DRAFT
TOXICOLOGICAL PROFILE FOR NICKEL

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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ADMIN RECORD

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for nickel was released in 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
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The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

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QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 **How Can (Chemical X) Affect Children?**
Section 1.7 **How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7 **Children's Susceptibility**
Section 6.6 **Exposures of Children**

Other Sections of Interest:

Section 3.8 **Biomarkers of Exposure and Effect**
Section 3.11 **Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0093
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

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PEER REVIEW

A peer review panel was assembled for nickel. The panel consisted of the following members:

1. George Daston, Ph.D., Research Fellow, Miami Valley Laboratories, Proctor & Gamble Company, Cincinnati OH;

2. A. Phillip Leber, Ph.D., DABT, Project Manager, Toxicology and Product Acceptability, The Goodyear Tire & Rubber Company, Akron OH; and

3. Sam Kacew, Ph.D., ATS, Professor, Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa ON, Canada.

These experts collectively have knowledge of nickel's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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CONTENTS

DISCLAIMER ii
UPDATE STATEMENT iii
FOREWORD iv
QUICK REFERENCE FOR HEALTH CARE PROVIDERS vii
CONTRIBUTORS ix
PEER REVIEW xi
CONTENTS xiii
LIST OF FIGURES xvii
LIST OF TABLES xix

1. PUBLIC HEALTH STATEMENT 1
1.1 WHAT IS NICKEL? 1
1.2 WHAT HAPPENS TO NICKEL WHEN IT ENTERS THE ENVIRONMENT? 2
1.3 HOW MIGHT I BE EXPOSED TO NICKEL? 3
1.4 HOW CAN NICKEL ENTER AND LEAVE MY BODY? 4
1.5 HOW CAN NICKEL AFFECT MY HEALTH? 5
1.6 HOW CAN NICKEL AFFECT CHILDREN? 7
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO NICKEL? 8
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO NICKEL? 8
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 8
1.10 WHERE CAN I GET MORE INFORMATION? 9

2. RELEVANCE TO PUBLIC HEALTH 11
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO NICKEL IN THE UNITED STATES 11
2.2 SUMMARY OF HEALTH EFFECTS 12
2.3 MINIMAL RISK LEVELS (MRLs) 16

3. HEALTH EFFECTS 23
3.1 INTRODUCTION 23
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 23
3.2.1 Inhalation Exposure 25
3.2.1.1 Death 25
3.2.1.2 Systemic Effects 59
3.2.1.3 Immunological and Lymphoreticular Effects 68
3.2.1.4 Neurological Effects 70
3.2.1.5 Reproductive Effects 71
3.2.1.6 Developmental Effects 72
3.2.1.7 Cancer 73
3.2.2 Oral Exposure 76
3.2.2.1 Death 76
3.2.2.2 Systemic Effects 95
3.2.2.3 Immunological and Lymphoreticular Effects 101
3.2.2.4 Neurological Effects 103
3.2.2.5 Reproductive Effects 103
3.2.2.6 Developmental Effects 105

3.2.2.7 Cancer 107
3.2.3 Dermal Exposure 108
3.2.3.1 Death 108
3.2.3.2 Systemic Effects 108
3.2.3.3 Immunological and Lymphoreticular Effects 113
3.2.3.4 Neurological Effects 114
3.2.3.5 Reproductive Effects 114
3.2.3.6 Developmental Effects 114
3.2.3.7 Cancer 114
3.3 GENOTOXICITY 115
3.4 TOXICOKINETICS 120
3.4.1 Absorption 121
3.4.1.1 Inhalation Exposure 121
3.4.1.2 Oral Exposure 122
3.4.1.3 Dermal Exposure 123
3.4.2 Distribution 124
3.4.2.1 Inhalation Exposure 124
3.4.2.2 Oral Exposure 126
3.4.2.3 Dermal Exposure 127
3.4.2.4 Other Routes of Exposure 127
3.4.3 Metabolism 128
3.4.4 Elimination and Excretion 128
3.4.4.1 Inhalation Exposure 128
3.4.4.2 Oral Exposure 129
3.4.4.3 Dermal Exposure 130
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models 130
3.5 MECHANISMS OF ACTION 139
3.5.1 Pharmacokinetic Mechanisms 139
3.5.2 Mechanisms of Toxicity 140
3.5.3 Animal-to-Human Extrapolations 142
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS 143
3.7 CHILDREN'S SUSCEPTIBILITY 144
3.8 BIOMARKERS OF EXPOSURE AND EFFECT 146
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Nickel 147
3.8.2 Biomarkers Used to Characterize Effects Caused by Nickel 149
3.9 INTERACTIONS WITH OTHER CHEMICALS 150
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 151
3.11 METHODS FOR REDUCING TOXIC EFFECTS 152
3.11.1 Reducing Peak Absorption Following Exposure 152
3.11.2 Reducing Body Burden 153
3.11.3 Interfering with the Mechanism of Action for Toxic Effects 154
3.12 ADEQUACY OF THE DATABASE 155
3.12.1 Existing Information on Health Effects of Nickel 156
3.12.2 Identification of Data Needs 156
3.12.3 Ongoing Studies 167

4. CHEMICAL AND PHYSICAL INFORMATION 169
4.1 CHEMICAL IDENTITY 169
4.2 PHYSICAL AND CHEMICAL PROPERTIES 169

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 179

5.1 PRODUCTION 179
5.2 IMPORT/EXPORT 181
5.3 USE 186
5.4 DISPOSAL 187

6. POTENTIAL FOR HUMAN EXPOSURE 189
6.1 OVERVIEW 189
6.2 RELEASES TO THE ENVIRONMENT 199
6.2.1 Air 199
6.2.2 Water 202
6.2.3 Soil 204
6.3 ENVIRONMENTAL FATE 206
6.3.1 Transport and Partitioning 206
6.3.2 Transformation and Degradation 214
6.3.2.1 Air 215
6.3.2.2 Water 215
6.3.2.3 Sediment and Soil 216
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 217
6.4.1 Air 217
6.4.2 Water 220
6.4.3 Sediment and Soil 224
6.4.4 Other Environmental Media 226
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 229
6.6 EXPOSURES OF CHILDREN 238
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 240
6.8 ADEQUACY OF THE DATABASE 240
6.8.1 Identification of Data Needs 241
6.8.2 Ongoing Studies 244

7. ANALYTICAL METHODS 249
7.1 BIOLOGICAL MATERIALS 249
7.2 ENVIRONMENTAL SAMPLES 250
7.3 ADEQUACY OF THE DATABASE 258
7.3.1 Identification of Data Needs 259
7.3.2 Ongoing Studies 260

8. REGULATIONS AND ADVISORIES 262

9. REFERENCES 271

10. GLOSSARY 325

APPENDICES

A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS A-1

B. USER'S GUIDE B-1

C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS C-1

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LIST OF FIGURES

3-1 Levels of Significant Exposure to Nickel - Inhalation 53

3-2 Levels of Significant Exposure to Nickel - Oral 91

3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 132

3-4. Diagram of the Compartmental Model of Nickel Metabolism 133

3-5. Existing Information on Health Effects of Nickel 157

6-1. Frequency of NPL Sites with Nickel Contamination 190

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LIST OF TABLES

3-1 Levels of Significant Exposure to Nickel - Inhalation 27

3-2. Alveolar/Bronchiolar Neoplasms and Adrenal Medulla Proliferative Lesions in Rats 77

3-3. Alveolar/Bronchiolar Neoplasms in Mice 78

3-4 Levels of Significant Exposure to Nickel - Oral 80

3-5 Levels of Significant Exposure to Nickel - Dermal 109

3-6. Genotoxicity of Nickel *In Vivo* 116

3-7. Genotoxicity of Nickel *In Vitro* 117

3-8. Kinetic Parameters of Nickel Sulfate Absorption, Distribution, and Elimination in Humans 134

3-9. Clearance Rate Coefficient Constants of Nickel Compounds 137

3-10. Ongoing Studies on Nickel Health Effects 168

4-1. Chemical Identity of Nickel and Compounds 170

4-2. Physical and Chemical Properties of Nickel and Compounds 175

5-1. Facilities that Produce, Process, or Use Nickel Metal 182

5-2. Facilities that Produce, Process, or Use Nickel Compounds 184

6-1. Releases to the Environment from Facilities that Produce, Process, or Use Nickel 191

6-2. Releases to the Environment from Facilities that Produce, Process, or Use Nickel Compounds 194

6-3. Concentrations of Nickel Measured in Sheetflow Samples taken from Different Urban Source Areas in Birmingham, Alabama 205

6-4. Total Dietary Exposure Estimates of Study Participants to Nickel Based on the Dietary Information Obtained from the NHEXAS Arizona Study 231

6-5. Dietary Exposure Estimates of U.S. Populations to Nickel Based on the Dietary Exposure Potential Model (DEPM) 233

6-6. Nickel Levels in Air and Distribution of Different Forms of Nickel as a Proportion (by Weight) of Total Nickel in Selected Departments and Time Periods at a Nickel Refinery in Norway 235

6-7. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Nickel 245

7-1. Analytical Methods for Determining Nickel in Biological Materials 251

7-2. Analytical Methods for Determining Nickel in Environmental Samples 254

7-3. Ongoing Studies on Analytical Methods for Quantifying Nickel 261

8-1. Regulations and Guidelines Applicable to Nickel 264

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about nickel and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Nickel has been found in at least 862 of the 1,636 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which nickel is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to nickel, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it/them. You must also consider the other chemicals you're exposed to and your age, gender, diet, family traits, lifestyle, state of health, occupation, and location of residence.

1.1 WHAT IS NICKEL?

Pure nickel is a hard, silvery-white metal, which has properties that make it very desirable for combining with other metals to form mixtures called alloys. Some of the metals that nickel can be alloyed with are iron, copper, chromium, and zinc. These alloys are used in making metal coins and jewelry and in industry for making items such as valves and heat exchangers. Most nickel is used to make stainless steel. There are also compounds consisting of nickel combined with many other elements, including chlorine, sulfur, and oxygen. Many of these nickel compounds are water soluble (dissolve fairly easily in water) and have a characteristic green

color. Nickel and its compounds have no characteristic odor or taste. Nickel compounds are used for nickel plating, to color ceramics, to make some batteries, and as substances known as catalysts that increase the rate of chemical reactions.

Nickel combined with other elements occurs naturally in the earth's crust. It is found in all soil, and is also emitted from volcanoes. Nickel is the 24th most abundant element. In the environment, it is primarily found combined with oxygen or sulfur as oxides or sulfides. Nickel is also found in meteorites and on the ocean floor in lumps of minerals called sea floor nodules. The earth's core is composed of 6% nickel. Nickel is released into the atmosphere during nickel mining and by industries that make or use nickel, nickel alloys, or nickel compounds. These industries also might discharge nickel in waste water. Nickel is also released into the atmosphere by oil-burning power plants, coal-burning power plants, and trash incinerators.

There are no nickel mining operations in the United States. Much of our nickel used in industries comes from recycling nickel-containing alloys and we also import it from Canada. Much of our domestic nickel comes from recycling nickel-containing alloys.

See Chapters 4 and 5 of this profile for more information on the properties, sources, and uses of nickel and its compounds.

1.2 WHAT HAPPENS TO NICKEL WHEN IT ENTERS THE ENVIRONMENT?

Nickel may be released to the environment from the stacks of large furnaces used to make alloys or from power plants and trash incinerators. The nickel that comes out of the stacks of power plants attaches to small particles of dust that settle to the ground or are taken out of the air in rain or snow. It usually takes many days for nickel to be removed from the air. If the nickel is attached to very small particles, it can take more than a month to settle out of the air. Nickel can also be released in industrial waste water. A lot of nickel released into the environment ends up in soil or sediment where it strongly attaches to particles containing iron or manganese. Under acidic conditions, nickel is more mobile in soil and might seep into groundwater. Nickel does not appear to concentrate in fish. Studies show that some plants can take up and accumulate

nickel. However, it has been shown that nickel does not accumulate in small animals living on land that has been treated with nickel-containing sludge.

See Chapter 6 for more information on the fate of nickel in the environment.

1.3 HOW MIGHT I BE EXPOSED TO NICKEL?

Nickel normally occurs at very low levels in the environment, so very sensitive methods are needed to detect nickel in most environmental samples. Food is the major source of exposure to nickel. You may also be exposed to nickel by breathing air, drinking water, or smoking tobacco containing nickel. Skin contact with soil, bath or shower water, or metals containing nickel, as well as, metals plated with nickel can also result in exposure. Stainless steel and coins contain nickel. Some jewelry is plated with nickel or made from nickel alloys. Patients may be exposed to nickel in artificial body parts made from nickel-containing alloys.

We often do not know the exact form of nickel we are exposed to, including at most hazardous waste sites. Much of the nickel found in air, soil, sediment, and rock is so strongly attached to dust and soil particles or embedded in minerals that it is not readily taken up by plants and animals and, therefore, cannot easily affect your health. In water and waste water, nickel can exist either dissolved in water or attached to material suspended in water.

Nickel in air is attached to small particles. Over a 6-year period (1977–1982) in the United States, average nickel concentrations in cities and in the country ranged from 7 to 12 nanograms per cubic meter (ng/m^3; 1 ng/m^3 is equivalent to 1 billionth of a gram in a cubic meter of air). More recently, EPA estimates that the average nickel concentration in air in the United States has decreased to 2.2 ng/m^3, based on air quality information obtained from 1996.

The concentration of nickel in the water of rivers and lakes is very low, with the average concentration usually less than 10 parts of nickel in a billion parts of water (ppb). The level of nickel in water is often so low that we cannot measure it unless we use very sensitive instruments. The average concentration of nickel in drinking water is between 3 and 7 ppb.

However, you may be exposed to higher-than-average levels of nickel in drinking water if you live near industries that process or use nickel. The highest levels of nickel in drinking water, about 72 ppb, were found near areas of a large natural nickel deposit is mined and refined.

Soil usually contains between 4 and 80 parts of nickel in a million parts of soil (ppm; 1 ppm= 1,000 ppb). The highest soil concentrations (up to 9,000 ppm) are found near industries that extract nickel from ore. High concentrations of nickel occur as dust is released into air from stacks during processing and settles on the ground. You may be exposed to nickel in soil by skin contact. Children may also be exposed to nickel by eating soil.

Food contains nickel and is the major source of nickel exposure for the general population. You eat about 170 micrograms (μg; 1 μg=1,000 ng) of nickel in your food every day. Foods naturally high in nickel include chocolate, soybeans, nuts, and oatmeal. Our daily intake of nickel from drinking water is only about 2 μg. We breathe in between 0.1 and 1 μg nickel/day, excluding nickel in tobacco smoke. We are exposed to nickel when we handle coins and touch other metals containing nickel.

You may be exposed to higher levels of nickel if you work in industries that process or use nickel. You also may be exposed to nickel by breathing dust or fumes (as from welding) or by skin contact with nickel-containing metal and dust or solutions containing dissolved nickel compounds. A national survey conducted from 1980 to 1983 estimated that 727,240 workers are potentially exposed to nickel metal, nickel alloys, or nickel compounds.

For more information on the potential for exposure to nickel, please see Chapter 6.

1.4 HOW CAN NICKEL ENTER AND LEAVE MY BODY?

Nickel can enter your body when you breathe air containing nickel, when you drink water or eat food that contains nickel, and when your skin comes into contact with nickel. If you breathe air that contains nickel, the amount of nickel you inhale that reaches your lungs and enters your blood depends on the size of the nickel particles. If the particles are large, they stay in your nose.

If the particles are small, they can enter deep into your lungs. More nickel is absorbed from your lungs into your body when the nickel particles can dissolve easily in water. When the particles do not dissolve easily in water, the nickel may remain in your lungs for a long time. Some of these nickel particles can leave the lungs with mucus that you spit out or swallow. More nickel will pass into your body through your stomach and intestines if you drink water containing nickel than if you eat food containing the same amount of nickel. A small amount of nickel can enter your bloodstream from skin contact. After nickel gets into your body, it can go to all organs, but it mainly goes to the kidneys. The nickel that gets into your bloodstream leaves in the urine. After nickel is eaten, most of it leaves quickly in the feces, and the small amount that gets into your blood leaves in the urine. For more information on how nickel can enter and leave your body, see Chapter 3.

1.5 HOW CAN NICKEL AFFECT MY HEALTH?

To protect the public from the harmful effects of chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, distributed in the body, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

The most common harmful health effect of nickel in humans is an allergic reaction to nickel. Approximately 10–15% of the population is sensitive to nickel. A person can become sensitive to nickel when jewelry or other things containing nickel are in direct contact with the skin. Wearing earrings containing nickel in pierced ears may also sensitize a person to nickel. Once a person is sensitized to nickel, further contact with the metal will produce a reaction. The most common reaction is a skin rash at the site of contact. In some sensitized people, dermatitis (a

type of skin rash) may develop in an area of the skin that is away from the site of contact. For example, hand eczema (another type of skin rash) is fairly common among people sensitized to nickel. Less frequently, some people who are sensitive to nickel have asthma attacks following exposure to nickel. People who are sensitive to nickel have reactions when nickel comes into contact with the skin. Some sensitized individuals react when they eat nickel in food or water or breathe dust containing nickel. More women are sensitive to nickel than men. This difference between men and women is thought to be a result of greater exposure of women to nickel through jewelry and other metal items.

People who are not sensitive to nickel must eat very large amounts of nickel to suffer harmful health effects. Workers who accidentally drank light-green water containing 250 ppm of nickel from a contaminated drinking fountain had stomach aches and suffered adverse effects in their blood (increased red blood cells) and kidneys (increased protein in the urine). This concentration of nickel is more than 100,000 times greater than the amount usually found in drinking water.

The most serious harmful health effects from exposure to nickel, such as chronic bronchitis, reduced lung function, and cancer of the lung and nasal sinus, have occurred in people who have breathed dust containing nickel compounds while working in nickel refineries or nickel-processing plants. The levels of nickel in these workplaces were much higher than usual (background) levels in the environment. Lung and nasal sinus cancers occurred in workers who were exposed to more than 10 mg nickel/m^3 as nickel compounds that were hard to dissolve (such as nickel subsulfide). Exposure to high levels of nickel compounds that dissolve easily in water (soluble) may also result in cancer when nickel compounds that are hard to dissolve (less soluble) are present, or when other chemicals that can cause cancer are present. The concentrations of soluble and less-soluble nickel compounds that were found to have caused cancers were 100,000 to 1 million times greater than the usual level of nickel in the air in the United States. The U.S. Department of Health and Human Services (DHHS) has determined that nickel metal may reasonably be anticipated to be a carcinogen and nickel compounds are known human carcinogens. The International Agency for Research on Cancer (IARC) has determined that some nickel compounds are carcinogenic to humans and that metallic nickel may possibly be

carcinogenic to humans. The EPA has determined that nickel refinery dust and nickel subsulfide are human carcinogens.

Lung inflammation and damage to the nasal cavity have been observed in animals exposed to nickel compounds. At high concentrations, the lung damage is severe enough to affect lung function. Long-term exposure to lower levels of a nickel compound that dissolves easily in water did not cause cancer in animals. Lung cancer developed in rats exposed for a long time to nickel compounds that do not dissolve easily in water.

Oral exposure of humans to high levels of soluble nickel compounds through the environment is extremely unlikely. Because humans have only rarely been exposed to high levels of nickel in water or food, much of our knowledge of the harmful effects of nickel is based on animal studies. Eating or drinking levels of nickel much greater than the levels normally found in food and water have been reported to cause lung disease in dogs and rats and to affect the stomach, blood, liver, kidneys, and immune system in rats and mice, as well as their reproduction and development.

See Chapter 3 for more information on the health effects of nickel exposure.

1.6 HOW CAN NICKEL AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

It is likely that the health effects seen in children exposed to nickel will be similar to the effects seen in adults. We do not know whether children differ from adults in their susceptibility to nickel. Human studies that examined whether nickel can harm the developing fetus are inconclusive. Animal studies have found increases in newborn deaths and decreases in newborn weight after ingesting nickel. These doses are 1,000 times higher than levels typically found in drinking water. It is likely that nickel can be transferred from the mother to an infant in breast milk and can cross the placenta.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO NICKEL?

If your doctor finds that you have been exposed to significant amounts of nickel or nickel compounds, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

People may be exposed to nickel by wearing jewelry that contains nickel. In some people, wearing jewelry that contains nickel causes skin irritation. Avoiding jewelery containing nickel will eliminate risks of exposure to this source of this metal.

Other sources of nickel exposure are through foods that you eat and drinking water. However, the amount of nickel in foods and drinking water are too low to be of concern.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO NICKEL?

Measurements of the amount of nickel in your blood, feces, and urine can be used to estimate your exposure to nickel. More nickel was found in the urine of workers who were exposed to nickel compounds that dissolve easily in water (soluble) than in the urine of workers exposed to compounds that are hard to dissolve (less soluble). This means that it is easier to tell if you have been exposed to soluble nickel compounds than less-soluble compounds. The nickel measurements do not accurately predict potential health effects from exposure to nickel. More information on medical tests can be found in Chapters 3 and 7.

1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by

law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for nickel include the following:

OSHA has set an enforceable limit of 1.0 mg nickel/m^3 for metallic nickel and nickel compounds in workroom air to protect workers during an 8-hour shift over a 40-hour work week. EPA recommends that drinking water levels for nickel should not be more than 0.7 mg per liter.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop E-29
Atlanta, GA 30333
Fax: 1-404-498-0093

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO NICKEL IN THE UNITED STATES

Nickel is a very hard metal that occurs naturally in soils and volcanic dust. Nickel is used in combination with other metals to form alloys used for coins, jewelry, and stainless steel. Nickel compounds are used for electroplating, to color ceramics, and in battery production.

Nickel is released to the atmosphere by windblown dust, volcanoes, combustion of fuel oil, municipal incineration, and industries involved in nickel refining, steel production, and other nickel alloy production. The form of nickel emitted to the atmosphere is dependent upon the source. Complex nickel oxides, nickel sulfate, and metallic nickel are associated with combustion, incineration, and smelting and refining processes. Ambient air concentrations of nickel range between 7 and 12 ng/m^3, mainly in the form of aerosols and can be as high as 150 ng/m^3 near point sources. Based on 1996 air quality data, EPA has reported U.S. levels of 2.2 ng/m^3. Ambient air levels of nickel are expected to be higher in urban air than in rural air. Concentrations of nickel in indoor air are generally <10 ng/m^3.

Background levels of nickel in soils vary widely depending on local geology and anthropogenic inputs, but concentrations typically range between 4 and 80 ppm. Some areas of the United States may contain natural levels as high as 5,000 ppm. Concentrations of nickel in household dust can be high and therefore pose an increased risk to young children who have greater contact with floors. Nickel concentrations in surface water and groundwater range between 3 and 10 μg/L. Nickel levels in drinking water in the United States generally range from 0.55 to 25 μg/L (1.1 to 50 μg/day, estimated using a reference water intake of 2 L/day) and average between 2–4 μg/L (4–8 μg/day). Elevated levels of nickel may exist as a result of the corrosion and leaching of nickel alloys used in valves and faucets. For the general population, the predominant route of exposure to nickel is through food intake. Nickel intake in the United States ranges between 69 and 162 μg/day. Based on these average water and food nickel levels, a daily dose of 0.001–0.016 mg/kg/day can be estimated using a reference body weight of 70 kg.

Nickel does not bioaccumulate to a great extent in animals. There is evidence of uptake and accumulation in certain plants.

Nickel is an essential trace element in animals, although the functional importance of nickel has not been clearly demonstrated. It is considered essential based on reports of nickel deficiency in several animal species (e.g., rats, chicks, cows, goats). Nickel deficiency is manifested primarily in the liver; effects include abnormal cellular morphology, oxidative metabolism, and increases and decreases in lipid levels. Decreases in growth and hemoglobin concentration and impaired glucose metabolism have also been observed. The essentiality of nickel in humans has not been established, and nickel dietary recommendations have not been established for humans.

A 70-kg reference man contains 10 mg of nickel, giving an average body concentration of 0.1 ppm. Reference values for nickel in healthy adults is 0.2 μg/L in serum and 1–3 μg/L in urine. A National Health and Nutritional Examination Survey II of hair from a random sample of 271 adults found mean nickel levels of 0.39 ppm, with 10% having levels >1.50 ppm.

