on the environment and of the risks associated with exposure of the general population in Canada to nickel:

1. Better characterization of inorganic nickel in various foodstuffs and indoor air.

2. Additional data on concentrations, forms, and bioavailability of nickel in various environmental media, in the general environment, and in the vicinity of point sources.

3. Additional well conducted and documented carcinogenicity bioassays for various forms of nickel following both inhalation and ingestion in experimental animals.

4. Studies of the reproductive, cardiovascular, and neurological effects of nickel compounds in experimental animals.

5. Additional follow-up and, if possible, generation of information on the historical exposure of workers to nickel and accounting for potential confounders such as smoking or concomitant exposure to other compounds in the industrial processes in the occupationally exposed cohorts used as a basis for quantitative assessment of cancer potency. Initiation of studies of additional cohorts for whom exposure could be better characterized.

6. Additional toxicological studies on the effects of nickel on wild mammals (including prey availability studies). In addition, more data on concentrations of nickel in Canadian wildlife.

7. Studies on the toxicity of nickel in sediments to invertebrates.

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