2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to nickel via inhalation, oral, and dermal routes of exposure. The targets of toxicity appear to be similar across exposure routes with the exception of portal of entry effects. The primary targets are the respiratory tract following inhalation exposure, the reproductive system and the developing organism following inhalation and oral exposure, and the immune system following inhalation, oral, or dermal exposure.

Information on the toxicity of nickel in humans comes from occupational studies, primarily nickel refinery workers, and studies and reports of allergic contact dermatitis in nickel-sensitized individuals. Neoplastic and nonneoplastic lung and nasal effects have been found in occupational exposure studies. Exposure to other metals confounds the interpretation of these data. Nickel sensitivity has been observed in workers and the general population. The contact dermatitis is the result of an allergic reaction to nickel and has been reported following dermal contact with airborne nickel, liquid solution, or metal items such as jewelry and prosthetic devices that contain nickel as well as oral exposure to nickel compounds.

The animal studies support the available human data that the respiratory tract and immune systems are sensitive targets of toxicity. Additionally, animal studies suggest that the reproductive system and the developing organism may also be sensitive to nickel. Inflammatory lung effects have been observed in a number of animal studies involving exposure to nickel sulfate, nickel subsulfide, or nickel oxide; damage to the nasal olfactory epithelium has also been observed in animals exposed to nickel sulfate or nickel

subsulfide. Long-term exposure to less-soluble nickel compounds (nickel subsulfide or nickel oxide) resulted in lung cancer. A number of animal studies have found impaired immune function following inhalation, oral, or dermal exposure to several nickel compounds. Male reproductive effects consisting of histological alterations, sperm parameter alterations, and impaired fertility have been observed in animals following oral exposure (not tested after dermal exposure). The primary developmental effect observed in animals orally exposed to nickel is increased fetal/pup mortality or decreased survival.

A greater detailed discussion of nickel-induced respiratory effects, cancer, immunological effects, reproductive effects, and developmental effects follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Respiratory Effects. Numerous human and animal studies have identified the respiratory tract as the most sensitive target of inhaled nickel toxicity. Chronic bronchitis, emphysema, and impaired lung function have been observed in nickel welders and foundry workers. Co-exposure to other toxic metals such as uranium, iron, lead, and chromium confounds the interpretation of these studies. The predominant respiratory effect in animals exposed to nickel sulfate, nickel subsulfide, or nickel oxide is lung inflammation. Other lung effects include increased lung weight, alveolar macrophage hyperplasia, interstitial infiltrates, proteinosis, fibrosis, and impaired lung function (as evidenced by labored breathing). In addition to the pulmonary effects, nickel sulfate and nickel subsulfide exposure resulted in atrophy of the nasal olfactory epithelium; the lowest-adverse-effect level (LOAEL) values for these lesions were similar to or higher than the LOAELs for lung inflammation. Damage to the olfactory epithelium was not observed following exposure to nickel oxide.

A series of studies conducted by NTP allow for the comparison of the toxicity of nickel sulfate, nickel subsulfide, and nickel oxide in rats and mice. Following acute- or intermediate-duration exposure, the toxicity of the different nickel compounds is related to its solubility, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The difference in the toxicity across compounds is probably due to the ability of water-soluble nickel compounds to cross the cell membrane and interact with cytoplasmic proteins. In contrast, the severity of inflammatory and proliferative lesions following chronic exposure was greater in rats exposed to nickel subsulfide or nickel oxide, as compared to nickel sulfate. Additionally, parenchymal damage secondary to inflammation was evident in the rats exposed to nickel subsulfide and nickel oxide, but not nickel sulfate. For all durations and nickel compounds tested, rats appear to be more sensitive to the lung effects than mice; significant increases in the incidence of lung inflammation were observed at lower concentrations in the rats than mice.

However, mice were more susceptible to the lethal effects (presumably from impaired lung function) than rats.

Cancer. The carcinogenic effect of nickel has been well documented in occupationally-exposed individuals. Several cohorts of workers, particularly nickel refinery workers, found significant increases in the risk and incidence of lung and nasal cancers. For most of the studies, the exact nickel compound is not known, although it is believed that nickel sulfate and the combination of nickel sulfides and oxides are the causative agents. A common limitation of the occupational studies involves co-exposure to other metals, particularly arsenic and chromium, which are also carcinogenic. Increases in the incidence of lung tumors have also been observed in animals exposed to nickel subsulfide or nickel oxide, but not after nickel sulfate exposure.

The Department of Health and Human Services has determined that metallic nickel may reasonably be anticipated to be a human carcinogen and nickel compounds are known to be human carcinogens. Similarly, IARC classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). EPA has classified nickel refinery dust and nickel subsulfide in Group A (human carcinogen). Other nickel compounds have not been classified by the EPA. Based on the occupational data, inhalation unit risk levels of 2.4×10^{-4} $(\mu g/m^3)^{-1}$ and 4.8×10^{-4} $(\mu g/m^3)^{-1}$ were derived by EPA for nickel refinery dust and nickel subsulfide, respectively.

Although the evidence is sufficient to consider less-soluble nickel compounds as carcinogens following inhalation exposure, how environmental exposure to nickel affects cancer risk is not clear. Nickel levels in the environment are much lower than those that were associated with cancer in workers. In the environment, nickel is also more likely to be in the form of a mineral lattice rather than the more active nickel refinery dust that contains nickel subsulfide, the form of nickel most consistently associated with cancer. Although soluble nickel compounds may not be directly carcinogenic, as indicated by the negative results in the nickel sulfate bioassay, inhalation of nickel sulfate did result in an inflammatory response in the lungs of animals. Because sustained tissue damage can serve to promote carcinogenesis, epidemiology studies of humans who are exposed to many substances may not be able to distinguish between the carcinogenic activity of less-soluble nickel compounds and the promoting activity of toxic concentrations of soluble nickel compounds.

Immunological Effects. The immunotoxicity of nickel has been established in human and animal studies following inhalation, oral, and dermal exposure. In humans, the immune response to nickel is

elicited as allergic contact dermatitis, a rash that develops shortly after exposure to metallic nickel or nickel compounds. Nickel sensitization typically involves initial exposure to a large nickel dose; thereafter, much lower doses or concentrations are needed to elicit a response. Nickel-induced dermatitis is not typically seen in nonsensitized humans. A number of studies have examined the prevalence of nickel sensitization in humans. In a survey of the general population, 11% of the subjects tested positive for nickel sensitization. Somewhat higher rates (approximately 15–20%) are found in subjects undergoing patch tests to identify the cause of contact dermatitis. These studies clearly demonstrated a higher prevalence in young women; this is probably due to a higher rate of ear piercing in this segment of the population rather than increased susceptibility to sensitization. Small oral doses of nickel (0.02 mg Ni/kg) can cause a flare-up in dermatitis among nickel-sensitized individuals. Animal studies demonstrate the potential of nickel to induce immune effects in nonsensitized individuals. Alterations in parameters of nonspecific immunity (e.g., natural killer cells, tumor necrosis factor, macrophage activity) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) have been observed in animals following inhalation or oral exposure.

Reproductive Effects. The available data suggest that the male reproductive system may be a sensitive target of ingested nickel toxicity; more minor reproductive effects have also been observed following inhalation exposure. Exposure of rats and mice to relatively low oral doses (1.9 mg/kg/day) of nickel chloride or nickel sulfate resulted in histological alterations in the epididymis and seminal vesicles; although other studies in rats and dogs have not found histological alterations following oral exposure to nickel for 90 days or 2 years. Decreases in sperm concentration, motility, and abnormalities have also been reported in mice orally exposed to nickel sulfate, nickel chloride, or nickel nitrate (Pandey et al. 2000; Pandy and Srivastava 2000; Sobti and Gill 1989). Significant alterations in fertility have been observed in some, but not all studies. Decreases in fertility were observed in male rats, but not in female rats orally exposed to nickel. However, a multigeneration study involving male and female exposure to nickel chloride did not find any significant alterations in fertility in rats.

Developmental Effects. Serious developmental effects have been reported in animals. Decreases in pup survival has been consistently observed in several studies that involved exposure prior to mating and during gestation and lactation. Decreased pup survival has also been observed in a study in which nickel-exposed males were mated with unexposed females. Decreases in pup body weights have also been reported. Differences in the study designs and the method of nickel chloride administration complicates identification of the threshold for developmental effects. The lowest LOAEL values range from 1.3 to 90 mg Ni/kg/day and the highest no-observed-adverse-effect level (NOAEL) values range from 4 to

45 mg Ni/kg/day. Interpretation of these data is also complicated by the maternal toxicity, particularly decreases in body weight gain, which frequently occurred at the same dose levels. Inhalation exposure resulted in relatively minor effects, including decreases in fetal body weight.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

The acute toxicity of nickel has been assessed in several animal studies involving exposure to nickel sulfate (Evans et al. 1995; NTP 1996c), nickel chloride (Adkins et al. 1979; Graham et al. 1978), nickel subsulfide (Benson et al. 1995b; NTP 1996b), and nickel oxide (NTP 1996a). The observed effects include inflammatory changes in the lungs (Benson et al. 1995a; NTP 1996a, 1996b, 1996c), atrophy of the nasal olfactory epithelium (Evans et al. 1995; NTP 1996b, 1996c), hyperplasia in the bronchial and mediastinal lymph nodes (NTP 1996b, 1996c), impaired immune function (Adkins et al. 1979; Graham et al. 1978), and decreases in body weight gain (NTP 1996b, 1996c), which are probably secondary to the lung damage. NOAEL values for respiratory tract effects were not established for nickel sulfate or nickel subsulfide. In studies by the National Toxicology Program (NTP 1996b, 1996c) (6 hours/day for 12 days in a 16-day period), chronic lung inflammation and atrophy of the nasal olfactory epithelium were observed at the lowest tested nickel sulfate (0.7 mg Ni/m^3) and nickel subsulfide (0.44 mg Ni/m^3) concentrations. At 0.7 and 3.65 mg Ni/m^3 as nickel sulfate and nickel subsulfide, respectively, the inflammation was accompanied by labored breathing, suggestive of impaired lung function. Alveolitis was also observed in rats exposed to 0.22 mg Ni/m^3 as nickel subsulfide 6 hours/day for 7 days (Benson et al. 1995b). In mice, the LOAELs for chronic lung inflammation were 0.7 and 1.83 mg Ni/m^3 for nickel sulfate and nickel subsulfide, respectively. Nickel oxide was less toxic than the other two nickel compounds. The NOAEL and LOAEL values for acute lung inflammation were 3.9 and 7.9 mg Ni/m^3 in rats, respectively; in mice, the highest concentration tested (23.6 mg Ni/m^3) was a NOAEL for respiratory effects. Based on these data and data from longer-term studies (NTP 1996a, 1996b, 1996c), nickel sulfate appears to be the most toxic to the respiratory tract of the three nickel compounds tested by NTP. The higher degree of toxicity is probably related to its solubility and increased ability to cross the cell membrane and interact with cytoplasmic proteins. Although the acute-duration nickel subsulfide study used lower concentrations than the nickel sulfate study, there is some evidence to suggest that the nickel sulfate effects were more severe. At 0.7 mg Ni/m^3 as nickel sulfate, the chronic lung inflammation was given a severity score of 1.2–1.8 (minimal to mild) and was accompanied by labored breathing and a 28% decrease in body weight. The lung inflammation in rats exposed to 0.44 or 0.88 mg Ni/m^3 as nickel

subsulfide was scored as minimal (1.0) and was not accompanied by altered respiration or body weight effects.

These acute-duration studies provide strong evidence that the respiratory tract is the most sensitive target of nickel toxicity. The three NTP (1996a, 1996b, 1996c) studies demonstrate that nickel sulfate is more toxic to the lungs than nickel subsulfide or nickel oxide. Because the lowest concentration tested in the nickel sulfate study (0.7 mg Ni/m^3) was a serious LOAEL for respiratory and body weight effects, this study cannot be used for MRL derivation. An immunotoxicity study by Graham et al. (1978) established a lower LOAEL (0.25 mg Ni/m^3) for a soluble nickel compound, nickel chloride; the NOAEL was 0.1 mg Ni/m^3. This study was not selected as the basis for MRL because the respiratory tract was not examined and it is not known if the NOAEL for immunotoxicity would also be a NOAEL for respiratory effects.

- An MRL of 0.0002 mg Ni/m^3 has been derived for intermediate-duration exposure to nickel.

The intermediate-duration toxicity of nickel has been assessed in several animal studies involving exposure to metallic nickel, nickel sulfate, nickel chloride, nickel subsulfide, and nickel oxide. The observed effects include inflammatory changes in the lungs (Benson et al. 1995b; Horie et al. 1985; NTP 1996a, 1996b, 1996c), alveolar macrophage hyperplasia (Benson et al. 1995b; Johansson and Camner 1986; NTP 1996a, 1996b, 1996c), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), hyperplasia in the bronchial and mediastinal lymph nodes (NTP 1996b, 1996c), impaired immune function (Adkins et al. 1979; Graham et al. 1978; Haley et al. 1990; Johansson et al. 1980, 1987, 1988a, 1989; Johansson and Camner 1986; Morimoto et al. 1995; Spiegelberg et al. 1984), decreases in body weight gain (NTP 1996b, 1996c; Weischer et al. 1980), which are probably secondary to the lung damage, decreased sperm concentration (NTP 1996a), and developmental toxicity (Weischer et al. 1980).

As with the acute-duration studies, the most sensitive target of nickel toxicity is the lungs. Chronic lung inflammation was observed at the lowest-adverse-effect levels following 13-week (6 hours/day, 5 days/week) exposures to nickel sulfate, nickel subsulfide, or nickel oxide (NTP 1996a, 1996b, 1996c). Intermediate-duration studies clearly demonstrate that nickel sulfate is more toxic than nickel subsulfide and nickel oxide. In rats, the respective NOAEL and LOAEL values for chronic lung inflammation were 0.06 and 0.11 mg Ni/m^3 for nickel sulfate (NTP 1996c), 0.11 and 0.22 mg Ni/m^3 for nickel subsulfide (NTP 1996b), and 2.0 and 3.9 mg Ni/m^3 for nickel oxide (NTP 1996a). Atrophy of the nasal olfactory epithelium was observed at 0.22 and 0.44 mg Ni/m^3 as nickel sulfate (NTP 1996c) and nickel subsulfide (NTP 1996b), respectively. Similar effects were observed in mice. For nickel sulfate and nickel subsulfide, the LOAEL values for mice were higher than the LOAELs identified in rats; the LOAEL for

chronic inflammation following exposure to nickel oxide was the same in rats and mice. The LOAEL values for immunotoxicity, reproductive toxicity, and developmental toxicity were higher than the LOAEL values for respiratory effects in rats exposed to nickel sulfate.

Derivation of an intermediate-duration MRL based on the NTP study of nickel sulfate (NTP 1996c) would be protective against the toxicity of other nickel compounds. In the nickel sulfate study, alveolar macrophage hyperplasia was observed in rats exposed at the two lowest concentrations (0.03 and 0.06 mg Ni/m^3). NTP noted that when lung effects only consisted of alveolar macrophage hyperplasia, there was only a slight increase in the number of alveolar macrophages and the differences between controls and nickel-exposed animals were subtle; the severity score for the alveolar macrophage hyperplasia was 1.0 (minimal). The minimal alveolar macrophage hyperplasia was not considered adverse because it is considered to be part of the normal physiologic response to inhaled particles and it is not believed to compromise the lung's ability to clear foreign matter. This is supported by the Benson et al. (1995a) study, which found no effect on the clearance of a nickel sulfate tracer in animals exposed to 0.03 or 0.11 mg Ni/m^3 as nickel sulfate for 6 months. Thus, the 0.06 mg Ni/m^3 concentration was identified as a NOAEL and adjusted for intermittent exposure ($NOAEL_{ADJ}$).

The intermediate-duration inhalation MRL of 0.0002 mg Ni/m^3 was derived by dividing the $NOAEL_{HEC}$ of 0.0052 mg Ni/m^3 by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability). The $NOAEL_{HEC}$ was calculated using the following equations:

$$NOAEL_{ADJ} = 0.06 \text{ mg Ni/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.011 \text{mg Ni/m}^3$$
$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.011 \text{ mg Ni/m}^3 \times 0.474 = 0.0052 \text{ mg Ni/m}^3$$

The regional deposited dose ratio (RDDR) for the pulmonary region was used to extrapolate deposited doses in rats to deposited doses in humans. The RDDR was calculated using EPA software and the following parameters: particle size (MMAD) of 2.11 μm with a geometric standard deviation (sigma g) of 2.7 (as reported in Table K1 of NTP 1996c); default human body weight (70 kg), minute volume (13 L), and pulmonary surface area (54 m^2); and default female F344 rat body weight (0.124 kg), minute volume (101.3 mL), and pulmonary surface area (0.34 m^2).

- An MRL of 9×10^{-5} mg Ni/m^3 has been derived for chronic-duration exposure to nickel.

One human study (Vyskocil et al. 1994a) and several animal studies (NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974; Takenaka et al. 1985; Tananka et al. 1988) assessed the noncarcinogenic toxicity

of nickel sulfate, nickel chloride, nickel subsulfide, and nickel oxide. These studies found inflammatory changes in the lungs (NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974; Tanaka et al. 1988), atrophy of the nasal olfactory epithelium (NTP 1996b, 1996c), evidence of renal damage (Vyskocil et al. 1994a), adverse adrenal effects (NTP 1996a), decreased body weight gain, which was probably associated with impaired lung function (NTP 1996b, 1996c; Takenaka et al. 1985), and damage to the bronchial lymph nodes (NTP 1996a, 1996b, 1996c).

As with the acute- and intermediate-duration exposures, chronic exposure to nickel sulfate, nickel subsulfide, or nickel oxide resulted in chronic active lung inflammation. A 2-year exposure (6 hours/day, 5 days/week) to nickel sulfate (NTP 1996c) resulted in chronic lung inflammation and bronchialization at 0.06 mg Ni/m^3 and atrophy of the olfactory epithelium at 0.11 mg Ni/m^3; no adverse respiratory effects were observed at 0.03 mg Ni/m^3. A similar exposure to nickel subsulfide (NTP 1996b) resulted in chronic inflammation, alveolar epithelium hyperplasia, fibrosis, and rapid and shallow breathing at 0.11 mg Ni/m^3, and atrophy of the nasal olfactory epithelium at 0.73 mg Ni/m^3. Chronic lung inflammation and alveolar epithelial hyperplasia were observed at the lowest nickel oxide concentration tested (0.5 mg Ni/m^3) (NTP 1996a). Similar effects were observed in mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 2 years; however, the LOAEL values were higher than for rats. The NTP (1996c) study of nickel sulfate identified the lowest LOAEL for respiratory effects (0.06 mg Ni/m^3); the NOAEL of 0.03 mg Ni/m^3 associated with this LOAEL was used to derive a chronic-duration inhalation MRL for nickel.

The chronic-duration inhalation MRL of 9×10^{-5} mg Ni/m^3 was derived by dividing the $NOAEL_{HEC}$ of 0.0027 mg Ni/m^3 by an uncertainty factor of 30 (3 for species to species extrapolation with dosimetric adjustments and 10 for human variability). The $NOAEL_{HEC}$ was calculated using the following equations:

$$NOAEL_{ADJ} = 0.03 \text{ mg Ni/m}^3 \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.0054 \text{ mg Ni/m}^3$$
$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.0054 \text{ mg Ni/m}^3 \times 0.506 = 0.0027 \text{ mg Ni/m}^3$$

The RDDR for the pulmonary region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculated the RDDR: mean particle size (MMAD) of 2.5 μm with a geometric standard deviation (sigma g) of 2.38 (as reported in Table K1 of NTP 1996c); default human body weight (70 kg), minute volume (13 L), and pulmonary surface area (54 m^2); and default female F344 rat body weight (0.229 kg), minute volume (167.3 mL), and pulmonary surface area (0.34 m^2).

Oral MRLs

Information on the acute oral toxicity of nickel in humans comes from reports of accidental exposures and studies of nickel-sensitized individuals. Gastrointestinal upset (vomiting, cramps, diarrhea) and neurological symptoms (giddiness, headache, weariness) were observed in workers accidentally ingesting water containing approximately 7.1–35.7 mg Ni/kg as nickel sulfate and nickel chloride; boric acid was also present in the water (Sunderman et al. 1988). Allergic dermatitis was observed in previously nickel-sensitized individuals ingesting 0.01–0.97 mg Ni/kg as nickel sulfate (Burrows et al. 1981; Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Kaaber et al. 1978). Reliable data on the acute oral toxicity of nickel in animals is limited to two studies that examined a limited number of end points. A reproductive toxicity study in mice found significant increases in sperm head abnormalities in mice exposed to a single gavage dose of 23 mg Ni/kg as nickel nitrate (Sobti and Gill 1989). No developmental effects were observed in the offspring of mice exposed via gavage to 90.6 mg Ni/kg/day as nickel chloride on gestational days 8–12 (Seidenberg et al. 1986). Intermediate-duration studies suggest that the developing organism may be a sensitive target of nickel toxicity; however, this end point has not been adequately examined following acute-duration exposure; thus, an acute-duration oral MRL for nickel has not been derived.

A number of animal studies have assessed the toxicity of nickel following intermediate-duration oral exposure. Significant decreases in body weight and organ weight (liver, kidney, pituitary) were consistently observed in rats exposed to 8.6 mg Ni/kg/day and higher as nickel chloride (American Biogenics Corporation 1988; RTI 1988a, 1988b; Weischer et al. 1980), nickel acetate (Whanger 1973), or nickel sulfate (Dieter et al. 1988). Other systemic effects included changes in blood glucose levels at 8.6 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988) and 0.38 mg Ni/kg/day as nickel chloride (Weischer et al. 1980), kidney damage (minimal convoluted tubular damage) at 108 mg Ni/kg/day as nickel sulfate (Dieter et al. 1988), and adverse lung effects at 8.6 and 20 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988; RTI 1988b). A number of reproductive and developmental toxicity studies provide suggestive evidence that the reproductive system and the developing organism are sensitive targets of nickel toxicity in animals. Inconsistent results have been reported for the reproductive toxicity of nickel. Decreased sperm motility and count and sperm abnormalities were observed at 1.9 mg Ni/kg/day and higher as nickel sulfate (Pandey and Srivastava 2000; Pandey et al. 1999) and decreased fertility was observed in studies in which males and females were exposed to 3.6 mg Ni/kg/day as nickel chloride (Käkelä et al. 1999). However, impaired reproduction has not been observed in a multigeneration study of rats exposed to nickel chloride in

drinking water (RTI 1988a, 1988b). There is stronger evidence that perinatal exposure to nickel results in decreased survival, as measured by live litter size and neonatal mortality, in pups of rat dams exposed to nickel chloride in drinking water prior to mating and during gestation and lactation (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). Interpretation and comparison of the studies is complicated by differences in study design and maternal toxicity, which often occurs at the same dose levels as the developmental effects. The available data are not sufficient to establish a threshold for developmental effects to nickel chloride; the lowest LOAEL values identified in the studies range from 1.3 to 90 mg Ni/kg/day and the highest NOAEL values range from 4 to 45 mg Ni/kg/day. Because decreased pup survival is considered a serious LOAEL and a NOAEL for developmental effects has not been clearly identified, an intermediate-duration oral MRL was not derived for nickel.

The essentiality of nickel in humans has not been established (IOM 2002). In the U.S., dietary intake of nickel ranges from 69 to 162 μg/day (Pennington and Jones 1987) and average drinking water intakes range from 2 to 4 μg/L (4–8 μ/day, estimated using a reference water intake of 2 L/day). Based on these water and food nickel levels, a daily dose of 0.001–0.016 mg/kg/day can be estimated using a reference water intake of 2 L/day and body weight of 70 kg.

Data on the chronic toxicity of ingested nickel are limited to one animal study that found significant decreases in body weight and liver weights in rats exposed to 75 mg Ni/kg/day as nickel sulfate in the diet and decreases in body weight, increases in liver weight, and adverse renal and lung effects in dogs 62.5 mg Ni/kg/day (Ambrose et al. 1976). The available chronic-duration database was considered inadequate for MRL derivation because intermediate-duration studies found significant decreases in survival of the offspring of rats exposed to ≥1.3 mg Ni/kg/day (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993).

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of nickel. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

Several different nickel compounds will be discussed in this profile. These compounds can be grouped according to their solubility in water: soluble compounds include nickel chloride, nickel sulfate, and nickel nitrate, and less-soluble compounds include nickel oxide and nickel subsulfide. Both the soluble and less-soluble nickel compounds are important with regard to all relevant routes of exposure. Generally, the soluble compounds are considered more toxic than the less-soluble compounds, although the less-soluble compounds are more likely to be carcinogenic at the site of deposition. Metallic nickel is also considered in this profile. All doses are presented as the amount or concentration of nickel to which subjects were exposed. Nickel carbonyl, a highly toxic nickel compound, is not considered in this profile. The data regarding the toxicity of nickel carbonyl are substantial; however, the likelihood of exposure at hazardous waste sites is very low. In ambient air, nickel carbonyl is relatively unstable with a half-life of ≈100 seconds (Stedman and Hikade 1980). Because nickel carbonyl is highly reactive, it is not likely to be found at hazardous waste sites. Also, nickel carbonyl is not very soluble in water; therefore, it will not be found in drinking water.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of nickel are indicated in Table 3-1 and Figure 3-1. Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for nickel. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of

effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Death from adult respiratory distress syndrome was reported in one person who sprayed nickel with a metal arc process without wearing personal protective equipment (Rendall et al. 1994). Several days after the exposure, urinary concentrations of nickel were 700 μg/L, in comparison to levels of <0.1–13.3 μg/L in persons not occupationally exposed to nickel (Sunderman 1993). The death occurred 13 days after the 90-minute exposure to an estimated concentration of 382 mg Ni/m^3 of principally metallic nickel with the majority of particle sizes of <1.4 μm. Histological examination of the lungs revealed alveolar wall damage and edema in alveolar spaces, and marked tubular necrosis was noted in the kidneys.

Human data regarding chronic inhalation exposure to nickel are limited to occupational exposure studies. The majority of these studies analyzed the toxicity of nickel, usually in the form of nickel oxide, metallic nickel, or nickel refinery dust, by calculating Standard Mortality Ratios (SMR) for all causes of death. Generally, the studies report a higher incidence of cancer deaths from lung and nasal cancers in the exposed workers (see Section 3.2.1.8). Two studies have also reported a higher incidence of deaths resulting from nonmalignant respiratory disease (Cornell and Landis 1984; Polednak 1981). However, all

of the workers were exposed to other metals (arsenic, uranium, iron, lead, chromium), so it cannot be concluded that nickel was the sole causative agent. Other studies of humans occupationally exposed to nickel compounds have not reported increased mortality resulting from respiratory diseases (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh 1982; Redmond 1984; Shannon et al. 1984b, 1991).

During the first 2 days after a single 2-hour exposure, 4 of 28 rats died after exposure to nickel sulfate at 36.5 mg Ni/m^3 (Hirano et al. 1994b). Severe hemorrhage of the lungs was observed in the lungs of the rats that died. During inhalation exposure of 6 hours/day, 5 days/week, for up to 12 exposures, rats and mice exposed to 12.2 or 1.4 mg Ni/m^3, respectively, as nickel sulfate and mice exposed to 7.33 mg Ni/m^3 as nickel subsulfide died, but those exposed to nickel oxide did not (NTP 1996a, 1996b, 1996c). Mice were more sensitive to lethality than rats; at 1.4 mg Ni/m^3 as nickel sulfate, all mice and no rats died, and at 7.33 mg Ni/m^3 as nickel subsulfide, all mice and 2 of 10 rats died. No rats or mice died following exposure to 23.6 mg Ni/m^3 as nickel oxide. No deaths were reported in rats or mice following 13 weeks of exposure (6 hours/day, 5 days/week) to nickel at 7.9, 1.83, or 0.44 mg Ni/m^3 as nickel oxide, nickel subsulfide, or nickel sulfate, respectively (NTP 1996a, 1996b, 1996c). Hamsters survived exposure to ≤48.4 mg Ni/m^3 as nickel oxide for 15 or 61 days (Wehner and Craig 1972).

Significant mortality was observed during the last 26 weeks of a 78-week inhalation study of rats exposed to 0.7 mg Ni/m^3 as nickel subsulfide (Ottolenghi et al. 1974). Less than 5% of the treated rats survived the study (78 weeks of exposure plus 30 weeks of observation) compared to 31% of the controls (Ottolenghi et al. 1974). All rats, guinea pigs, and mice exposed to 15 mg Ni/m^3 as metallic nickel for ≤21 months died before the end of the study, with most of the guinea pigs and mice dying by 15 months (Hueper 1958). Lung lesions including edema, hyperemia, and hemorrhage were the principal effects noted. However, no controls were used in this study. A significant decrease in mean survival time was observed in rats exposed 23 hours/day for life to 0.06 mg Ni/m^3 as nickel oxide (Takenaka et al. 1985). The average survival times for rats exposed to 0 or 0.06 mg Ni/m^3 were 125.2 and 87.7 weeks, respectively. Survival was not affected in rats exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c). Survival of mice was also not affected by exposure to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, for 104 weeks (NTP 1996a, 1996b, 1996c).

LOAEL values from each reliable study for death in each species, duration category, and nickel compound are recorded in Table 3-1 and plotted in Figure 3-1.

Table 3-1 Levels of Significant Exposure to Nickel - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Human	90 min				382 M (death of one man)	Rendall et al. 1994 metal
2	Rat (Wistar)	2 hr				36.5 M (4/28 died)	Hirano et al. 1994b sulfate
3	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day				12.2 F (5/5 died)	NTP 1996c sulfate
4	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day				7.33 (10/10 died)	NTP 1996b subsulfide
5	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day				1.4 (10/10 died)	NTP 1996c sulfate
Systemic							
6	Rat (Fischer- 344)	1, 2, 4, 7, 12 d 6hr/d	Resp		0.22 (alveolitis)		Benson et al. 1995b subsulfide
7	Rat (Long- Evans)	4, 8, 12 or 16 d 6 hr/d	Resp		0.635 M (atrophy of olfactory epithelium)		Evans et al. 1995 sulfate

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
8	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day	Resp	3.9 F	7.9 F (acute lung inflammation)		NTP 1996a oxide
			Cardio	23.6			
			Gastro	23.6			
			Musc/skel	23.6			
			Hepatic	23.6			
			Renal	23.6			
			Endocr	23.6			
			Dermal	23.6			
			Bd Wt	23.6			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)		LOAEL Serious (mg/m³)		Reference Chemical Form
9	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day	Resp		0.44	(chronic lung inflammation, atrophy of olfactory epithelium)	3.65 F	(chronic lung inflammation with necrosis and labored breathing)	NTP 1996b subsulfide
			Cardio	7.33					
			Gastro	7.33					
			Hepatic	7.33					
			Renal	7.33					
			Endocr	7.33					
			Dermal	7.33					
			Bd Wt	1.83			3.65	(22-28% decrease in body weight gain)	

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
10	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day	Resp			0.7 (chronic lung inflammation; degeneration of bronchiolar epithelium; labored breathing; atrophy of olfactory epithelium)	NTP 1996c sulfate
			Cardio	12.2			
			Gastro	12.2			
			Musc/skel	12.2			
			Hepatic	12.2			
			Renal	12.2			
			Endocr	12.2			
			Dermal	12.2			
			Bd Wt			0.7 M (final body weights 28% lower than controls)	

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
11	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day	Resp	23.6			NTP 1996a oxide
			Cardio	23.6			
			Gastro	23.6			
			Hepatic	23.6			
			Renal	23.6			
			Endocr	23.6			
			Dermal	23.6			
			Bd Wt	23.6			
12	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day	Resp	0.44	1.83 (chronic lung inflammation) 0.88 (atrophy of olfactory epithelium)		NTP 1996b subsulfide
			Gastro	7.33			
			Hemato	7.33			
			Musc/skel	7.33			
			Hepatic	7.33			
			Renal	7.33			
			Endocr	7.33			
			Dermal	7.33			
			Bd Wt	1.83 M		3.65 M (emaciation)	

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
13	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day	Resp		0.7 (chronic lung inflammation)	1.4 (necrotizing lung inflammation)	NTP 1996c sulfate
			Cardio	1.4			
			Gastro	1.4			
			Musc/skel	1.4			
			Hepatic	1.4			
			Renal	1.4			
			Endocr	1.4			
			Dermal	1.4			
			Bd Wt	0.7		1.4 (animals appeared emaciated)	
	Immuno/ Lymphoret						
14	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
15	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		7.33			NTP 1996b subsulfide
16	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day		0.7 F	1.4 F (hyperplasia in bronchial and mediastinal lymph nodes)		NTP 1996c sulfate
17	Mouse (CD-1)	2 hr		0.369 F			Adkins et al. 1979 chloride
					0.499 F (increased susceptibility to Streptococcal infection)		

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
18	Mouse (CD-1)	2 hr			0.657 F (decreased ability to clear bacteria from lungs)		Adkins et al. 1979 chloride
19	Mouse (CD-1)	2 hr			0.455 F (increased susceptibility to Streptococcal infection)		Adkins et al. 1979 sulfate
20	Mouse (Swiss)	2 hr		0.1 F	0.25 F (impaired humoral immunity)		Graham et al. 1978 chloride
21	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
22	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		0.44	0.88 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide
23	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day		3.1			NTP 1996c sulfate
	Neurological						
24	Rat (Long- Evans)	4, 8, 12, 16 d 6 hr/d			0.635 M (decrease in number of bipolar receptor cells in nasal olfactory epithelium)		Evans et al. 1995 sulfate
	Reproductive						
25	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
26	Rat (Fischer- 344)	12 days in 16 day period 6 hours/day		7.33			NTP 1996b subsulfide

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
27	Rat (Fischer- 344)	12 days in 16 day period 6 hr/day		12.2			NTP 1996c sulfate
28	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		23.6			NTP 1996a oxide
29	Mouse (B6C3F1)	12 days in 16 day period 6 hours/day		3.65			NTP 1996b subsulfide
30	Mouse (B6C3F1)	12 days in 16 day period 6 hr/day		1.4			NTP 1996c sulfate
INTERMEDIATE EXPOSURE							
Systemic							
31	Rat (Fischer- 344)	up to 6 mo 5d/wk 6hr/d	Resp	0.49 M	1.96 M (moderate alveolitis that persisted at least 4 months after the exposure)		Benson et al. 1995a oxide
			Bd Wt	1.96 M			
32	Rat (Fischer- 344)	up to 6 mo 5d/wk 6hr/d	Resp		0.11 M (alveolitis that persisted for 4 months after exposure)		Benson et al. 1995a sulfate
33	Rat (Wistar)	> 2 wk 6 d/wk 12 hr/d	Resp		0.12 M (alveolar wall thickening)		Bingham et al. 1972 oxide
34	Rat (Wistar)	>2 wk 6 d/wk 12 hr/d	Resp		0.109 M (hyperplasia of the bronchial epithelium and peribronchial lymphocytic infiltration)		Bingham et al. 1972 chloride

Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
35	Rat (Wistar)	1 mo 5d/wk 6hr/d	Resp		0.5 M (interstitial pneumonia)		Horie et al. 1985 oxide
36	Rat (Fischer- 344)	13 weeks 5d/wk 6hr/d	Resp	2	3.9 (chronic active lung inflammation and granulmatous inflammation)		NTP 1996a oxide
			Cardio	7.9			
			Gastro	7.9			
			Musc/skel	7.9			
			Hepatic	7.9			
			Renal	7.9			
			Endocr	7.9			
			Dermal	7.9			
			Bd Wt	7.9			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
37	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day	Resp	0.11	0.44 (atrophy of olfactory epithelium) 0.22 (chronic inflammation and interstitial infiltrates)	1.83 (labored breathing during weeks 2-7)	NTP 1996b subsulfide
			Cardio	1.83			
			Gastro	1.83			
			Musc/skel	1.83			
			Hepatic	1.83			
			Renal	1.83			
			Endocr	1.83			
			Dermal	1.83			
			Bd Wt	1.83			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
38	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day	Resp	0.06 F[b]	0.11 F (chronic lung inflammation, interstitial infiltrates)		NTP 1996c sulfate
					0.22 (atrophy of olfactory epithelium)		
			Cardio	0.44			
			Gastro	0.44			
			Musc/skel	0.44			
			Hepatic	0.44			
			Renal	0.44			
			Endocr	0.44			
			Dermal	0.44			
			Bd Wt	0.44			
39	Rat (Wistar)	28 d 23.6 hr/d	Hepatic	0.784 M			Weischer et al. 1980 oxide
			Renal	0.784 M			
			Bd Wt	0.178 M		0.385 M (30% decrease in body weight gain)	
			Metab	0.178 M	0.385 M (increased serum glucose)		
40	Rat (Wistar)	21 d 23.6 hr/d	Bd Wt			0.8 F (36% decrease in body weight gain)	Weischer et al. 1980 oxide
			Metab		0.8 F (decreased serum glucose level)		

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
41	Mouse (B6C3F1)	up to 6mo 5d/wk 6hr/d	Resp		0.98 M (interstitial pneumonia)		Benson et al. 1995a oxide
			Bd Wt	3.93 M			
42	Mouse (B6C3F1)	up to 6mo 5d/wk 6hr/d	Resp	0.06 M	0.22 M (interstitial pneumonia)		Benson et al. 1995a sulfate
43	Mouse (B6C3F1)	13 weeks 5d/wk 6hr/d	Resp	2 F	3.9 F (perivascular lymphocytic infiltrates)		NTP 1996a oxide
			Cardio	7.9			
			Gastro	7.9			
			Musc/skel	7.9			
			Hepatic	7.9			
			Renal	7.9			
			Endocr	7.9			
			Dermal	7.9			
			Bd Wt	7.9			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
44	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day	Resp	0.22 M	0.88 M (chronic lung inflammation and fibrosis)		NTP 1996b subsulfide
					0.44 M (atrophy of olfactory epithelium)		
			Cardio	1.83			
			Gastro	1.83			
			Hemato	1.83			
			Musc/skel	1.83			
			Renal	1.83			
			Endocr	1.83			
			Dermal	1.83			
			Bd Wt	1.83			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
45	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day	Resp	0.22 F	0.44 F (chronic lung inflammation and fibrosis)		NTP 1996c sulfate
			Cardio	0.44			
			Gastro	0.44			
			Musc/skel	0.44			
			Hepatic	0.44			
			Renal	0.44			
			Endocr	0.44			
			Dermal	0.44			
			Bd Wt	0.44			
46	Rabbit (NS)	1-8 mo 5d/wk 6hr/d	Resp		0.2 M (increased volume density of alveolar type II cells)		Johansson and Camner 1986 chloride or metallic
	Immuno/ Lymphoret						
47	Rat (Wistar)	4wk 5d/wk 8hr/d			9.2 M (increased production of tumor necrosis factor by alveolar macrophages)		Morimoto et al. 1995 oxide
48	Rat (Fischer- 344)	13 weeks 5d/wk 6hr/d		0.9	2 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996a oxide

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
49	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		0.11	0.22 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide
50	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		0.11	0.22 (lymphoid hyperplasia in bronchial and mediastinal lymph nodes)		NTP 1996c sulfate
51	Rat (Wistar)	4 wk continuous		0.1	0.2 (impaired humoral immunity)		Spiegelberg et al. 1984 oxide
52	Rat (Wistar)	4 mo continuous		0.025	0.15 (impaired humoral immunity)		Spiegelberg et al. 1984 oxide
53	Mouse (B6C3F1)	65 d 5d/wk 6hr/d			0.47 F (decreased alveolar macrophage activity)		Haley et al. 1990 oxide
54	Mouse (B6C3F1)	65 d 5d/wk 6hr/d		0.11 F	0.45 F (decreased resistance to tumor challenge)		Haley et al. 1990 sulfate
55	Mouse (B6C3F1)	65 d 5d/wk 6hr/d		0.11 F	0.45 F (decreased alveolar macrophage phagocytic activity)		Haley et al. 1990 subsulfide
56	Mouse (B6C3F1)	13 weeks 5d/wk 6hr/d		0.9	2 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996a oxide

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
57	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		0.44 F	0.88 F (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide
58	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		0.22 F	0.44 F (hyperplasia of bronchial lymph nodes)		NTP 1996c sulfate
59	Rabbit (NS)	3 or 6 mo 5d/wk 6hr/d			1 M (inactive macrophage surfaces)		Johansson et al. 1980 metallic
60	Rabbit (NS)	4-6 wk 5d/wk 6hr/d			0.6 M (decrease lysozyme activity in alveolar macrophages)		Johansson et al. 1987 chloride
61	Rabbit (NS)	4 mo 5d/wk 6hr/d			0.6 M (decreased macrophage lysosomal activity)		Johansson et al. 1988a, 1989 chloride
	Reproductive						
62	Rat (Fischer- 344)	13 weeks 5d/wk 6hr/d		3.9 M	7.9 M (decreased sperm concentration)		NTP 1996a oxide
63	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		1.83			NTP 1996b subsulfide
64	Rat (Fischer- 344)	13 weeks 5 days/week 6 hours/day		0.44			NTP 1996c sulfate

Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
65	Mouse (B6C3F1)	13 weeks 5d/wk 6hr/d		7.9			NTP 1996a oxide
66	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		1.83			NTP 1996b subsulfide
67	Mouse (B6C3F1)	13 weeks 5 days/week 6 hours/day		0.44			NTP 1996c sulfate
	Developmental						
68	Rat (Wistar)	Gd 1-21 23.6 hr/day		0.8	1.6 (decreased fetal body weights)		Weischer et al. 1980 oxide
	CHRONIC EXPOSURE						
	Death						
69	Rat (Wistar)	21 mo 4-5d/wk 6hr/d				15 (100/100 deaths)	Hueper 1958 metallic
70	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d				0.7 (<11/226 survived)	Ottolenghi et al. 1974 subsulfide
71	Rat (Wistar)	31 mo 7d/wk 23hr/d				0.06 M (decreased survival time)	Takenaka et al. 1985 oxide
72	Mouse (C57)	21 mo 4-5d/wk 6hr/d				15 F (20/20 died)	Hueper 1958 metallic

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
73	Gn Pig (strain 13)	21 mo 4-5d/wk 6hr/d				15 (42/42 died)	Hueper 1958 metallic
	Systemic						
74	Human	occupa-tional	Renal		0.75 F (increased urinary excretion of N-acetyl-b-D- glucosamidase, total proteins, b2 -microglobulin, and retinol binding protein)		Vyskocil et al. 1994a sulfate, chloride
75	Rat (Fischer- 344)	2 yr 5d/wk 6hrs/d	Resp		0.5 (chronic lung inflammation)		NTP 1996a oxide
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Musc/skel	2			
			Hepatic	2			
			Renal	2			
			Endocr	1 F	2 F (benign pheochromocytoma and adrenal medulla hyperplasia)		
			Dermal	2			
			Bd Wt	2			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
76	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week	Resp		0.73 (atrophy of nasal olfactory epithelium)	0.11 (chronic inflammation, alveolar epithelium hyperplasia, fibrosis, rapid and shallow breathing)	NTP 1996b subsulfide
			Cardio	0.73			
			Gastro	0.73			
			Musc/skel	0.73			
			Renal	0.73			
			Endocr		0.11 M (pheochromocytoma)		
			Bd Wt	0.11	0.73 (11-12% decrease in body weight gain)		
77	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d	Resp	0.03[c]	0.11 (atrophy of olfactory epithelium) 0.06 (chronic inflammation, bronchialization)		NTP 1996c sulfate
			Cardio	0.11			
			Gastro	0.11			
			Hemato	0.11			
			Hepatic	0.11			
			Renal	0.11			
			Endocr	0.11			
			Dermal	0.11			
			Bd Wt	0.11			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
78	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d	Resp			0.7 (pneumonitis; bronchitis; emphysema)	Ottolenghi et al. 1974 subsulfide
			Cardio	0.7			
			Gastro	0.7			
			Hepatic	0.7			
			Renal	0.7			
			Endocr	0.7			
			Bd Wt			0.7 (body weight 20-30% less than controls)	
79	Rat (Wistar)	31 mo 7d/wk 23hr/d	Resp		0.06 M (increased lung weight; congestion; alveolar proteinosis)		Takenaka et al. 1985 oxide
			Bd Wt			0.06 M (weight loss amount not stated)	
80	Rat (Wistar)	12 mo 5d/wk 7hr/d	Resp			0.2 (pneumonia)	Tanaka et al. 1988 oxide
			Hepatic	0.9			
			Renal	0.9			
			Bd Wt	0.9			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
81	Mouse (B6C3F1)	2 yr 5d/wk 6hrs/d	Resp		1 (chronic lung inflammation, bronchialization, alveolar proteinosis)		NTP 1996a oxide
			Cardio	3.9			
			Gastro	3.9			
			Hemato	3.9			
			Musc/skel	3.9			
			Hepatic	3.9			
			Renal	3.9			
			Endocr	3.9			
			Dermal	3.9			
			Bd Wt	3.9			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
82	Mouse (B6C3F1)	2 years 6 hours/day 5 days/week	Resp		0.44 (chronic active lung inflammation, bronchialization, alveolar proteinosis, fibrosis)		NTP 1996b subsulfide
			Cardio	0.88			
			Gastro	0.88			
			Hepatic	0.88			
			Renal	0.88			
			Endocr	0.88			
			Dermal	0.88			
			Bd Wt	0.88			

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
83	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d	Resp		0.11 M (atrophy of olfactory epithelium) 0.06 F (chronic active lung inflammation, alveolar proteinosis)		NTP 1996c sulfate
			Cardio	0.22			
			Gastro	0.22			
			Hemato	0.22			
			Hepatic	0.22			
			Renal	0.22			
			Endocr	0.22			
			Dermal	0.22			
			Bd Wt	0.22			
	Immuno/ Lymphoret						
84	Rat (Fischer- 344)	2 yr 5d/wk 6hrs/d			0.5 M (lymphoid hyperplasia in bronchial lymph node)		NTP 1996a oxide
85	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week			0.11 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide
86	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		0.06	0.11 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996c sulfate

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
87	Mouse (B6C3F1)	2 yr 5d/wk 6hrs/d			1 (bronchial lymph node hyperplasia)		NTP 1996a oxide
88	Mouse (B6C3F1)	2 years 6 hours/day 5 days/week			0.44 (lymphoid hyperplasia in bronchial lymph nodes)		NTP 1996b subsulfide
89	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		0.11	0.22 (bronchial lymph node hyperplasia)		NTP 1996c sulfate
	Reproductive						
90	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		2			NTP 1996a oxide
91	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week		0.73			NTP 1996b subsulfide
92	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		0.11			NTP 1996c sulfate
93	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		3.9			NTP 1996a oxide
94	Mouse (B6C3F1)	2 years 6 hours/day 5 days/week		0.88			NTP 1996b subsulfide

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
95	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		0.22			NTP 1996c sulfate
	Cancer						
96	Human	occupa-tional				10 M (CEL: lung and nasal cancers)	Int Committee on Ni Carcinogenesis in Man 1990 less soluble
97	Human	occupa-tional				1 (CEL: lung and nasal cancers)	Int Committee on Ni Carcinogenesis in Man 1990 soluble
98	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d				1 M (CEL: alveolar/bronchiolar adenoma or carcinoma)	NTP 1996a oxide
99	Rat (Fischer- 344)	2 years 6 hours/day 5 days/week				0.73 (CEL:alveolar/bronchiolar adenoma or carcinoma)	NTP 1996b subsulfide

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Table 3-1 Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form
100	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d				0.7 (CEL: lung adenomas, adenocarcinomas, squamous cell carcinoma, 14% treated, 1% controls)	Ottolenghi et al. 1974 subsulfide

a The number corresponds to entries in Figure 3-1.

b Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.0002 mg Ni/m3 ; concentration adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the Regional Deposited Dose Ratio (RDDR) of 0.474 for the pulmonary region, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to human with dosimetric adjustment, and 10 for human variability).

c Used to derive a chronic-duration inhalation minimal risk level (MRL) of 0.00009 mg Ni/m3 ; concentration adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the Regional Deposited Dose Ratio (RDDR) of 0.506 for the pulmonary region, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to human with dosimetric adjustment, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; hemato = hematological; hr = hour(s); Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; Ni = nickel; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

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Figure 3-1. Levels of Significant Exposure to Nickel - Inhalation

Acute (≤14 days)

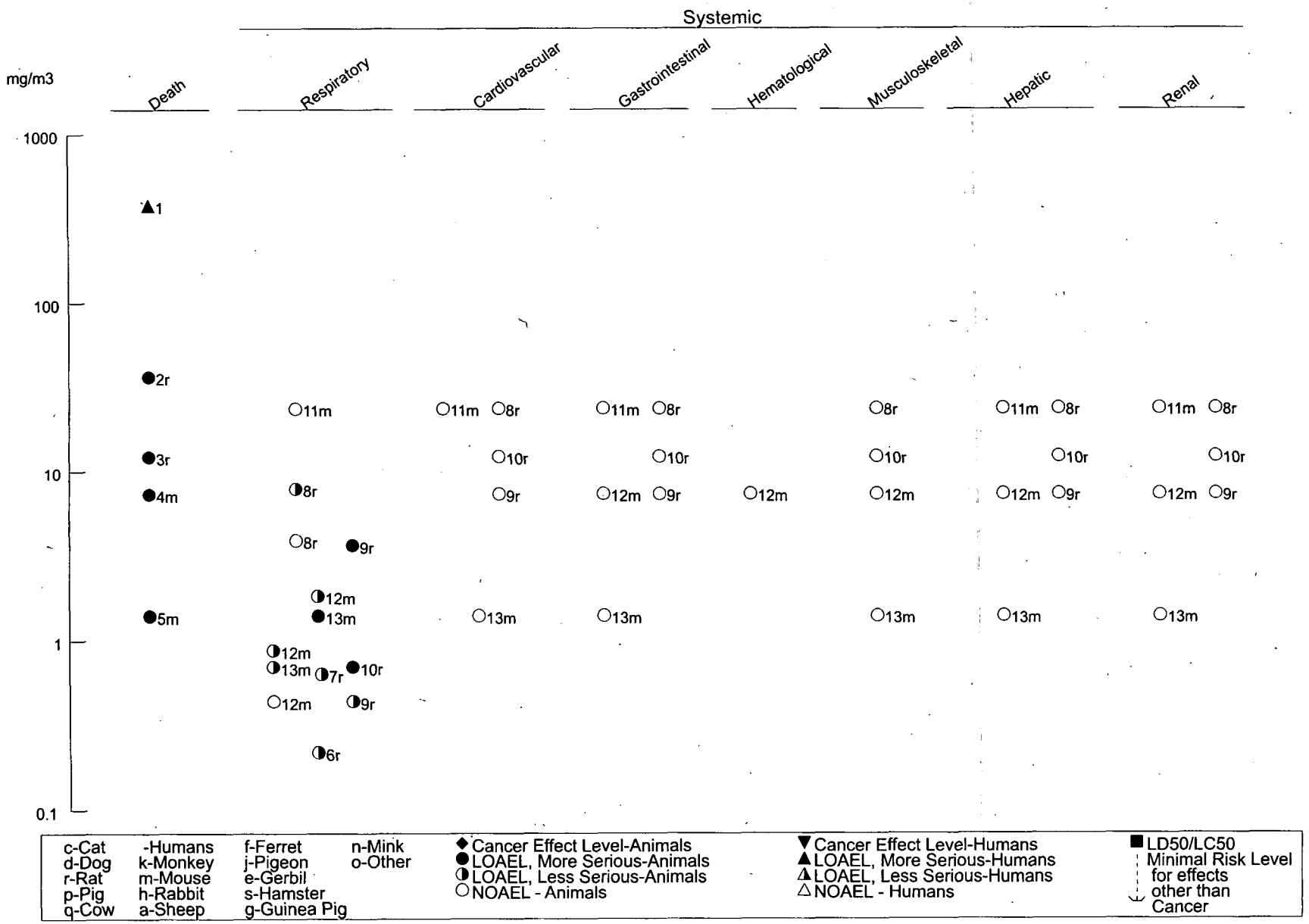

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Figure 3-1. Levels of Significant Exposure to Nickel - Inhalation (*Continued*)

Acute (≤14 days)

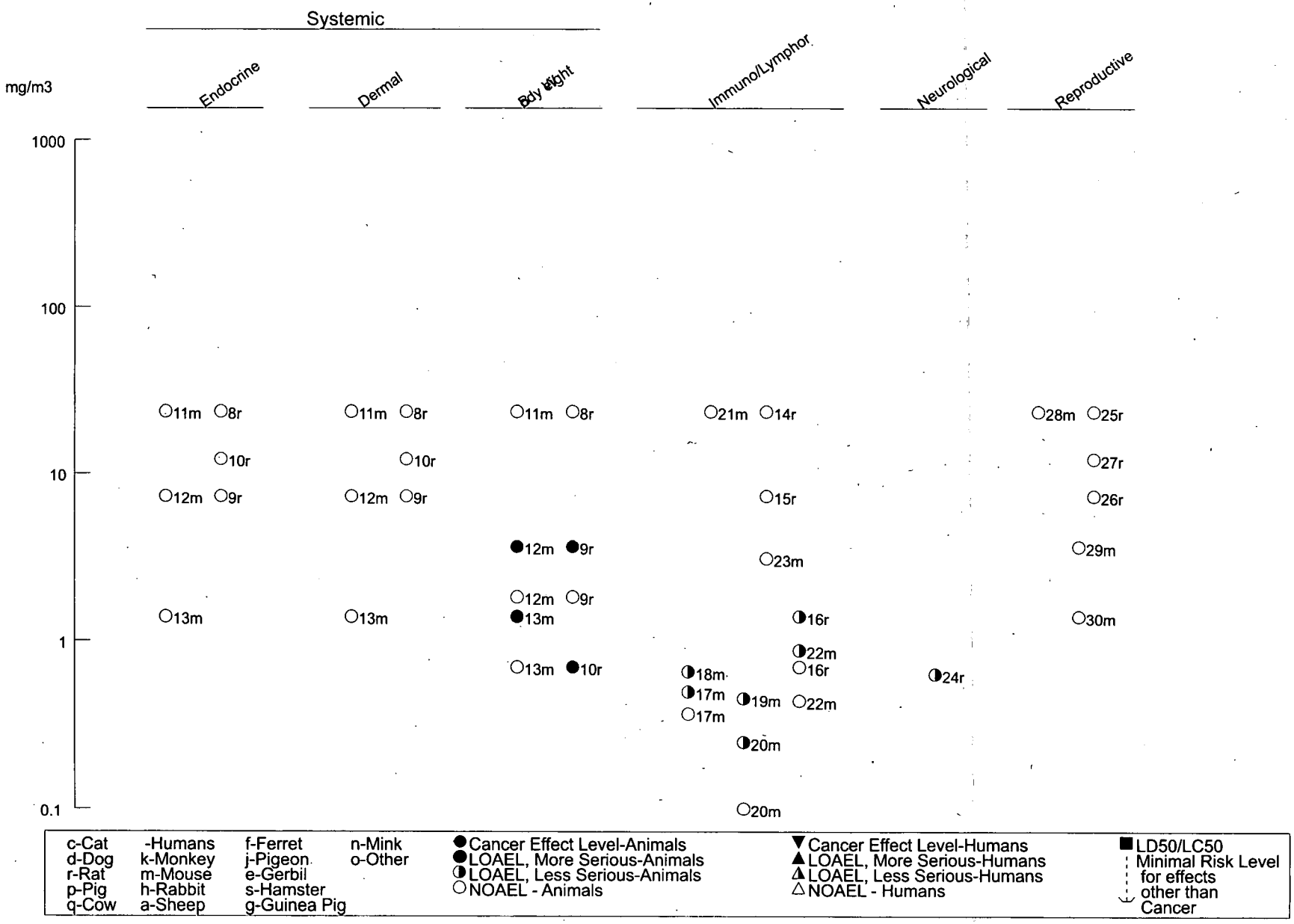

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Figure 3-1. Levels of Significant Exposure to Nickel - Inhalation (*Continued*)

Intermediate (15-364 days)

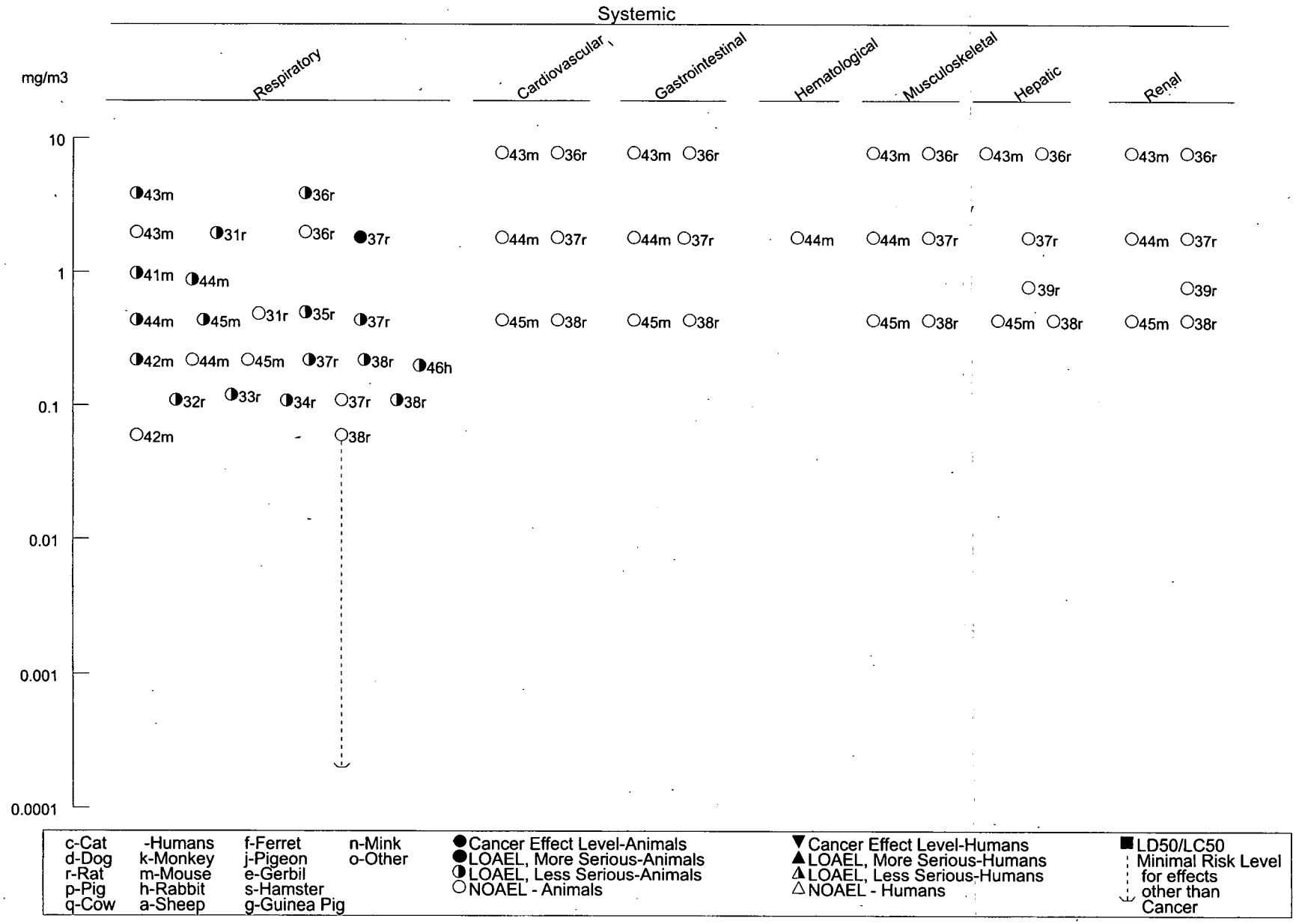

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Figure 3-1. Levels of Significant Exposure to Nickel - Inhalation (*Continued*)

Intermediate (15-364 days)

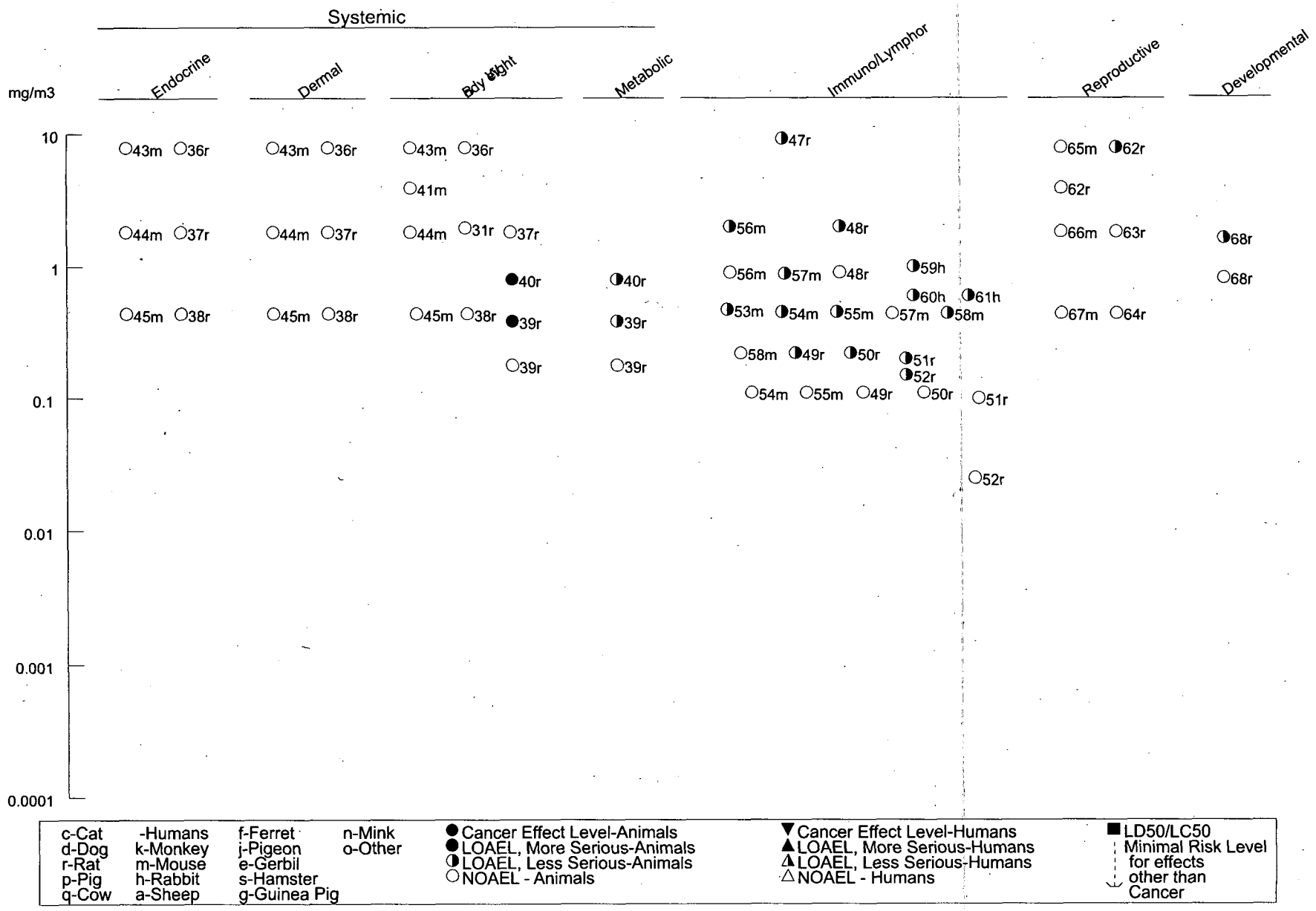

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Figure 3-1. Levels of Significant Exposure to Nickel - Inhalation (*Continued*)

Chronic (≥365 days)

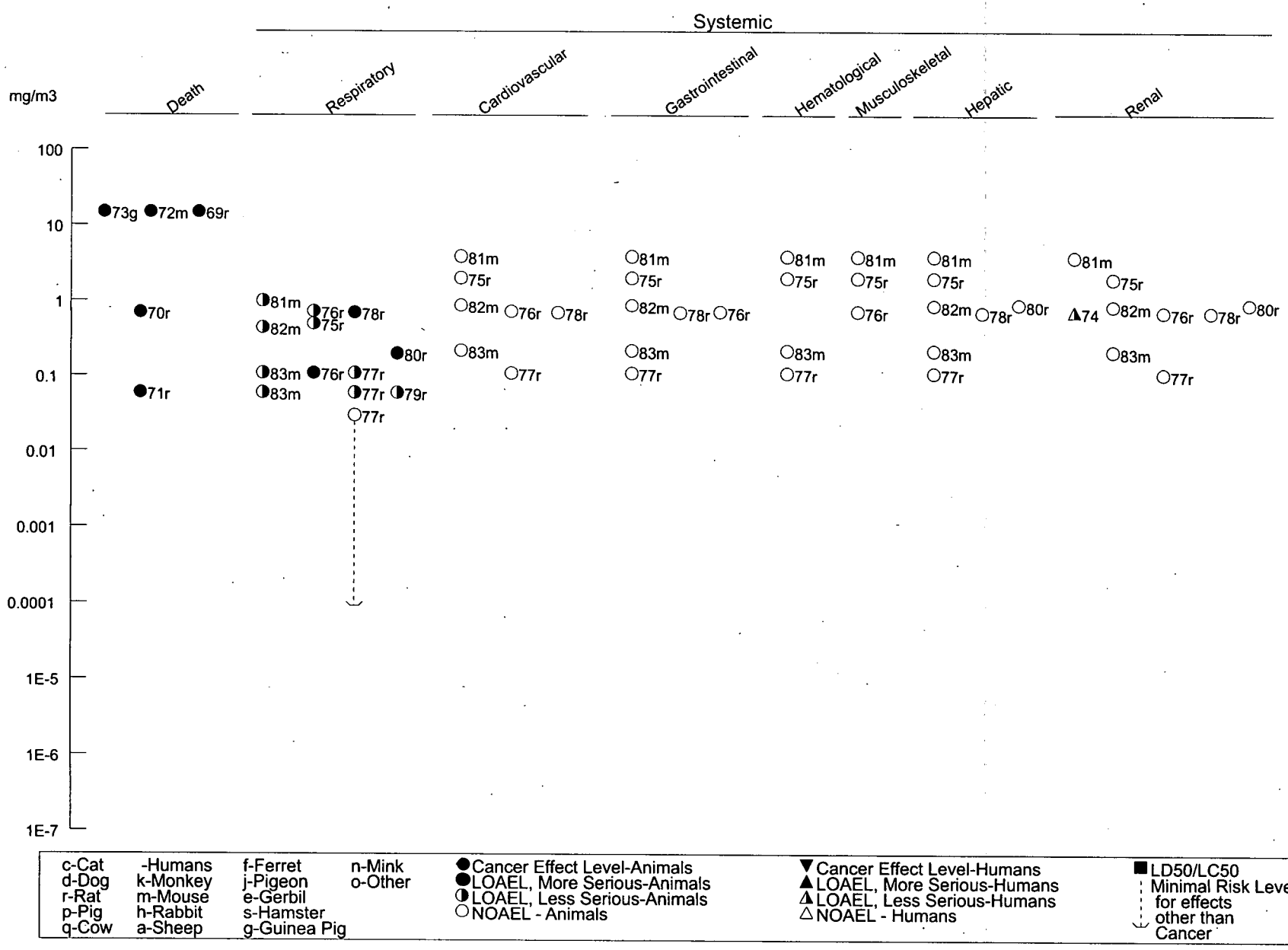

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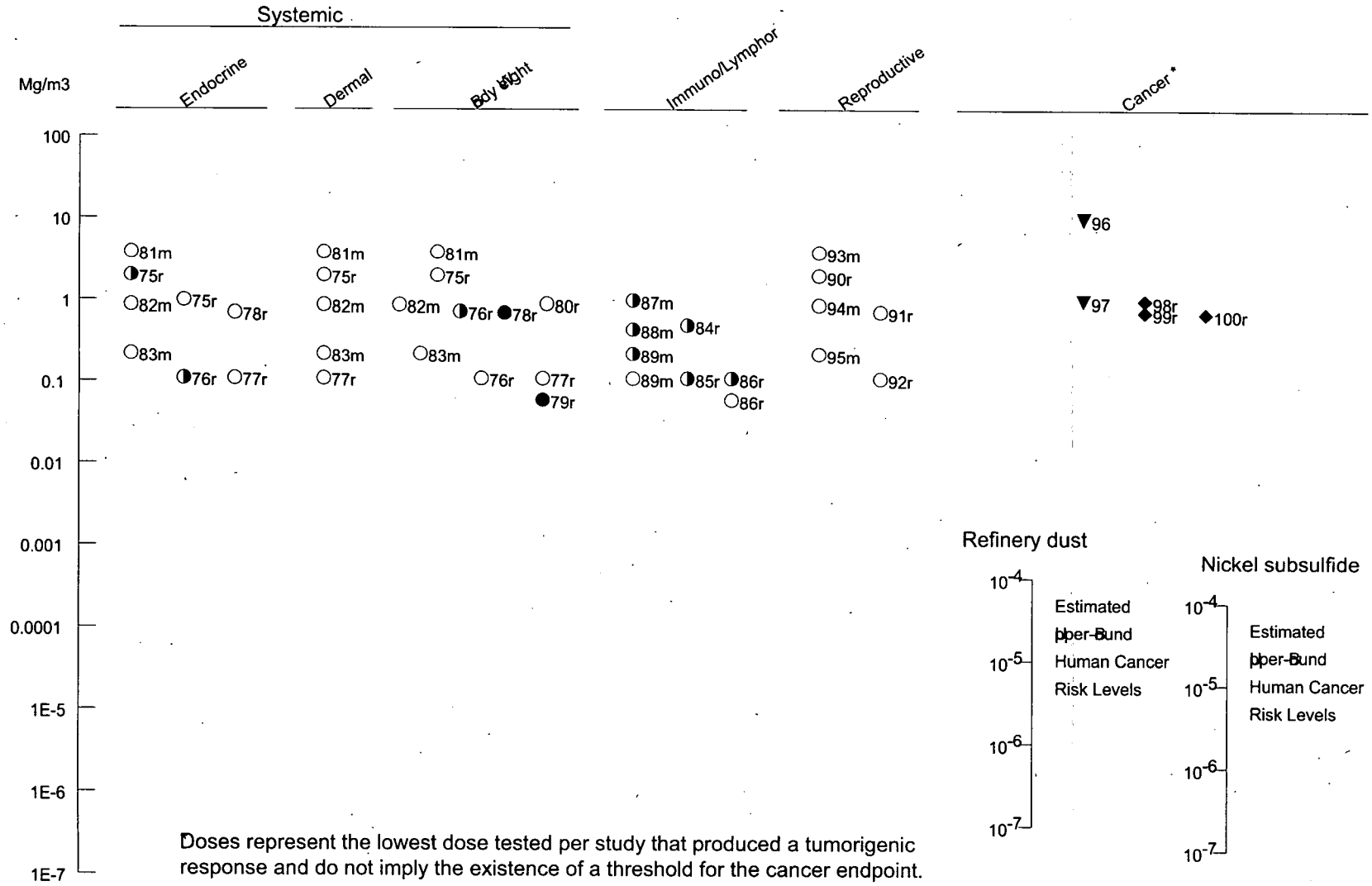
Figure 3-1. Levels of Significant Exposure to Nickel - Inhalation (*Continued*)

Chronic (≥365 days)



3.2.1.2 Systemic Effects

No studies were located regarding ocular effects in humans or animals after inhalation exposure to nickel. Other systemic effects are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species, duration category, and nickel compound are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Studies in both humans and animals indicate that the respiratory system is the primary target of nickel toxicity following inhalation exposure. A single case of death from adult respiratory distress syndrome has been reported following a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994). Histological changes noted in the lungs of this case included alveolar wall damage, with fibrotic changes, and edema in the alveolar space. A statistically significant increase in the incidence in deaths from respiratory disease was found in welders chronically exposed to nickel, usually as nickel oxide or metallic nickel; 71 deaths from respiratory disease was observed, as compared to 50.83 expected (Cornell and Landis 1984). A nonstatistically significant increase in deaths due to respiratory disease was observed in a study by Polednak (1981). This study provides some limited information on nickel exposure levels; recent nickel air levels of 0.04–0.57 mg Ni/m^3 were reported; however, these levels may not be reflective of historical exposure. The adverse respiratory effects in the workers included chronic bronchitis, emphysema, and reduced vital capacity. The workers were also exposed to a variety of other metals, including arsenic, uranium, iron, lead, and chromium, so it cannot be concluded that nickel was the sole causative agent. Other studies have not shown increases in the incidence of deaths from respiratory disease (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh 1982; Redmond 1984; Shannon et al. 1984b, 1991). Reduced vital capacity and expiratory flows were observed in stainless steel welders (Kilburn et al. 1990). Alveolar volume and total thoracic gas volume were unaffected. Because the welders were also exposed to high levels of chromium, the role of nickel in the etiology of the impaired lung function is not known. Examination of chest radiographs of nickel sinter plant workers exposed to nickel at concentrations as high as 100 mg/m^3 did not reveal an increase in small irregular opacities, which would be indicative of inflammatory or fibrogenic response in the lungs (Muir et al. 1993). Asthma induced by occupational exposure to nickel has been documented (Dolovich et al. 1984; Novey et al. 1983; Shirakawa et al. 1990). The asthma can result from either primary irritation or from an allergic response.

Studies in rats and mice demonstrate that chronic active inflammation in the lungs is the most prominent effect following inhalation exposure to nickel sulfate, nickel subsulfide, or nickel oxide. In acutely-exposed rats, chronic lung inflammation was observed at the lowest nickel sulfate (0.7 mg Ni/m^3) and nickel subsulfide (0.44 mg Ni/m^3) concentrations tested in 12-day exposure studies (6 hours/day, 12 days in a 16-day period) (NTP 1996b, 1996c). At higher concentrations of nickel sulfate and nickel subsulfide (1.4 and 3.65 mg Ni/m^3, respectively), the inflammation was accompanied by labored breathing. The chronic active lung inflammation was characterized by focal accumulation of alveolar macrophages and interstitial (nickel subsulfide) or inflammatory cell (nickel sulfate) infiltrates. At the higher concentrations, necrotic cellular debris was also present. Bronchiolar epithelium degeneration was also observed in rats exposed to 0.7 mg Ni/m^3 as nickel sulfate (NTP 1996c). Consistent with these findings, is the observation of alveolitis in rats exposed to 0.22 mg Ni/m^3 as nickel subsulfide 6 hours/day for 7 days (Benson et al. 1995b). Additionally, exposure to 0.95 mg Ni/m^3 as nickel subsulfide resulted in alveolitis and alveolar proteinosis after 4 days of exposure, but not after 1 or 2 days of exposure (Benson et al. 1995b). In contrast, acute lung inflammation, consisting of neutrophilic infiltrates, was first observed in rats exposed to nickel oxide at 7.9 mg Ni/m^3 (NTP 1996a); chronic lung inflammation was not observed at doses as high as 23.6 mg Ni/m^3. Mice appear to be less sensitive than rats to the acute toxicity of nickel with LOAELs for chronic inflammation of 0.7, 1.83, and >23.6 mg Ni/m^3 as nickel sulfate, nickel subsulfide, and nickel oxide, respectively (NTP 1996a, 1996b, 1996c).

As with acute exposure, chronic lung inflammation was typically observed at the lowest adverse effect level following intermediate-duration exposure. Thirteen-week (6 hours/day, 5 days/week) studies of rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide (NTP 1996a, 1996b, 1996c) identified LOAELs for chronic active lung inflammation of 0.11, 0.22, and 3.9 mg Ni/m^3, respectively; NOAEL values of 0.06, 0.11, and 2 mg Ni/m^3, respectively, were also identified for chronic inflammation. Alveolitis was reported in rats exposed to 0.11 mg Ni/m^3 as nickel sulfate and 1.96 mg Ni/m^3 as nickel oxide for 6 months (6 hours/day, 5 days/week) (Benson et al. 1995a) and interstitial pneumonia was observed at 0.5 mg Ni/m^3 as nickel oxide for 1 month (6 hours/day, 5 days/week) (Horie et al. 1985). A number of other lung effects have also been observed in rats exposed to nickel for intermediate durations. Minimal alveolar macrophage hyperplasia was observed at the lowest nickel sulfate, nickel subsulfide, and nickel oxide concentrations tested (0.03, 0.11, and 0.4 mg Ni/m^3, respectively) (NTP 1996a, 1996b, 1996c). These slight changes in the number of macrophages were not considered adverse because it is considered to be part of the normal physiologic response to inhaled particles and it is not believed to compromise the lung's ability to clear foreign matter. At higher nickel concentrations, mild to moderate changes in alveolar macrophage hyperplasia were found. The effect of nickel on alveolar macrophages is

also discussed in Section 3.2.1.3, Immunological and Lymphoreticular Effects. Interstitial infiltrates were observed in rats exposed to ≥0.11 or 0.22 mg Ni/m^3 as nickel sulfate or nickel subsulfide (NTP 1996b, 1996c) or 0.109 mg Ni/m^3 as nickel chloride (Bingham et al. 1972), granulomatous inflammation was observed in rats exposed to 3.9 mg Ni/m^3 as nickel oxide (NTP 1996a), alveolar wall thickening was observed in rats exposed to 0.12 mg Ni/m^3 as nickel oxide (Bingham et al. 1972), and hyperplasia of the bronchial epithelium was observed in rats exposed to 0.109 mg Ni/m^3 as nickel chloride (Bingham et al. 1972). The highest NOAEL values for respiratory effects in rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for intermediate durations were 0.06 mg Ni/m^3 (NTP 1996c), 0.11 mg Ni/m^3 (NTP 1996b), and 0.49 mg Ni/m^3 (Benson et al. 1995a). An intermediate-duration inhalation MRL was derived from the NOAEL (0.06 mg Ni/m^3) and LOAEL (0.11 mg Ni/m^3) identified from the NTP (1996c) study of nickel sulfate, as described in the footnote to Table 3-1 and Appendix A.

Similar effects have been observed in mice exposed to nickel for intermediate durations, although the LOAELs for the lung effects tend to be higher suggesting a lower sensitivity compared to rats. Chronic active lung inflammation was observed in mice exposed to ≥0.44 and 0.88 mg Ni/m^3 as nickel sulfate or nickel subsulfide, respectively (NTP 1996b, 1996c). Lung inflammation was not found in mice exposed to nickel oxide at concentrations as high as 7.9 mg Ni/m^3 (NTP 1996a); however, perivascular lymphocyte infiltrates were observed at 3.9 and 7.9 mg Ni/m^3 (NTP 1996a). Interstitial pneumonia has also been observed in mice exposed to 0.22 or 0.98 mg Ni/m^3 as nickel sulfate or nickel oxide (Benson et al. 1995a). Other lung effects in mice include minimal alveolar macrophage hyperplasia at 0.11, 0.22, or 0.4 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c); interstitial infiltrates at ≥0.44 or 0.44 mg Ni/m^3 as nickel subsulfide or nickel sulfate, respectively, (NTP 1996b, 1996c), and fibrosis at 0.44 and 0.88 mg Ni/m^3 as nickel sulfate or nickel subsulfide, respectively (NTP 1996b, 1996c). As with the rats, minimal alveolar macrophage hyperplasia was not considered adverse. The highest NOAEL values for respiratory effects in mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide for intermediate durations were 0.22, 0.22, and 2.0 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c).

Chronic exposure to nickel (6 hours/day, 5 days/week for 2 years) resulted in chronic active lung inflammation (or pneumonia) in rats and mice at 0.06 mg Ni/m^3 as nickel sulfate, in rats at 0.11 mg Ni/m^3 and higher as nickel subsulfide (NTP 1996b; Ottolenghi et al. 1990), in mice at 0.44 mg Ni/m^3 and higher as nickel subsulfide (NTP 1996b), in rats at 0.2 mg Ni/m^3 and higher as nickel oxide (NTP 1996a; Tanaka et al. 1988), and in mice at 1 mg Ni/m^3 as nickel oxide (NTP 1996a). Additional lung effects that were found at the same dose levels as inflammation included alveolar epithelium hyperplasia (or

bronchialization), fibrosis in rats and mice exposed to nickel subsulfide (NTP 1996b), and bronchialization and/or alveolar proteinosis in mice exposed to nickel oxide (NTP 1996a; Takenaka et al. 1985). With the exception of the NTP (1996c) study of nickel sulfate in rats, NOAEL values for respiratory effects following chronic duration exposure were not identified. The NOAEL of 0.03 mg Ni/m^3 and LOAEL of 0.06 mg Ni/m^3 identified in rats exposed to nickel sulfate (NTP 1996c) were used to derive a chronic-duration inhalation MRL for nickel, as described in the footnote to Table 3-1 and Appendix A.

The NTP (1996a, 1996b, 1996c) studies allows for the comparison of the toxicity of nickel sulfate, nickel subsulfide, and nickel oxide in rats and mice. Following acute- or intermediate-duration exposure, the toxicity of the different nickel compounds is related to its solubility, with soluble nickel sulfate being the most toxic and insoluble nickel oxide being the least toxic. The difference in the toxicity across compounds is probably due to the ability of water-soluble nickel compounds to cross the cell membrane and interact with cytoplasmic proteins. In contrast, the severity of inflammatory and proliferative lesions following chronic exposure was greater in rats exposed to nickel subsulfide or nickel oxide, as compared to nickel sulfate. Additionally, parenchymal damage secondary to inflammation was evident in the rats exposed to nickel subsulfide and nickel oxide, but not nickel sulfate. For all durations and nickel compounds tested, rats appear to be more sensitive to the lung effects than mice; significant increases in the incidence of chronic lung inflammation were observed at lower concentrations in the rats than mice. Intermediate-duration studies (Benson et al. 1995a; Horie et al. 1985) that monitored animals for months after exposure termination suggest that nickel-induced lung damage is not readily reversible after exposure termination. In the Benson et al. (1995a) studies, alveolitis was observed in rats exposed to 0.11 mg Ni/m^3 as nickel sulfate and 1.96 mg Ni/m^3 as nickel oxide at the end of the 6-month exposure period and 4 months after exposure termination. Horie et al. (1985) reported interstitial pneumonia in rats exposed 6 hours/day, 5 days/week to 0.5 mg Ni/m^3 as nickel oxide for 1 month. Twelve and 20 months after termination of exposure to 6.3 mg Ni/m^3, squamous metaplasia of the bronchial epithelium, hyperplasia of the bronchial gland, and chronic bronchitis were observed.

In addition to the lung effects, several studies have demonstrated that exposure to nickel sulfate or nickel subsulfide can induce atrophy of the nasal olfactory epithelium (Evans et al. 1995; NTP 1996b, 1996c). The nasal lesions are typically observed at higher concentrations than the lung effects. In a study designed specifically to examine the effects of nickel on the olfactory system, rats were exposed to nickel sulfate at 0 or 0.635 mg Ni/m^3 6 hours/day for 16 days (Evans et al. 1995). Histological changes in the olfactory epithelium of exposed rats included a slight reduction in the number of bipolar sensory receptor

cells, a decrease in the thickness of the olfactory epithelium resulting from a loss of sustentacular cells, a thinning of apical cytoplasm, and a reduction in the number of sensory cilia on the surface of the cells. After a recovery period of 22 days, fewer sensory cilia was the only change that remained, indicating that the effects of an intermediate-duration exposure to nickel were reversible.

Cardiovascular Effects. No increases in the number of deaths from cardiovascular diseases were reported in workers exposed to nickel (Cornell and Landis 1984; Cox et al. 1981; Cragle et al. 1984).

Microscopic examinations of the hearts of rats and mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 12 6-hour exposures over 16 days did not reveal any changes at concentrations as high as 12.2, 7.33, or 23.6 mg Ni/m^3, respectively, in rats and 1.4, 7.33, or 23.6 mg Ni/m^3, respectively, in mice (NTP 1996a, 1996b, 1996c). No cardiovascular effects were observed in rats or mice exposed to 0.44, 1.83, or 7.9 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Similarly, chronic exposure (6 hours/day, 5 days/week) of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice to, 0.22, 0.88, or 3.9 mg Ni/m^3, respectively, did not result in microscopic changes in the heart (NTP 1996a, 1996b, 1996c). Intermittent exposure (6 hours/day, 5 days/week) of rats to 0.7 mg Ni/m^3 as nickel subsulfide for 78 weeks also did not affect the microscopic appearance of the heart (Ottolenghi et al. 1974).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to nickel.

Microscopic examinations of the gastrointestinal tract of mice and rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 12 6-hour exposures did not reveal any changes at concentrations as high as 12.2, 7.33, or 23.6 mg Ni/m^3, respectively, in rats and 1.4, 7.33, or 23.6 mg Ni/m^3, respectively, in mice (NTP 1996a, 1996b, 1996c). Likewise, no histological alterations were observed in the gastrointestinal tracts of rats and mice exposed to 0.44, 1.83, or 7.9 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice to 0.22, 0.88, or 3.9 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, did not result in microscopic changes in the gastrointestinal tract (NTP 1996a, 1996b, 1996c). Intermittent exposure (6 hours/day, 5 days/week) of

rats to 0.7 mg Ni/m^3 as nickel subsulfide for 78 weeks also did not affect the microscopic appearance of the intestines (Ottolenghi et al. 1974).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to nickel.

A number of hematological alterations were observed in studies by Weischer et al. (1980) and NTP (1996a, 1996b, 1996c). A decrease in hematocrit level was observed in male rats continuously exposed to 0.178 or 0.385 mg Ni/m^3 as nickel oxide for 28 days (Weischer et al. 1980); no significant alterations were observed at 0.785 mg Ni/m^3. The biological significance of a decrease in hematocrit level in the absence of hemoglobin or erythrocyte alterations is not known. In non-pregnant females continuously exposed to nickel oxide for 21 days, increases in hematocrit and hemoglobin levels were observed at 0.8 mg Ni/m^3 and higher; an increase in mean cell volume and a decrease in erythrocyte levels were observed at 1.6 mg Ni/m^3 and higher (Weischer et al. 1980). Similarly, increases in hematocrit, hemoglobin, and erythrocyte levels were observed in rats exposed to nickel subsulfide at 0.73 mg Ni/m^3 6 hours/day, 5 days/week for 2 years (NTP 1996b). As noted by NTP 1996(b), increases in hematocrit, hemoglobin, and erythrocytes are consistent with erythropoietin production in response to tissue hypoxia, possibly as a result of the nickel-induced lung damage. Chronic exposure of rats to nickel oxide or nickel sulfate at concentrations up to 2 or 0.11 mg Ni/m^3, respectively, and chronic exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in significant hematological effects (NTP 1996a, 1996b, 1996c).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to nickel.

No histological alterations were observed in bone of rats and mice exposed to nickel sulfate 6 hours/day for 12 days/16 days (highest NOAEL is 12.2 mg Ni/m^3), 5 days/week for 13 weeks (0.44 mg Ni/m^3), or 5 days/week for 2 years (0.11 and 0.22 mg Ni/m^3 for rats and mice) (NTP 1996c). No alterations were observed in bone or muscle of rats and mice exposed to nickel oxide (6 hours/day, 5 days/week) at 23.6 mg Ni/m^3 for 16 days (12 days/16 days), 7.9 mg Ni/m^3 for 13 weeks, or 2 (rats) or 3.9 mg Ni/m^3 (mice) for 2 years (NTP 1996a). Similarly, exposure to nickel subsulfide 6 hours/day, 5 days/week did not result in alterations in bone or muscle in rats at 7.33 mg Ni/m^3 for 13 weeks or 0.73 mg Ni/m^3 for 2 years or mice at 7.33 mg Ni/m^3 for 16 days, 1.83 mg Ni/m^3 for 13 weeks, or 0.88 mg Ni/m^3 (mice) for

2 years (NTP 1996b). Rats were not evaluated for muscular effects of nickel subsulfide for the 16-day or 2-year exposures.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to nickel.

No histological alterations were observed in the livers of rats or mice exposed to nickel subsulfide, nickel sulfate, or nickel oxide at concentrations of 7.33, 12.2, or 23.6 mg Ni/m^3, respectively, in rats and 1.4, 12.2, or 23.6 mg Ni/m^3, respectively, in mice exposed 6 hours/day, 12 days in a 16-day period (NTP 1996a, 1996b, 1996c) or 1.83, 0.44, or 7.9 mg Ni/m^3 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Following chronic exposure, no histological changes were observed in the livers of rats exposed to nickel subsulfide at 0.7 mg Ni/m^3 (Ottolenghi et al. 1974) or 0.73 mg Ni/m^3 (NTP 1996b), to nickel oxide at 0.9 mg Ni/m^3 (Tanaka et al. 1988) or 2 mg Ni/m^3 (NTP 1996a), or to nickel sulfate at 0.11 mg Ni/m^3 (NTP 1996c). Chronic exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the liver (NTP 1996a, 1996b, 1996c).

Renal Effects. Marked tubular necrosis was observed in the kidneys of a man who died of adult respiratory distress syndrome 13 days after a 90-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994). Several days after the exposure, urinary concentrations of nickel were 700 μg/L, in comparison to levels of <0.1–13.3 μg/L in persons not occupationally exposed to nickel (Sunderman 1993).

In nickel refinery workers, a significant association was found between nickelemia and increased urinary β_2-microglobulin levels (Sunderman and Horak 1981). Five of 11 workers with urinary nickel concentrations >100 μg/L had increased levels of urinary β_2-microglobulin (>240 μg/L). Urinary levels of total proteins, β_2-microglobulin, retinol binding protein, and *N*-acetyl-β-D-glucosaminidase (NAG) were increased in 12 women, and urinary lysozyme and NAG were increased in 14 men occupationally exposed to soluble nickel (sulfate, chloride) compounds at an average concentration of 0.75 mg Ni/m^3 (Vyskocil et al. 1994a). Although the average exposure concentration was the same for women and men, women were more highly exposed as indicated by urine concentrations of 10.3 μg Ni/g creatinine in women compared to 5 μg Ni/g creatinine in men. The markers that were changed reflected tubular dysfunction. No effects on markers of glomerular function, urinary albumin, or transferrin were noted.

No histological alterations were observed in the kidneys of rats or mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide 6 hours/day, 5 days/week, at concentrations of ≤12.2, 7.33, or 23.6 mg Ni/m^3, respectively, for 16 days (12 days in a 16-day period) (NTP 1996a, 1996b, 1996c), or ≤0.44, 1.83, or 7.9 mg Ni/m^3, respectively, for 13 weeks (NTP 1996a, 1996b, 1996c), or 0.9 mg Ni/m^3 as nickel oxide for 12 months (Tanaka et al. 1988). Chronic exposure of rats to nickel oxide (NTP 1996a; Tanaka et al. 1988), nickel subsulfide (NTP 1996b), or nickel sulfate (NTP 1996c) at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, did not result in histological alterations in the kidneys. Additionally, no alterations were observed in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to nickel.

Histological examinations did not reveal any changes in the adrenal glands, pancreas, parathyroid, pituitary, or thyroid glands in rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 6-hour exposures over 16 days or for 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). The NOAEL values for endocrine effects were 12.2, 23.6, and 7.33 mg Ni/m^3 in rats and mice exposed to nickel sulfate, nickel oxide, and nickel subsulfide, respectively, for the shorter duration study and 0.44, 7.9, and 1.83 mg Ni/m^3, respectively, for the 13-week study. In rats exposed intermittently to nickel subsulfide at 0.7 mg Ni/m^3 for 78 weeks, no histological changes were observed in the thyroid or adrenal glands (Ottolenghi et al. 1974). Adrenal medulla hyperplasia and increased incidences of benign pheochromocytoma were observed in female rats exposed to 2 mg Ni/m^3 as nickel oxide (NTP 1996a) and male and female rats exposed to 0.73 mg Ni/m^3 as nickel subsulfide for 2 years (NTP 1996b); an increased incidence of benign pheochromocytoma was also observed in male rats exposed to 0.11 mg Ni/m^3 as nickel subsulfide. These effects were not observed in rats exposed chronically to nickel sulfate at concentrations up to 0.11 mg Ni/m^3, or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations of 3.9, 0.88, or 0.22 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c).

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure. However, contact dermatitis in persons exposed to nickel compounds is one of the most common effects of nickel exposure (see Section 3.2.3.2). In addition, immunological studies indicate that the dermatitis is an allergic response to nickel, and significant effects on the immune system have been noted in workers exposed to nickel (see Section 3.2.1.3).

Microscopic changes in the skin were not observed in rats or mice exposed to nickel as nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 12.2, 7.33, or 23.6 mg Ni/m^3, respectively, for 6 hours/day for 12 days in a 16-day period (NTP 1996a, 1996b, 1996c) or 0.44, 1.83, or 7.9 mg Ni/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic exposure of rats to nickel sulfate, nickel subsulfide, or nickel oxide at concentrations up to 0.11, 0.73, or 2 mg Ni/m^3, respectively, or exposure of mice at concentrations up to 0.22, 0.88, or 3.9 mg Ni/m^3, respectively, did not result in microscopic changes in the skin (NTP 1996a, 1996b, 1996c).

Body Weight Effects. Significant decreases in body weight gain have been observed in rats and mice exposed to nickel sulfate, nickel subsulfide, and nickel oxide for acute, intermediate, and chronic exposure durations. In many of the studies, the decreases in body weight gain were associated with lung inflammation, impaired lung function (as evidenced by labored breathing), and lethality. Exposure to nickel sulfate resulted in serious decreases in body weight gain (terminal body weights >25% lower than controls) in rats exposed to 0.7 mg Ni/m^3 and higher and in mice exposed to 1.4 mg Ni/m^3 6 hours/day for 12 days in a 16-day period (NTP 1996c); no significant alterations in body weight gain were observed in mice exposed to 0.7 mg Ni/m^3. No significant alterations in body weight gain were observed in rats or mice exposed to 0.44 mg Ni/m^3 for 13 weeks (NTP 1996c), rats exposed to 0.11 mg Ni/m^3 for 2 years (NTP 1996c), or mice exposed to 0.22 mg Ni/m^3 for 2 years (NTP 1996c).

For nickel subsulfide, serious decreases in body weight gain (22–28%) and emaciation were observed in rats and mice, respectively, exposed to 3.65 mg Ni/m^3 for 6 hours/day for 12 days in a 16-day period (NTP 1996b); a NOAEL of 1.85 mg Ni/m^3 was also identified. No alterations in body weight were observed at 1.83 mg Ni/m^3 6 hours/day, 5 days/week for 13 weeks. Exposure to approximately 0.7 mg Ni/m^3 6 hours/day, 5 days/week for chronic-duration resulted in 11–30% decreases in body weight gains in rats (NTP 1996b; Ottolenghi et al. 1974). No alterations were observed in mice exposed to 0.88 mg Ni/m^3 6 hours/day, 5 days/week for 2 years (NTP 1996b).

Most studies did not find significant alterations in rats and mice exposed to nickel oxide. A NOAEL of 23.6 mg Ni/m^3 was identified in rats and mice exposed to 23.6 mg Ni/m^3 6 hours/day for 12 days in a 16-day period (NTP 1996a). For intermediate exposure, NOAELs of 1.9–7.9 mg Ni/m^3 were identified in rats and mice (Benson et al. 1995a; NTP 1996a). However, Weischer et al. (1980) reported 30–36% decreases in body weight gain in male and female rats exposed to 0.385 or 0.8 mg Ni/m^3, respectively, continuously for 21–28 days. In pregnant rats, an 11% decrease in body weight gain was observed at

0.8 mg Ni/m^3 compared to the 36% decrease observed in similarly exposed non-pregnant rats. NTP (1996a) did not find significant alterations in body weight gain in rats and mice exposed to 2 or 3.9 mg Ni/m^3, respectively, 6 hours/day, 5 days/week for 2 years; a NOAEL of 0.9 mg Ni/m^3 was also identified in rats exposed 7 hours/day, 5 days/week for 12 months (Tanaka et al. 1988). In contrast, Takenaka et al. (1985) reported weight loss in rats continuously exposed to 0.06 mg Ni/m^3 for 31 months; the weight loss began after 13 months of exposure. These data suggest that continuous exposure is more toxic than intermittent exposure (duration adjusted NOAEL from the rat NTP study is 0.36 mg Ni/m^3). Continuous exposure would result in higher lung burdens than intermittent exposure, which would lead to increased lung damage.

Metabolic Effects. No studies were located regarding metabolic effects in humans after inhalation exposure to nickel.

Significant increases in serum glucose levels were observed in male rats continuously exposed to 0.385 or 0.784 mg Ni/m^3 as nickel oxide for 28 days (Weischer et al. 1980). In females rats continuously exposed to nickel oxide, decreases in serum glucose levels were observed at 0.8 and 1.6 mg Ni/m^3; at 3.2 mg Ni/m^3, serum glucose levels did not significantly differ from controls (Weischer et al. 1980). These data suggest that there may be a gender difference. Although no adverse pancreatic effects have been noted in inhalation studies, a single-dose intravenous injection study has reported increases in serum glucose levels and effects on pancreatic cells in rabbits at doses of 4.5–9 mg Ni/kg as nickel chloride (Kadota and Kurita 1955); Weischer et al. (1980) also found increases in serum glucose in male rats exposed to nickel chloride in water for 28 days. It is possible that changes in serum glucose reflect an effect on the pancreas.

3.2.1.3 Immunological and Lymphoreticular Effects

A number of immunological and lymphoreticular effects have been reported in humans and animals. In 38 production workers exposed to nickel (compound not specified), significant increases in levels of immunoglobulin G (IgG), IgA, and IgM and a significant decrease in IgE levels were observed (Bencko et al. 1983, 1986). Significant increases in other serum proteins, which may be involved in cell-mediated immunity (including α_1-antitrypsin, α_2-macroglobulin, ceruloplasmin), were also observed. The increase in immunoglobulins and serum proteins suggests that the immune system was stimulated by nickel exposure. Similar but less-pronounced effects were observed in workers exposed to cobalt. A relationship between nickel and cobalt sensitization is further supported by the finding that nickel-reactive

IgE antibodies were observed in eight patients with hard-metal asthma induced by cobalt exposure (Shirakawa et al. 1990). Exposure levels were not reported.

Alterations in innate (or non-specific) and acquired immunity have been observed in animals. Several studies examined alveolar macrophage functions. A significant reduction in macrophage phagocytic activity was observed in rats exposed to an unspecified concentration of nickel chloride for 2 hours (Adkins et al. 1979) or in mice exposed to 0.47 mg Ni/m^3 as nickel oxide or 0.45 mg Ni/m^3 as nickel subsulfide 6 hours/day, 5 days/week for 65 days (Haley et al. 1990). No alteration of macrophage phagocytic activity was observed in mice exposed to ≤0.45 mg Ni/m^3 as nickel sulfate 6 hours/day, 5 days/week for 65 days (Haley et al. 1990). Other alveolar macrophage alterations include decreased lysozyme activity in rabbits exposed to 0.6 mg Ni/m^3 as nickel chloride 6 hours/day, 5 days/week for 4–6 weeks (Bingham et al. 1987; Johansson et al. 1987, 1988a, 1989), alterations in macrophage production of tumor necrosis factor (Goutet et al. 2000; Morimoto et al. 1995), and morphological alterations. Morimoto et al. (1995) found increased production of tumor necrosis factor in rats exposed to 9.2 mg Ni/m^3 as nickel oxide 8 hours/day, 5 days/week for 4 weeks. In contrast, Goutet et al. (2000) found a decrease in tumor necrosis factor production in rats following a single intratracheal instillation of nickel sulfate. The conflicting results may be due to exposure route, duration, or concentration differences between the studies. Alveolar macrophages from rabbits exposed to 1 mg Ni/m^3 as metallic nickel 6 hours/day, 5 days/week for 3–6 months (Johansson et al. 1980) or 0.6 mg Ni/m^3 as nickel chloride 6 hours/days, 5 days/week for 4–6 weeks (Johansson et al. 1987) or 4 months (Johansson et al. 1988a, 1989) had increases in membrane-bound lamellar bodies. Exposure to metallic nickel also resulted in macrophages with smooth surfaces; the frequency of occurrence was duration-related (Johansson et al. 1980).

Several studies have examined the relationship between nickel exposures and acquired immune function. An increase in susceptibility to *Streptococci* infection was observed in mice exposed to 0.499 mg Ni/m^3 as nickel chloride or 0.455 mg Ni/m^3 as nickel sulfate for 2 hours (Adkins et al. 1979); mice exposed to 0.657 mg Ni/m^3 as nickel chloride also developed septicemia from the *Streptococci* infection and had a reduced ability to clear the inhaled bacteria (Adkins et al. 1979). Other studies have found an impaired response to sheep red blood cells (decrease in the number of antibody production spleen cells) in mice exposed to 0.25 mg Ni/m^3 as nickel chloride for 2 hours (Graham et al. 1978) or rats continuously exposed to 0.2 mg Ni/m^3 as nickel oxide for 4 weeks or 0.15 mg Ni/m^3 for 4 months (Spiegelberg et al. 1984). A decreased resistance to a tumor challenge was also observed in mice exposed to 0.45 mg Ni/m^3 as nickel sulfate 6 hours/day, 5 days/week for 65 days (Haley et al. 1990).

A significant portion of nickel that is removed from the lung enters the lymphatic system, often causing damage to the lymph nodes. Lymphoid hyperplasia in the bronchial and mediastinal lymph nodes was observed in rats exposed to 1.4 mg Ni/m^3 as nickel sulfate (NTP 1996c) or mice exposed to 0.88 mg Ni/m^3 as nickel subsulfide (NTP 1996b) 6 hours/day for 12 days in a 16-day period; no effects were observed in rats exposed to 7.33 mg Ni/m^3 as nickel subsulfide (NTP 1996b), rats and mice exposed to 23.5 mg Ni/m^3 as nickel oxide (NTP 1996a), and mice exposed to 3.1 mg Ni/m^2 as nickel sulfate (NTP 1996c). In intermediate-duration studies, a 6 hour/day, 5 day/week exposure resulted in lymphoid hyperplasia in bronchial lymph nodes of rats exposed to 0.22, 0.22, or 2 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.44, 0.88, or 2 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c). Similarly, lymphoid hyperplasia was observed in the bronchial lymph nodes of rats exposed to 0.11, 0.11, or 0.5 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively, and in mice exposed to 0.22, 0.44, or 1 mg Ni/m^3 as nickel sulfate, nickel subsulfide, or nickel oxide, respectively (NTP 1996a, 1996b, 1996c).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects for each species, duration category, and nickel compound are recorded in Table 3-1 and plotted Figure 3-1.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to nickel.

Microscopic examinations did not reveal any changes in the whole brains of rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 6-hour exposures over 16 days (NTP 1996a, 1996b, 1996c). The maximum concentrations that did not result in deaths or changes in brain histology were 3.1, 23.6, and 7.33 mg Ni/m^3 in rats for nickel sulfate, nickel oxide, and nickel subsulfide, respectively, and 0.7, 23.6, and 3.65 mg/m^3 in mice for nickel sulfate, nickel oxide, and nickel subsulfide, respectively. In intermediate-duration studies, no histological alterations were observed in the whole brains of rats and mice exposed to 0.44, 7.9, or 1.83 mg Ni/m^3 as nickel sulfate, nickel oxide, or nickel subsulfide, respectively, 6 hours/day, 5 days/week for 13 weeks (NTP 1996a, 1996b, 1996c). In rats exposed intermittently (6 hours/day, 5 days/week) to nickel subsulfide at 0.7 mg Ni/m^3 for 78 weeks, histological changes were not observed in the brain (Ottolenghi et al. 1974). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3,

respectively, or exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the whole brain (NTP 1996a, 1996b, 1996c).

As noted in Section 3.2.1.2, atrophy of the olfactory epithelium has been observed in rats exposed to nickel sulfate and nickel subsulfide (Evans et al. 1995; NTP 1996a, 1996b, 1996c). To determine if changes in the olfactory epithelium result in any functional changes, Evans et al. (1995) completed behavioral studies of olfactory absolute threshold and olfactory discrimination in rats exposed to nickel sulfate at 0.635 mg/m^3 6 hours/day for 16 days. Although histological changes were observed in the olfactory epithelium, including atrophy and a decrease in the number of bipolar receptor cells, no functional changes were noted. Carnosine, a neurochemical marker, was reduced in the olfactory epithelium following 12 days of exposure but was back to control levels by exposure day 16, suggesting adaptation to nickel exposure.

The LOAEL value from the Evans et al. (1995) study is recorded in Table 3-1 and plotted in Figure 3-1; the NOAELs for histological alterations in the brain were not recorded in the LSE table because this is not a sensitive indicator of functional neurotoxicity.

3.2.1.5 Reproductive Effects

Compared to 352 local female construction workers in which the spontaneous abortion rate was 8.5%, an increase in spontaneous abortions to 15.9% was observed among 356 women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). Exposure concentrations were 0.08–0.196 mg Ni/m^3, primarily as nickel sulfate, and nickel concentrations in the urine were 3.2–22.6 μg/L. Nickel levels in the urine of persons not occupationally exposed are generally <0.1–13.3 μg/L (Sunderman 1993). The investigators noted that the nickel-exposed women manually lifted heavy nickel anodes and that they may have experienced heat stress.

Testicular degeneration was observed in rats and mice exposed to nickel sulfate (≥1.4 mg Ni/m^3) and nickel subsulfide (≥1.83 mg Ni/m^3 for rats and ≥3.65 mg Ni/m^3 for mice) 6 hours/day for 12 days over a 16-day period (NTP 1996a, 1996b, 1996c). The study authors indicated that testicular lesions were probably the result of emaciation rather than a direct effect of nickel. In intermediate-duration studies, sperm concentration was decreased by 21% in rats exposed to nickel oxide at 7.9 mg Ni/m^3, with no effects at 3.9 mg/m^3 (NTP 1996a). No effects on sperm motility, morphology, or concentration were

observed in rats exposed to nickel subsulfide or nickel sulfate at concentrations up to 1.83 and 0.44 mg Ni/m^3, respectively, or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 7.9, 1.83, or 0.44 mg Ni/m^3, respectively (NTP 1996a, 1996b, 1996c). Histological changes in the testes were not observed. No effect on the length of the estrous cycle was noted in mice or rats exposed to nickel sulfate at ≤0.44 mg Ni/m^3, nickel oxide at ≤7.9 mg Ni/m^3, or nickel subsulfide at ≤1.83 mg Ni/m^3 6 hours/day, 5 days/week, for 13 weeks (NTP 1996a, 1996b, 1996c). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg Ni/m^3, respectively, and exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg Ni/m^3, respectively, did not result in microscopic changes in the reproductive organs (NTP 1996a, 1996b, 1996c).

The highest NOAEL values from each reliable study for reproductive effects in each species, duration category, and nickel compound and the LOAEL for decreased sperm concentration in rats exposed to nickel oxide are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

Compared to 342 local female construction workers in which the structural malformation rate was 5.8%, an increase in structural malformations to 16.9% was observed among 356 women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). Although the specific structural malformations found were not stated, the investigators state that relative risks were 2.9 for all kinds of defects, 6.1 for cardiovascular system defects, and 1.9 for musculoskeletal defects. Exposure concentrations were 0.08–0.196 mg Ni/m^3, primarily as nickel sulfate, and nickel concentrations in the urine were 3.2–22.6 μg/L. Nickel levels in the urine of persons not occupationally exposed are generally <0.1–13.3 μg/L (Sunderman 1993). The investigators noted that the nickel-exposed women manually lifted heavy nickel anodes and that they may have experienced heat stress. Thus, a causative relationship between nickel exposure and developmental toxicity cannot be established from this study.

A decrease in fetal body weight was observed in the offspring of rats exposed to 1.6 mg Ni/m^3 as nickel oxide 23.6 hours/day on gestation days 1–21 (Weischer et al. 1980). No effect on fetal body weight was observed at 0.8 mg Ni/m^3, although decreased maternal body weight gain was observed at this concentration. No effects on the number of fetuses or on the weight of placenta were observed.

The NOAEL value and the LOAEL value from the Weischer et al. (1980) study are recorded in Table 3-1 and plotted Figure 3-1.

3.2.1.7 Cancer

Epidemiology studies of workers exposed to nickel have demonstrated a carcinogenic effect. Most studies of nickel-exposed workers are confounded, however, because exposure is to impure nickel compounds that often contain relatively high concentrations of other metals, including arsenic, which is also a carcinogen. Many nickel-exposed workers are also exposed to irritant gases including hydrogen sulfide, ammonia, chlorine, and sulfur dioxide (IARC 1990). Lung and nasal cancer were the forms of cancer in the nickel-exposed workers (Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; Magnus et al. 1982). The workers were primarily exposed to nickel refinery dust (Chovil et al. 1981; Doll et al. 1977). In one cohort of 1,916 refinery workers, the ratio of observed to expected deaths was 7:1 for lung cancer and 40:1 for nasal cancer (Pedersen et al. 1973).

In an analysis of 100 cases of nasal cancers in male nickel refinery workers, the cancers were primarily squamous cell carcinomas (48%), anaplastic and undifferentiated carcinomas (39%), and adenocarcinomas (6%) (Sunderman et al. 1989a). This distribution was comparable to that found in the general population. Higher concentrations of nickel were found in the nasal mucosa of active and retired workers compared to unexposed controls, and the nickel was cleared from the nasal mucosa with an estimated half-life of 3.5 years (Torjussen 1985; Torjussen and Andersen 1979). In an analysis of 259 cases of lung cancer in nickel refinery workers, the cancers were primarily squamous cell carcinomas (67%), anaplastic, small cell, and oat cell carcinomas (15%), and adenocarcinomas (8%) (Sunderman et al. 1989a). Compared to the general population, the workers had a greater incidence of squamous cell carcinomas and fewer adenocarcinomas. In the general population, lung cancer in women is more likely to be adenocarcinoma. Therefore, rather than indicating nickel-specific tumor types, these data may reflect the lack of women in the cohort of nickel workers and temporal trends over the 60 years during which the tumors were diagnosed (Sunderman et al. 1989a). The number of refinery workers with lung cancer that were women was not stated.

The latency period for the lung cancer has been found to be shorter than for nasal cancer. In a cohort of 2,247 refinery workers, an excess of lung cancer was found by 3–14 years after first employment, while an increase in nasal cancer was not found until 15–24 years after first employment (Magnus et al. 1982). The risk of respiratory tract cancers markedly decreased when the date of first exposure was later than

≈1930 (Doll et al. 1970, 1977; Pedersen et al. 1973). This was a result of reducing nickel dust exposure by altering the machinery used in the refining process and by the use of cotton face pads by the workers (Doll et al. 1977). The interaction between smoking and nickel exposure for the development of respiratory tract cancer was found to be additive rather than multiplicative (Magnus et al. 1982).

In a reanalysis of most of the epidemiology studies of nickel workers (discussed in the previous paragraphs), it was found that lung and nasal cancers were related primarily to exposure to less-soluble compounds at concentrations of ≥10 mg Ni/m^3 (primarily oxidic and sulfidic compounds) (International Committee on Nickel Carcinogenesis in Man 1990). A higher incidence of lung and nasal cancer was observed among workers exposed to both soluble and less-soluble nickel compounds, compared to those exposed to less-soluble nickel compounds alone, indicating an effect of soluble nickel, or an interaction between soluble and less-soluble nickel compounds. The effect of soluble nickel compounds was observed at concentrations of >1 mg Ni/m^3. No evidence was found that metallic nickel induces respiratory cancer. After reanalysis of all the data, the International Committee on Nickel Carcinogenesis in Man (1990) concluded that inhalation exposure to nickel compounds was not associated with cancers other than those of the lungs and nasal cavity.

In general, studies published after this re-analysis have supported these conclusions. Anttila et al. (1998), found a significant increase in the incidence of lung and tracheal cancer among nickel smelter workers with a latency period of 20 years; these workers were primarily exposed to soluble nickel compounds. Among nickel refinery workers primarily exposed to nickel sulfate, significant increases in the incidence of nasal cancer and lung cancer with a 20-year latency were observed (Antilla et al. 1998). A case control study by Grimsrund et al. (2002) found significant increases in smoking-adjusted lung cancer risks in workers with the highest cumulative exposures to water-soluble nickel compounds, a mixture of sulfidic nickel compounds, a mixture of oxidic nickel compounds, or metallic nickel. When the odds ratios were adjusted for smoking and exposure to water-soluble nickel, the odds ratios for sulfidic nickel, oxidic nickel, and metallic nickel were no longer statistically significant. Another study of the same population of workers (Grimsrud et al. 2003) found employment duration-related increases in lung cancer risks as compared to national population values and an internal control group. Additionally, a dose-response relationship between lung cancer risk and cumulative exposure to either total nickel or water-soluble nickel was found.

An increase in the incidence of respiratory cancer has not been observed in males living in New Caledonia, where about a quarter of the male population aged 25–70 either works or has worked in nickel

mining or refining (Goldberg et al. 1994). The investigators suggested that the reason for the lack of an effect was that these workers were exposed to lower concentrations of nickel (<2 mg/m^3) than other refinery workers, and the nickel was primarily in the form of nickel silicate oxide ore and negligible exposure to nickel subsulfide.

In a population of sinter plant workers, the risk of death from cancer of the lung or nose has not been shown to decrease even 30–40 years after the workers left the sinter plant (Muir et al. 1994). Although the workers left the sintering operation, many were still exposed to nickel compounds, in operations that have not been associated with cancer. The investigators note that persisting nickel deposits could act as carcinogenic agents.

In addition to these findings on nasal and lung cancer, several studies have also found significant increases in the occurrence of nonrespiratory tract cancer. Significant increases in the incidence of stomach cancer were observed among nickel refinery workers predominantly exposed to nickel sulfate (Antilla et al. 1998) and nickel platers (Pang et al. 1996). A meta-analysis of occupational exposure studies on pancreatic cancer (Ojajärvi et al. 2000) found a significant association between exposure to nickel and nickel compounds and pancreatic cancer risk.

The concentration of 1 mg Ni/m^3 as soluble nickel compounds and 10 mg Ni/m^3 as less-soluble nickel compounds are presented as human Cancer Effect Levels for lung and nasal cancers in Table 3-1 and Figure 3-1.

Acute (6 hours/day, 5 days/week, for 1 month) inhalation exposure to ≤6.3 mg Ni/m^3 as nickel oxide resulted in no significant increase in lung cancer in rats ≤20 months after exposure (Horie et al. 1985). Chronic (6 hours/day, 5 days/week, for 78 weeks) exposure to nickel subsulfide, however, resulted in an increase in lung tumors in rats exposed to 0.7 mg Ni/m^3 (Ottolenghi et al. 1974). The tumors included adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcoma. No increase in lung tumors was observed in mice following weekly intratracheal injections of ≤0.8 mg Ni/m^3 as nickel subsulfide for ≤15 weeks, followed by observation for ≤27 months (Fisher et al. 1986; McNeill et al. 1990). Tumor incidence may not have increased because of efficient clearance of nickel from the lungs and early repair of lung lesions following intratracheal administration (Fisher et al. 1986).

Two-year inhalation carcinogenicity bioassays have shown nickel oxide and nickel subsulfide to be carcinogenic in rats resulting in alveolar/bronchiolar adenomas and carcinomas, and benign and

malignant pheochromocytomas of the adrenal medulla (NTP 1996a, 1996b). In mice, there was no evidence of a carcinogenic effect of nickel subsulfide in either gender, no evidence of a carcinogenic effect of nickel oxide in males, and equivocal evidence of carcinogenic activity of nickel oxide in females based on observations of alveolar/bronchiolar adenomas and carcinomas. Nickel sulfate was not carcinogenic in either rats or mice (NTP 1996c). The tumor incidences and the exposure concentrations used in these studies are shown in Table 3-2 for rats and Table 3-3 for mice. The nickel concentrations as nickel subsulfide and nickel oxide resulting in cancer in rats are presented as Cancer Effect Levels in Table 3-1 and Figure 3-1.

The Department of Health and Human Services (NTP 2002) has determined that metallic nickel may reasonably be anticipated to be a human carcinogen and that nickel compounds are known to be human carcinogens. Similarly, IARC (1990) classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). EPA has classified nickel refinery dust and nickel subsulfide in Group A (human carcinogen) (IRIS 2003). Other nickel compounds have not been classified by the EPA. Based on the occupational data, inhalation unit risk levels of 2.4×10^{-4} $(\mu g/m^3)^{-1}$ and 4.8×10^{-4} $(\mu g/m^3)^{-1}$ were derived for nickel refinery dust and nickel subsulfide, respectively (IRIS 2003). The risk levels for these compounds are presented in Figure 3-1. The risk levels range from 4×10^{-1} to 4×10^{-4} $\mu g/m^3$ for a risk ranging from 1×10^{-4} to 1×10^{-7}, respectively, for nickel refinery dust (IRIS 2003) and 2×10^{-1} to 2×10^{-4} $\mu g/m^3$ for a risk ranging from 1×10^{-4} to 1×10^{-7}, respectively, for nickel subsulfide (IRIS 2003). These risk levels are presented in Figure 3-1.

3.2.2 Oral Exposure

3.2.2.1 Death

One human death following oral exposure to nickel was reported (Daldrup et al. 1983). Nickel sulfate crystals (rough estimate of 570 mg Ni/kg) were accidentally ingested by a 2-year-old child. Four hours after ingestion, cardiac arrest occurred, and the child died 8 hours after exposure.

Single-dose oral lethality studies indicate that soluble nickel compounds are more toxic than less-soluble nickel compounds. Oral LD_{50} values of 46 or 39 mg Ni/kg as nickel sulfate in male and female rats (Mastromatteo 1986) and 116 and 136 mg Ni/kg as nickel acetate in female rats and male mice, respectively (Haro et al. 1968) have been reported for soluble nickel compounds. In contrast, the oral

Table 3-2. Alveolar/Bronchiolar Neoplasms and Adrenal Medulla Proliferative Lesions in Rats[a]

	Number of rats with neoplasms or proliferative lesions/number of rats examined										
	Exposure to nickel sulfate hexahydrate (mg nickel/m^3)				Exposure to nickel subsulfide (mg nickel/m^3)			Exposure to nickel oxide (mg nickel/m^3)			
Effect	0	0.03	0.06	0.11	0	0.11	0.73	0	0.5	1	2
Male											
Alveolar/ brochiolar adenoma/ carcinoma	2/54	0/53	1/53	3/53	0/53	6/53[b]	11/53[c]	1/54	1/53	6/53[d]	4/52[d]
Adrenal medulla benign or malignant pheochromo-cytoma	16/54	19/55	13/55	12/55	14/53	30/53[c]	42/53[c]	27/54	24/53	27/53	35/54[c]
Female											
Alveolar/ brochiolar adenoma/ carcinoma	0/52	0/53	0/53	1/54	2/53	6/53[d]	9/53[b]	1/53	1/53	6/53d	5/54[d]
Adrenal medulla benign or malignant pheochromo-cytoma	2/52	4/53	2/53	3/54	3/53	7/53	36/53[c]	4/53	7/53	6/53	18/54[c]

[a]modified from Dunnick et al. 1995
[b]$p \leq 0.05$
[c]$p \leq 0.01$
[d]$p \leq 0.05$ versus historical data (1.4%, 3/210 males; 1.4%, 4/208 females)

Table 3-3. Alveolar/Bronchiolar Neoplasms in Mice[a]

	Number of rats with tumors/number of rats examined										
	Exposure to nickel sulfate hexahydrate (mg nickel/m^3)				Exposure to nickel subsulfide (mg nickel/m^3)			Exposure to nickel oxide (mg nickel/m^3)			
Effect	0	0.06	0.11	0.22	0	0.44	0.88	0	1	2	3.9
Male	13/61	18/61	7/62	8/61	13/61	5/59	6/58	9/57	14/67	15/66	14/69
Female	7/61	6/60	10/60	1/60	9/58	2/59	3/60	6/64	15/66[b]	12/63	8/64

[a]modified from Dunnick et al. 1995
[b]$p \leq 0.05$

LD_{50} values in rats for less-soluble nickel oxide and subsulfide were >3,930 and >3,665 mg Ni/kg, respectively (Mastromatteo 1986).

Rats died after gavage treatment for 91 days with 8.6 (6/52) or 25 (60/60) mg Ni/kg/day as nickel chloride hexahydrate (American Biogenics Corporation 1988). Clinical signs observed included lethargy, ataxia, irregular breathing, hypothermia, salivation, squinting, and loose stools. As part of a longer-term study, rats were provided with drinking water containing 1,000 ppm nickel as nickel chloride (approximately 140 mg/kg/day) (RTI 1988a). Within 2 weeks, 7/62 died and the dose was eliminated from the study. In other studies, no deaths were observed in rats to doses up to 92 mg Ni/kg as nickel chloride in drinking water for 15 days (RTI 1985) or 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999); no deaths were observed in mice provided with nickel sulfate in the drinking water at doses up to 150 mg Ni/kg/day for 180 days (Dieter et al. 1988).

In a multigeneration study (RTI 1988a, 1988b) in which rats were treated with nickel chloride in the drinking water, the death of female rats from pregnancy complications at the time of delivery suggests that females are more susceptible to nickel toxicity during parturition. Although the number of deaths was not significantly above controls and not clearly dose related (P_0: 0/31 in controls, 1/31 at 7 mg/kg/day, 3/30 at 30 mg/kg/day, and 3/31 at 55 mg/kg/day; F_1: 0/30 at 0 and 7 mg/kg/day, 3/30 at 30 mg/kg/day, and 1/30 at 55 mg/kg/day), death in dams during delivery is a relatively rare event. The results of this study (RTI 1988a, 1988b) are confounded by a decrease in food and water intake observed in the exposed animals. Deaths in offspring before weaning have also been reported in multigeneration, multilitter studies (RTI 1988a, 1988b; Schroeder and Mitchener 1971; Smith et al. 1993). Because cross-fostering studies have not been completed, it is not possible to know if the pre-weaning deaths are a result of an inherent defect in the pups, nickel exposure through the milk, or a change in the quality or quantity of the milk produced by the dam (Smith et al. 1993).

An increase in mortality was not observed in chronic studies in rats or dogs fed nickel sulfate in the diet at doses up to 188 mg/kg/day for rats and 62.5 mg/kg/day for dogs (Ambrose et al. 1976). In mice provided with 0.95 mg/Ni/kg as nickel acetate in drinking water until death (last death at 991 days for males and 904 days for females), an increase in life expectancy was observed (Schroeder and Mitchener 1975).

Oral LD_{50} values and all LOAEL values from each reliable study for death in each species and duration category are recorded in Table 3-4 and plotted in Figure 3-2.

Table 3-4 Levels of Significant Exposure to Nickel - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Fischer- 344)	once (G)				120 M (LD50) 116 F (LD50)	Haro et al. 1968 acetate
2	Rat (Sprague-Dawley)	once (G)				46 M (LD50) 39 F (LD50)	Mastromatteo 1986 sulfate
3	Rat (CD)	14d (W)				140 (7/64 died)	RTI 1988a, 1988b chloride
4	Mouse (Swiss-Webster)	once (G)				136 M (LD50) 139 F (LD50)	Haro et al. 1968 acetate
Systemic							
5	Human	2 d 2x/d (C)	Dermal	0.03			Burrows et al. 1981 sulfate
6	Human	once or 1 dose for 2 d (C)	Dermal	0.043 F	0.097 F (allergic dermatitis in sensitized individuals)		Gawkrodger et al. 1986 sulfate
7	Human	1 d (W)	Gastro		7.1 M (vomiting, cramps, diarrhea)		Sunderman et al. 1988 sulfide/chloride
8	Dog (Beagle)	3 days (F)	Gastro	25	62.5 (vomiting)		Ambrose et al. 1976 sulfate

Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
9	Human	1 d (W)			7.1 M (giddiness, headache, weariness)		Sunderman et al. 1988 sulfate/chloride
	Reproductive						
10	Mouse (Iacca)	once (GW)			23 M (3.7-fold increase in sperm head abnormalities)		Sobti and Gill 1989 nitrate
	Developmental						
11	Mouse (CD-1)	Gd 8-12 1x/day (G)		45.3			Gray et al. 1986 chloride
12	Mouse	Gd 8-12 (GW)		90.6			Seidenberg et al. 1986 chloride
	INTERMEDIATE EXPOSURE						
	Death						
13	Rat (Sprague-Dawley)	91 d daily (GW)				8.6 (6/52 died)	American Biogenics Corp 1988 chloride
	Systemic						
14	Human	91-178 d (W)	Dermal	0.02 F			Santucci et al. 1994 sulfate

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
15	Rat (Sprague-Dawley)	91 d daily (GW)	Resp		8.6 (pneumonitis)		American Biogenics Corp 1988 chloride
			Cardio	8.6			
			Gastro	8.6		25 (ulcerative gastritis and enteritis)	
			Hemato	1.2 F	8.6 F (increased platelet count)		
			Hepatic	8.6			
			Renal	8.6			
			Dermal	8.6			
			Ocular	8.6			
			Bd Wt	1.2 F	8.6 F (12% decrease in body weight gain)		
			Metab	1.2 F	8.6 F (decreased blood glucose level)		

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
16	Rat (Sprague-Dawley)	daily 13 weeks (W)	Resp		5.75 M (decreased alkaline phosphatase activity in bronchioalveolar lavage fluid)		Obone et al. 1999 sulfate
			Cardio	28.8 M			
			Gastro	28.8 M			
			Hepatic	28.8 M			
			Renal	5.75 M	14.4 M (increased realtive kidney weight, decreased urine volume and urine glucose)		
			Bd Wt	28.8 M			
17	Rat (CD)	F: 27-30 wk M:21-24 wk (W)	Resp	4 M	20 M (histiocytic cellular infiltration in lungs in F1 generation)		RTI 1988a, 1988b chloride
18	Rat (Long- Evans)	11 wk breeding-lactation 2 litters (W)	Endocr	6.8 F	31.6 F (21% decreased prolactin)		Smith et al. 1993 chloride
			Bd Wt	31.6 F			
19	Rat (Wistar)	3 or 6 mo (W)	Renal		7.6 F (increased urinary albumin)		Vyskocil et al. 1994b sulfate
			Bd Wt	7.6 F			

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
20	Rat (Wistar)	28 d (W)	Hemato	0.97 M			Weischer et al. 1980 chloride
			Hepatic	0.97 M			
			Renal	0.97 M			
			Bd Wt		0.23 M (20% decreased body weight gain)		
			Metab		0.23 M		
21	Rat (OSU brown)	6 wk (F)	Hemato	5 M	25 M (10% decreased hemoglobin)		Whanger 1973 acetate
			Bd Wt	5 M		25 M (88% decrease in body weight gain)	
22	Mouse (B6C3F1)	180 d daily (W)	Hepatic	150 F			Dieter et al. 1988 sulfate
			Renal	44 F	108 F (minimal convoluted tubular damage)		
			Bd Wt	44 F	108 F (body weight 10% lower than controls)	150 F (body weight 26% lower than controls)	
	Immuno/ Lymphoret						
23	Rat (Sprague-Dawley)	daily 13 weeks (W)		5.75 M	14.4 M (alterations in spleen and thymus lymphocyte T-cell and B-cell subpopulations)		Obone et al. 1999 sulfate

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
24	Mouse (B6C3F1)	180 d daily (W)			44 F (mild thymic atrophy, impaired B-cell immune function, decreased granulocyte macrophage progenitor cell levels)		Dieter et al. 1988 sulfate
25	Mouse (BALB/c)	10-11wk (W)			20.3 F (enhanced inflammatory response in the hearts of mice challenged with coxsackie virus B3)		Ilback et al. 1994 chloride
	Neurological						
26	Rat (Sprague-Dawley)	91 d daily (GW)		1.2		8.6 (ataxia, prostation, hypothermia)	American Biogenics Corp 1988 chloride
	Reproductive						
27	Rat (Wistar)	about 24 wk (F)		90			Ambrose et al. 1976 sulfate
28	Rat (Wistar)	daily 62 days (W)		13 F			Kakela et al. 1999 chloride
29	Rat (Wistar)	daily 28 or 42 days (W)				3.6 M (decreased fertility)	Kakela et al. 1999 chloride
30	Rat (Wistar)	daily 28–76 days (W)				3.6 (decreased fertility)	Kakela et al. 1999 chloride

Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
31	Rat (Sprague-Dawley)	daily 13 weeks (W)		28.8 M			Obone et al. 1999 sulfate
32	Rat (CD)	F: 27-30 wk M:21-24 wk (W)		7 F	30 F (increased gestation length in first P0 pregnancy)		RTI 1988a, 1988b chloride
33	Rat (Long- Evans)	11 wk breeding-lactation 2 litters (W)		31.6			Smith et al. 1993 chloride
34	Mouse (NS)	5 days/week 35 days (GW)		1.1 M	2.2 M (decreased sperm mobility; increased sperm abnormalities)		Pandey and Srivastava 2000 sulfate
35	Mouse (NS)	5 days/week 35 days (GW)		1.2 M	2.5 M (decreased sperm motility and count; increased sperm abnormalities)		Pandey and Srivastava 2000 chloride
36	Mouse (Swiss)	5 days/week 35 days (GW)			1.1 M (sperm abnormalities; histological alterations in cauda epididymides and seminal vesicles)		Pandey et al. 1999 sulfate
37	Mouse (Swiss)	5 days/week 35 days (GW)				2.2 M (decreased fertility)	Pandey et al. 1999 sulfate

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Developmental						
38	Rat (Wistar)	about 24 wk (F)				22.5 (increased number of stillborns)	Ambrose et al. 1976 sulfate
39	Rat (Wistar)	daily 62 days (W)		4 F		13 F (decreased litter size and pup survival)	Kakela et al. 1999 chloride
40	Rat (Wistar)	daily 28 or 42 days (W)				3.6 M (decreased pup viability and survival)	Kakela et al. 1999 chloride
41	Rat (Wistar)	daily 28–76 days (W)				3.6 (increased fetal mortality and decreased pup survival)	Kakela et al. 1999 chloride
42	Rat (CD)	F: 27-30 wk M:21-24 wk (W)		7 M		30 M (increased mortality in F1b rats on pnd 22-42; decreased pup body weight in F1b rats)	RTI 1988a, 1988b chloride
43	Rat (Long- Evans)	11 wk breeding-lactation 2 litters (W)				1.3 (decreased pup survival)	Smith et al. 1993 chloride
44	Mouse (CD-1)	Gd 2-17 (W)		80		160 (increased spontaneous abortions)	Berman and Rehnberg 1983 chloride

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
CHRONIC EXPOSURE							
Systemic							
45	Rat (Wistar)	2 yrs (F)	Resp	187.5			Ambrose et al. 1976 sulfate
			Cardio	187.5			
			Gastro	187.5			
			Hemato	187.5			
			Musc/skel	187.5			
			Hepatic	187.5			
			Renal	187.5			
			Endocr	187.5			
			Dermal	187.5			
			Bd Wt	7.5	75 (10-18% decreases in body weight gain)	187.5 (27-29% decreased body weight gain)	

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
46	Dog (Beagle)	2 yrs (F)	Resp	25		62.5 (cholesterol granulomas, emphysema, bronchiolectasis)	Ambrose et al. 1976 sulfate
			Cardio	62.5			
			Gastro	62.5			
			Hemato	25	62.5 (decreased hematocrit and hemoglobin levels)		
			Musc/skel	62.5			
			Hepatic	62.5			
			Renal	25	62.5 (polyuria in 2/6 dogs, increased kidney weight)		
			Endocr	62.5			
			Dermal	62.5			
			Bd Wt	25	62.5 (10% decrease in body weight gain)		
	Immuno/ Lymphoret						
47	Rat (Wistar)	2 yrs (F)		187.5			Ambrose et al. 1976 sulfate
48	Dog (Beagle)	2 yrs (F)		62.5			Ambrose et al. 1976 sulfate
	Neurological						
49	Rat (Wistar)	2 yrs (F)		187.5			Ambrose et al. 1976 sulfate

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Table 3-4 Levels of Significant Exposure to Nickel - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
50	Dog (Beagle)	2 yrs (F)		62.5			Ambrose et al. 1976 sulfate

a The number corresponds to entries in Figure 3-2.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; (GW) = gavage in water; hemato = hematological; Immuno = immunological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; Ni = nickel; NOAEL = no-observed-adverse-effect level; Resp = respiratory; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

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Figure 3-2. Levels of Significant Exposure to Nickel- Oral

Acute (≤14 days)

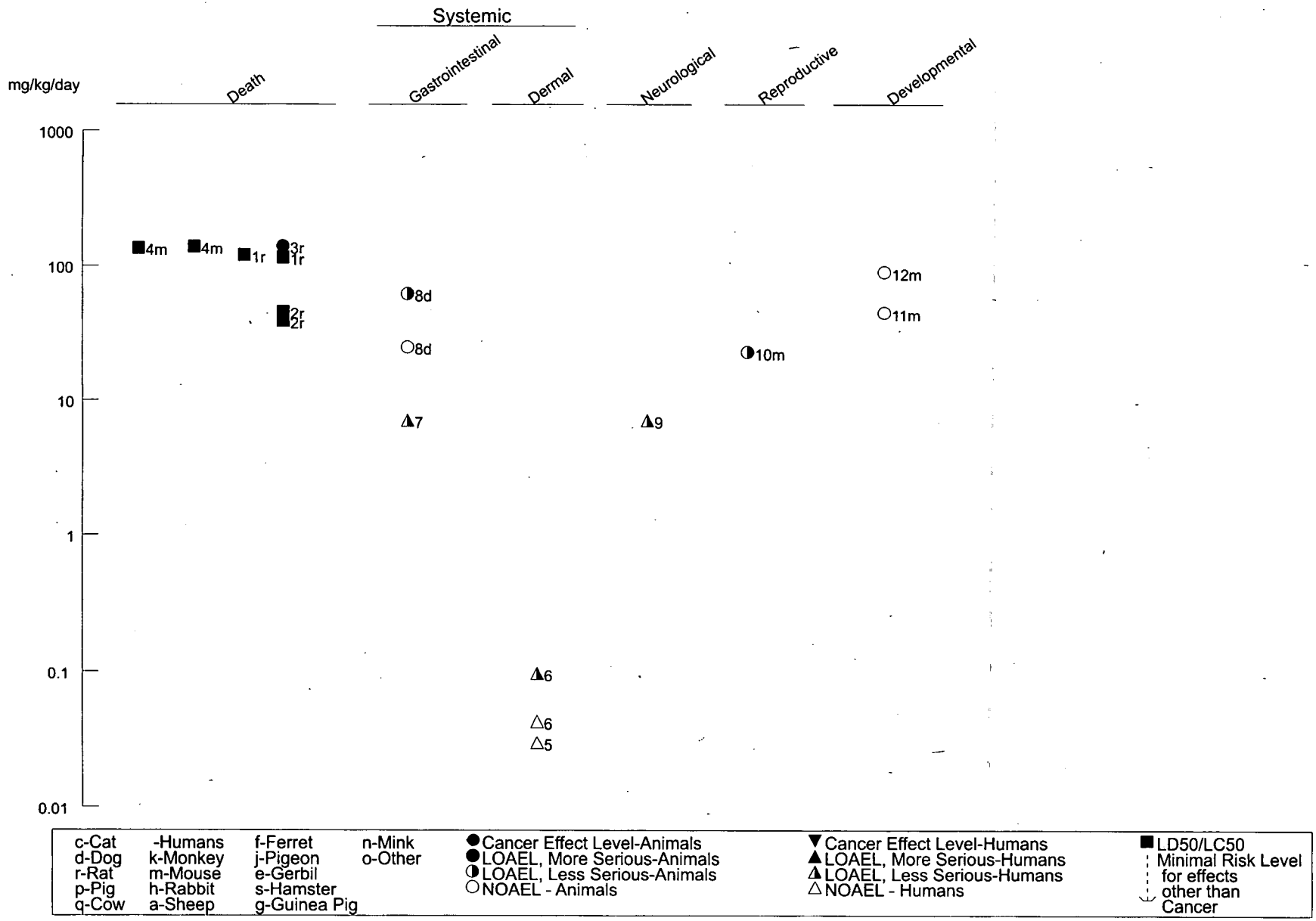

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Figure 3-2. Levels of Significant Exposure to Nickel- Oral (*Continued*)

Intermediate (15-364 days)

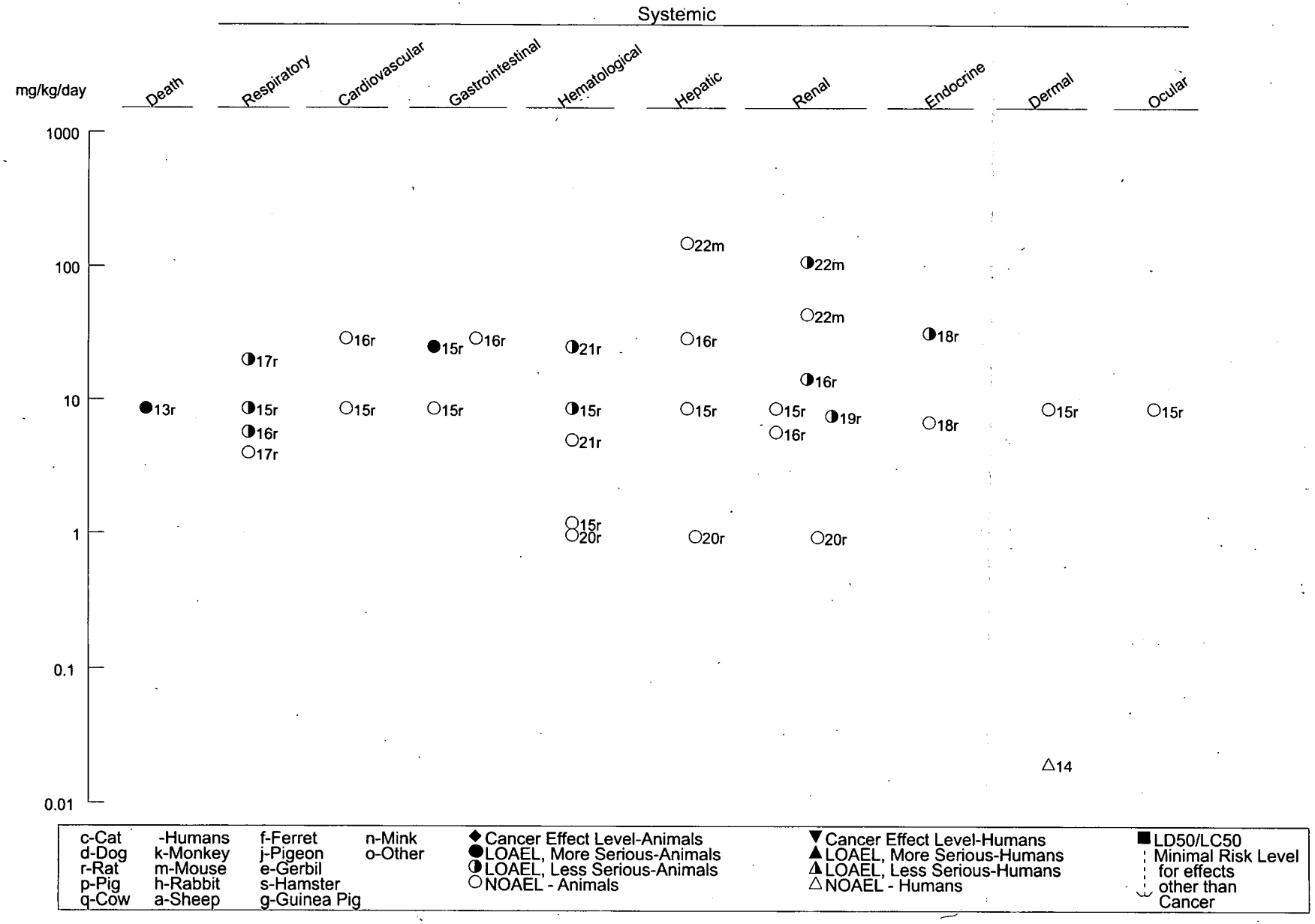

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Figure 3-2. Levels of Significant Exposure to Nickel- Oral (*Continued*)

Intermediate (15-364 days)

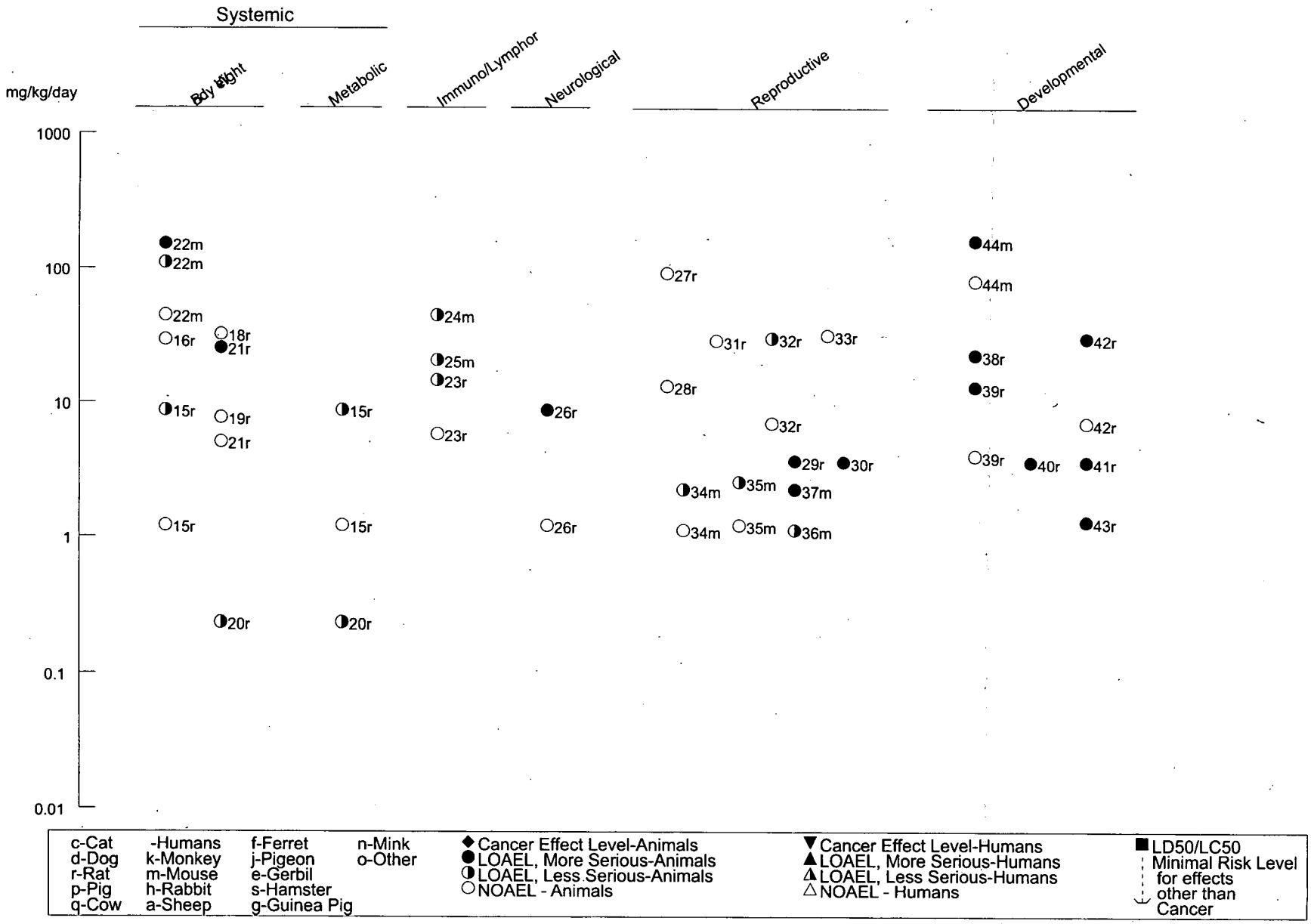

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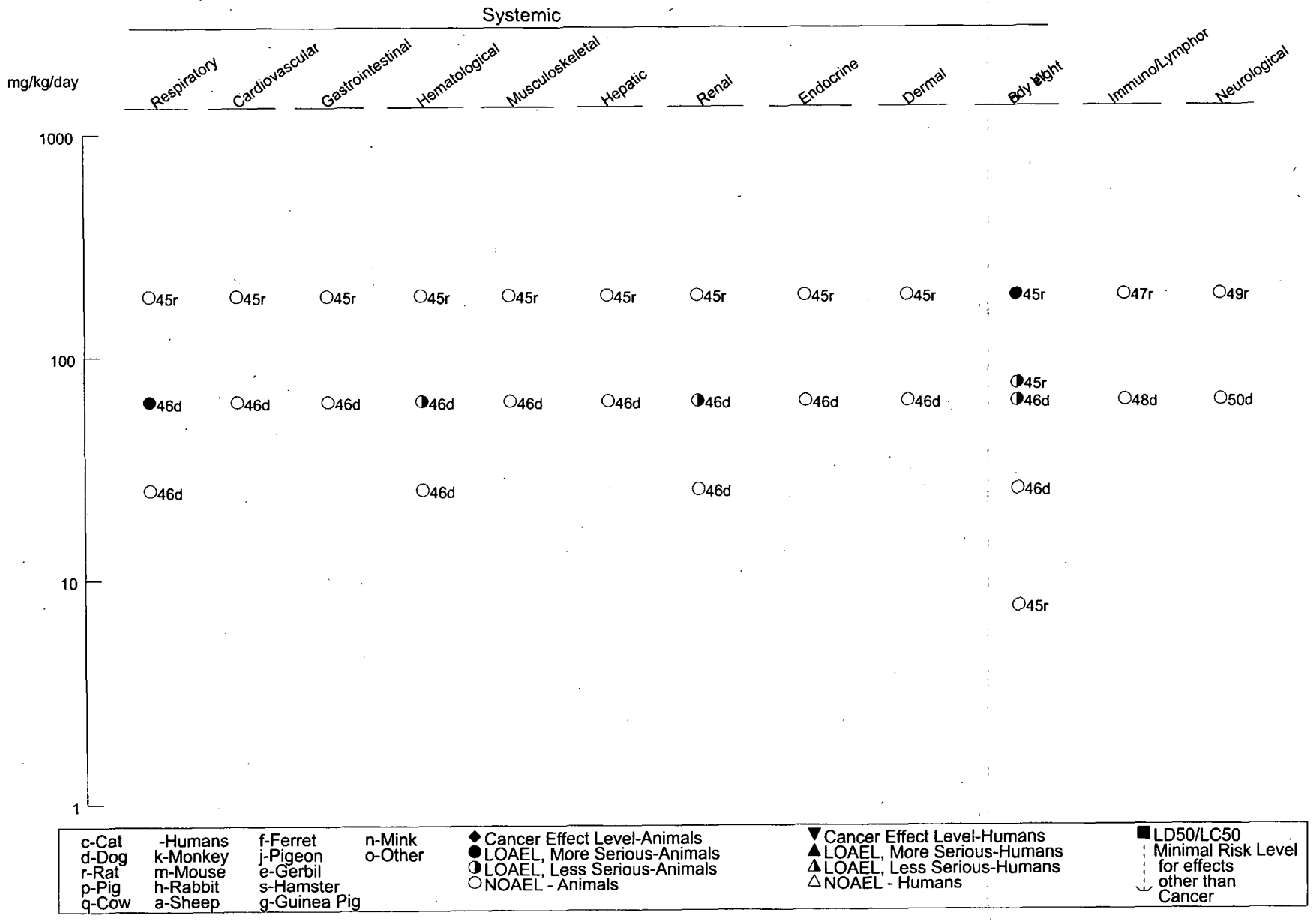
Figure 3-2. Levels of Significant Exposure to Nickel- Oral (*Continued*)

Chronic (≥365 days)



3.2.2.2 Systemic Effects

No studies were located regarding metabolic effects in humans or animals after oral exposure to nickel. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects for each species, duration category, and nickel compound are recorded in Table 3-4 and plotted in Figure 3-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to nickel.

Pneumonitis was observed in 6/19 male rats and 9/17 female rats treated for 91 days by gavage with 8.6 mg Ni/kg/day as nickel chloride (American Biogenics Corporation 1988). Significant increases in absolute and relative lung weights were observed in rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999). This study also found alterations in enzyme activity in bronchoalveolar lavage (BAL) fluid and lung tissues, including increases in protein levels in BAL fluid at 14.4 mg Ni/kg/day and higher, decreases in alkaline phosphatase activity in BAL fluid at 5.75 mg Ni/kg/day and higher, and decrease in alkaline phosphatase activity in lung tissue at 28.8 mg Ni/kg/day. No histological alterations were observed in the lungs. The study authors suggested that the decrease in alkaline phosphatase activity was indicative of decreased activity of type II alveolar cells and the increased total protein was indicative of increased air-blood barrier permeability. In a multigeneration study (RTI 1988a, 1988b), increased lung weights were observed in rats provided with nickel chloride in the drinking water at 55 mg Ni/kg/day, and an increase in cellular infiltration of the lungs was observed at 20 mg Ni/kg/day. This study is confounded by decreased food and water intake observed in exposed animals. Emphysema, bronchiolectasis, and cholesterol granulomas were also observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years, but not in rats exposed at up to 187.5 mg/kg/day for 2 years (Ambrose et al. 1976).

Cardiovascular Effects. Nickel sulfate crystals (rough estimate of 570 mg Ni/kg) were accidentally ingested by a 2-year-old child (Daldrup et al. 1983). Four hours after ingestion, cardiac arrest occurred, and the child died 8 hours after exposure.

Rats exposed to 8.6 mg Ni/kg/day as nickel chloride for 91 days had decreased heart weight (American Biogenics Corporation 1988), whereas rats exposed to 75 mg Ni/kg/day as nickel sulfate for 2 years had increased heart weight (Ambrose et al. 1976). Because the changes in heart weight were not accompanied by histological changes and decreases in body weight gain were also observed, the significance of these

changes is not known. Histological changes in the heart were not observed in rats treated with nickel chloride in the drinking water at 40 mg/kg/day for up to 30 weeks (RTI 1988a), rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water (Obone et al. 1999), or rats exposed to 187.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976), or dogs provided with nickel sulfate in the diet at a dose of 62.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976).

Gastrointestinal Effects. Symptoms of gastrointestinal distress were reported by workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The symptoms included nausea (15 workers), abdominal cramps (14 workers), diarrhea (4 workers), and vomiting (3 workers). Although the actual contribution of boric acid to these effects is not known, the investigators (Sunderman et al. 1988) indicate that the intake of 20–200 mg boric acid probably did not contribute to the observed effects because the effects of boric acid are generally observed only following ingestion of ≥4 g by adults.

Gastrointestinal effects were observed in rats that died following treatment by gavage with 25 mg Ni/kg/day as nickel chloride hexahydrate for up to 91 days (American Biogenics Corporation 1988). The effects included discolored gastrointestinal contents, ulcerative gastritis, and enteritis. Discolored (green) gastrointestinal contents were also observed at 1.2 and 8.6 mg/kg/day. The discoloration may have been due to the presence of nickel chloride in the gastrointestinal tract and is not considered an adverse effect. Adverse gastrointestinal effects were not observed in rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 13 weeks (Obone et al. 1999) or rats treated with nickel sulfate in the diet at 187.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976). During the first 3 days of a 2-year study, dogs vomited following treatment with nickel sulfate in the diet at 62.5 mg Ni/kg/day (Ambrose et al. 1976). The dose was lowered to 37.5 mg Ni/kg/day for 2 weeks, and then incrementally raised at 2-week intervals back to 62.5 mg/kg/day, at which time, no further gastrointestinal distress was noted. These studies indicate that high doses of nickel can be irritating to the gastrointestinal tract, although acclimation to high levels of dietary nickel can occur. The difference in the results of the American Biogenics Corporation (1988) and Ambrose et al. (1976) studies in rats is probably a result of the different routes of exposure; gavage treatment results in higher concentrations of nickel in the gastrointestinal tract than treatment in the diet.

Hematological Effects. A transient increase in blood reticulocytes was observed in workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Rat studies have indicated that intermediate-duration exposure to ≥0.7 mg Ni/kg/day as various nickel salts causes hematological effects. Effects included a decrease in hemoglobin in rats exposed to 25 mg Ni/kg/day as nickel acetate in the diet for 6 weeks (Whanger 1973), an increase in leukocyte levels in rats exposed to 0.49 mg Ni/kg/day as nickel chloride in drinking water for 28 days, but not at 0.97 mg Ni/kg/day (Weischer et al. 1980), and an increase in platelet counts in rats administered via gavage 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988). No hematological effects were observed in rats treated with nickel sulfate in the diet at a dose of 187.5 mg Ni/kg/day for 2 years (Ambrose et al. 1976). Low hematocrit levels were observed in dogs after chronic dietary exposure to 62.5 mg Ni/kg/day as nickel sulfate (Ambrose et al. 1976).

Musculoskeletal Effects. Muscular pain was reported by one worker who drank water contaminated with nickel sulfate, nickel chloride, and boric acid during one work shift (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Microscopic changes in skeletal muscle were not observed in rats or dogs fed nickel sulfate in the diet at doses up to 187.5 mg Ni/kg/day for rats and 62.5 mg Ni/kg/day for dogs (Ambrose et al. 1976).

Hepatic Effects. A transient increase in serum bilirubin was observed in 3 of 10 workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). The workers who reported symptoms (20 of 35) or were hospitalized (10 of 35) were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Decreased liver weight was observed in rats exposed to 0.97–75 mg Ni/kg/day as nickel chloride or nickel sulfate for 28 days to 2 years (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; Weischer et al. 1980) and mice exposed to 150 mg Ni/kg/day as nickel sulfate in drinking

water for 180 days (Dieter et al. 1988). A significant increase in relative liver weight, however, was observed in dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate for 2 years (Ambrose et al. 1976). Because histological changes in the liver were not observed in these studies and decreases in body weight gain were often observed at the same dose levels, the significance of the liver weight changes is unclear.

Renal Effects. A transient increase in urine albumin was observed in 3 of 10 workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1–35.7 mg Ni/kg. The contribution of boric acid to these effects is not known.

Renal tubular damage at the corticomedullary junction described as minor was observed in mice exposed to ≥108 mg Ni/kg/day as nickel sulfate in the drinking water for 180 days (Dieter et al. 1988). The renal effects included the loss of renal tubular epithelial cells and the presence of hyaline casts in the tubule (suggesting protein loss). No changes in markers of renal tubular function (urinary lactate dehydrogenase, NAG, and β_2-microglobulin levels) were observed in rats exposed to nickel sulfate in the drinking water for 6 months at a concentration that supplied doses of 6.9 mg/kg/day for males and 7.6 mg/kg/day for females (Vyskocil et al. 1994b). Urinary albumin levels, a marker of glomerular barrier dysfunction, was significantly increased in nickel-exposed female rats. Albumin excretion also tended to be higher in male rats, but did not reach statistical significance because of two control rats with very high values. The investigators noted that male rats develop a spontaneous nephrosis as they age and that this may have obscured the effect of nickel. Significant decreases in urine volume and urine glucose levels and increases in relative kidney weight at 14.4 or 28.8 mg Ni/kg/day and increases in BUN at 28.8 mg Ni/kg/day were observed in rats exposed to nickel sulfate in drinking water for 13 weeks (Obone et al. 1999); no changes in γ-glutamyl transpeptidase activity, NAG levels, or histological alterations were observed.

In dogs, polyuria and increased kidney weight were observed after exposure to 62.5 mg Ni/kg/day as nickel sulfate for 2 years; however, renal effects were not observed in similarly treated rats (Ambrose et al. 1976). Several studies in rats have reported significant changes in kidney weights following exposure to 0.97–55 mg Ni/kg/day as nickel salts for 28 days to 9 months (American Biogenics Corporation 1988; RTI 1988b; Weischer et al. 1980). However, there was no consistency in direction of the change; some studies reported increases in kidney weights while others reported decreases. The toxicological significance of these data is not known.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to nickel.

Although histological changes were not observed, increases in pituitary weights were observed in male but not female rats treated with nickel chloride at doses ≥20 mg Ni/kg/day for up to 30 weeks (RTI 1986, 1988a, 1988b). The multigeneration study (RTI 1988a, 1988b) is confounded by a decrease in both food and water intake. Decreased prolactin levels were observed in female rats treated with 31 mg Ni/kg/day as nickel chloride in the drinking water throughout the breeding and lactation of two litters (11 weeks before breeding, 2-week rest period after weaning of the first litter, followed by a second breeding) but not at a 6.8-mg/kg/day dose (Smith et al. 1993). Histological examinations did not reveal any adverse effects in the pituitary, thyroid, and adrenal glands or in the pancreas of rats and dogs treated with nickel sulfate in the diet for 2 years at 187.5 mg Ni/kg/day for rats and 62.5 mg Ni/kg/day for dogs (Ambrose et al. 1976).

Dermal Effects. Contact dermatitis, which results from dermal exposure to nickel, is the most prevalent effect of nickel in the general population (see Section 3.2.3.2). Several studies indicate that a single oral dose of nickel given as nickel sulfate can result in a flare-up in the dermatitis in nickel-sensitive individuals (Burrows et al. 1981; Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Kaaber et al. 1978; Veien et al. 1987). The lowest single dose resulting in dermatitis, including erythema on the body, worsening of hand eczema, and a flare-up at the patch test site, was 0.009 mg Ni/kg (Cronin et al. 1980). Limitations of these studies include small sample size, the observation of placebo effects, non-double-blind studies (possibly introducing investigator bias), and inadequate reporting of whether subjects were fasted overnight or whether there were other dietary restrictions (IRIS 1996). Although some sensitive individuals may react to very low oral doses of nickel, Menne and Maibach (1987) concluded that only a minor number of nickel-sensitive patients react to oral doses below 1.25 mg (0.02 mg/kg), but nearly all will react at 5.5 mg (0.08 mg/kg).

Nielsen et al. (1990) fed 12 women with hand eczema and known allergy to nickel a diet (oatmeal, soy beans, cocoa) with 5 times the normal level of nickel (about 0.007 mg/kg/day) for 4 days. An aggravation of hand eczema was found in 6/12 by day 4 after the start of the challenge, and although excess nickel was excreted by 2 days after the last treatment, further exacerbation of hand eczema was observed in 10/12 by day 11. It is not clear how well the diets were controlled after the challenge period, and the subjects may have eaten foods that contained vasoactive substances that could exacerbate an allergic

reaction. This study also suggests that withdrawal of nickel rather than the peak nickel levels may contribute to the dermatitis observed in some sensitive individuals.

Intermediate-duration studies suggest that longer term oral exposure can be tolerated by some nickel-sensitive individuals and may even serve to desensitize some individuals. Jordan and King (1979) found flaring of dermatitis in only 1/10 nickel-sensitive women given nickel sulfate at 0.007 mg/kg/day for 2 weeks. Patch test responses to nickel were reduced in nickel-sensitive women given one weekly dose of 0.05 or 0.07 (but not 0.007) mg Ni/kg as nickel sulfate for 6 weeks (Sjovall et al. 1987). Santucci et al. (1994) gave increasing daily doses of nickel (0.01–0.03 mg/kg/day) as nickel sulfate to eight nickel-sensitive women for up to 178 days. A significant clinical improvement in hand eczema was observed in all subjects after 1 month of treatment, and continued treatment resulted in healing of all dermal lesions except for those on the hands. Measurement of urine and serum nickel suggested a decrease in the absorption of nickel and an increase in the excretion of nickel with longer exposure. The Santucci et al. (1994) study indicates that a daily dose of 0.01–0.03 mg Ni/kg can be tolerated by some nickel-sensitive people and may also serve to reduce their sensitivity. Among 44 sensitive subjects treated with a regimen of 1–2 ng nickel sulfate every other day, or daily for up to 2–3 years, 7 stopped the treatment for unspecified reasons, 7 had reactivation of symptoms, and complete (29) or partial (1) disappearance of symptoms for 2–4 years was observed in 30 subjects. In guinea pigs sensitized before oral treatment with nickel, only a transient desensitization was observed (van Hoogstraten et al. 1994).

Oral exposure before the sensitizing exposure may also help prevent nickel sensitization in some individuals. A study of 2,159 subjects examining the relationship between ear piercing and orthodontic treatment found that nickel sensitivity was reduced when orthodontic treatment preceded ear piercing (23.3 versus 38.1%, $p<0.005$) (van Hoogstraten et al. 1994). The investigators hypothesized that the oral nickel exposure that occurred during orthodontic treatment helped prevent the sensitization that occurred following ear piercing with earrings containing nickel. Orthodontic treatment after ear piercing did not affect the risk of nickel sensitization. Further evidence that oral exposure to nickel before a sensitizing exposure can prevent hypersensitivity is provided by the observation that nickel sensitivity in mice could be consistently produced only when metal frames to cover the cages and metal water nipples that released nickel were replaced with glass covers and nipples free of nickel (van Hoogstraten et al. 1994). Oral treatment of guinea pigs with nickel sulfate (30 mg/week for 6 weeks) has also been shown to prevent dermal sensitization (van Hoogstraten et al. 1994). Skin exposure of guinea pigs to nickel (non-sensitizing contacts) before oral exposure was also shown to interfere with oral tolerance induction.

Histological changes in the skin have not been observed in rats treated by gavage with nickel chloride at a dose of 8.6 mg Ni/kg/day for 91 days (American Biogenics Corporation 1988), or in rats and dogs exposed to nickel sulfate in the diet for 2 years at doses of 187.5 and 62.5 mg Ni/kg/day, respectively (Ambrose et al. 1976). These studies suggest that the skin is not affected by orally administered nickel in animals that have not been previously sensitized to nickel.

Ocular Effects. In a pharmacokinetic study in humans, transient left homonymous hemianopsia (loss of sight in the corresponding lateral half of the eyes) occurred in one male subject following ingestion of 0.05 mg Ni/kg as nickel sulfate in the drinking water (Sunderman et al. 1989b). No adverse effects were found in other subjects (n=9) when lower doses of 0.018 and 0.012 mg Ni/kg were used.

No treatment-related ophthalmological changes were observed in rats treated by gavage with 8.6 mg Ni/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988).

Body Weight Effects. Decreased body weight gain of 10% or more, associated with reduced food and/or water intake, has been observed in rats treated by gavage with nickel chloride at 8.6 mg Ni/kg/day for 91 days (American Biogenics Corporation 1988), in rats treated with nickel chloride in the drinking water at 0.38 mg Ni/kg/day for 28 days (Weischer et al. 1980) or 55 mg Ni/kg/day for 30 weeks (RTI 1988a), and in rats treated with nickel sulfate in the diet at 75 mg Ni/kg/day for 2 years (Ambrose et al. 1976). Decreased body weight gain has also been reported in mice treated with nickel sulfate in drinking water at a dose of 108 mg Ni/kg/day for 180 days (Dieter et al. 1988), and in dogs treated with nickel sulfate in the diet at a dose of 62.4 mg/kg/day for 2 years (Ambrose et al. 1976). Decreases in body weight gain of 10% or more were not observed in rats treated with nickel chloride in the drinking water at 31.6 mg Ni/kg/day for 11 weeks (Smith et al. 1993), with nickel sulfate in drinking water at 28.8 mg Ni/kg/day for 13 weeks (Obone et al. 1999), or with nickel chloride at a dose of 7.6 mg Ni/kg/day for 3 or 6 months (Vyskocil et al. 1994b).

3.2.2.3 Immunological and Lymphoreticular Effects

Dermatitis resulting from nickel allergy is well reported in the literature (see Section 3.2.2.2 for further discussion of allergic dermatitis following oral exposure).

Effects on the immunological system following exposure to 44 mg Ni/kg/day and higher as nickel sulfate in the drinking water for 180 days were assessed in mice (Dieter et al. 1988). Mild thymic atrophy was

observed at 44 mg Ni/kg/day and higher and mild splenic atrophy was observed at 108 mg Ni/kg/day and higher. Although several tests of immune function were performed, only two alterations were found—decreased spleen cellularity at 150 mg Ni/kg/day and impaired lymphoproliferative response to the B-cell mitogen, *Escherichia coli* lipopolysaccharide (LPS), at 44 mg Ni/kg/day and higher; a marginal response to sheep red blood cells was also observed at 150 mg Ni/kg/day. No response to concanavalin A (con A), natural killer cell activity, or resistance to *Listeria monocytogenes* challenge were observed. In addition to the immune function responses, exposure to nickel sulfate resulted in alterations in bone marrow: decreases in bone marrow cellularity at 108 mg Ni/kg/day and higher, decreases in granulocyte-macrophage progenitor cells (CFU-GM) at 44 mg Ni/kg/day and higher, and multipotential stem cells (CFU-S) at 108 mg Ni/kg/day and higher. The stem cell alterations were associated with alterations in glucose-6-phosphate dehydrogenase activity—increased at 44 mg Ni/kg/day and decreased at 108 and 150 mg Ni/kg/day. Obone et al. (1999) reported alterations in T-cell and B-cell subpopulations in the thymus and splenic lymphocytes in rats exposed to nickel sulfate in drinking water for 13 weeks. In the spleen, the changes consisted of an increase in the total number of cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; an increase in CD^{4+} T cells at 14.4 mg Ni/kg/day and decrease at 28.8 mg Ni/kg/day; increases in CD^{8+} T cells at 14.4 and 28.8 mg Ni/kg/day; an increase in the number of B cells at 14.4 mg Ni/kg/day; and a decrease in the ratio of B cells to total cells at 14.4 mg Ni/kg/day. In the thymus, the changes consisted of an increase in the total number of cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; an increase in CD^{4+} T cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; a decrease in the ratio of CD^{4+} T cells to total cells at 28.8 mg Ni/kg/day; increases in CD^{8+} T cells at 5.75 and 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day; increases in the ratio of CD^{8+} T cells to total cells at 5.75 mg Ni/kg/day and higher; and an increase in the number of B cells at 14.4 mg Ni/kg/day and a decrease at 28.8 mg Ni/kg/day. When challenged with Coxsackie virus B3, an enhanced inflammatory response was observed in the hearts of mice treated with nickel chloride in drinking water at 20.3 mg Ni/kg/day for 10–11 weeks (Ilback et al. 1994). Nickel treatment had no adverse effect on virus-induced lethality, spleen or thymus weights, or the number of cells in the spleen or thymus. Gross and microscopic examinations of the spleen did not reveal any adverse effects in rats or dogs fed nickel sulfate in the diet for 2 years at doses of 187.5 mg/kg/day for rats and 62.5 mg/kg/day for dogs (Ambrose et al. 1976).

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species, duration category, and nickel compound are recorded in Table 3-4 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Neurological effects were observed in workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The dose to which the workers with symptoms were exposed was estimated to be 7.1–35.7 mg Ni/kg. The neurological effects included giddiness (seven workers), weariness (six workers), and headache (five workers). The contribution of boric acid to these effects is not known.

In a study designed to determine the absorption and elimination of nickel in humans, one male who ingested a single dose of 0.05 mg Ni/kg as nickel sulfate in drinking water developed left homonymous hemianopsia (loss of sight in the corresponding lateral half of the eyes) 7 hours later; the condition lasted for 2 hours (Sunderman et al. 1989b). The loss of sight occurred soon after the peak serum concentration of nickel was reached, leading the investigators to suspect a causal relationship between nickel exposure and the loss of sight. The doses given to other subjects were lowered to 0.018 and 0.012 mg Ni/kg with no adverse effects.

In a 90-day study, lethargy, ataxia, prostration, irregular breathing, and cool body temperature were observed in rats treated by gavage with nickel chloride (American Biogenics Corporation 1988). These effects were observed frequently at 25 mg Ni/kg/day, a dose at which all rats died, and at lower incidences at 8.6 mg Ni/kg/day, a dose at which 6/52 rats died. At the lower dose, it is not clear if the adverse neurological effects were observed only in the animals that died. No signs of neurological dysfunction were observed at 1.2 mg/kg/day. Microscopic examinations of whole brains did not reveal any changes in the brains of rats or dogs treated with nickel salts at doses of 8.6 mg Ni/kg/day for up to 2 years (Ambrose et al. 1976; American Biogenics Corporation 1988).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species, duration category, and nickel compound are recorded in Table 3-4 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to nickel.

Oral exposure to nickel results in an accumulation of nickel (in descending order of concentration) in the epididymis, testes, seminal vesicles, and prostate gland in mice (Pandey et al. 1999). The accumulation of nickel in male reproductive tissues resulted in histological damage in the epididymis and seminal vesicles and sperm damage. Regressed epithelium and vacuolated cells were observed in the epididymis of mice administered 1.1 mg Ni/kg as nickel sulfate via gavage 5 days/week for 35 days (Pandey et al. 1999). In the seminiferous tubules, the damage consisted of atrophy of centrally located tubules and disturbed spermatogenesis in mice administered 1.1 mg Ni/kg as nickel sulfate (5 days/week) (Pandey et al. 1999) or rats exposed to 3.6 mg Ni/kg/day as nickel chloride in drinking water (Käkelä et al. 1999). Other studies have not found histological alterations in male or female reproductive tissues in rats administered up to 25 mg Ni/kg/day as nickel chloride for 91 days (American Biogenic Corp 1988), rats exposed to 28.8 mg Ni/kg/day as nickel sulfate in drinking water for 90 days (Obone et al. 1999), rats exposed to 187.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976), or dogs exposed to 62.5 mg Ni/kg/day as nickel sulfate in the diet for 2 years (Ambrose et al. 1976).

Significant decreases in sperm count and sperm motility and sperm abnormalities were observed in mice administered ≥2.2 mg Ni/kg as nickel sulfate (decreased sperm count significant at 4.5 mg Ni/kg) or 2.5 mg Ni/kg as nickel chloride 5 days/week for 35 days (Pandey and Srivastava 2000); no sperm effects were observed at 1.1 or 1.2 mg Ni/kg as nickel sulfate or nickel chloride, respectively. Similarly, Pandey et al. (1999) reported decreases in sperm count and motility in mice administered 2.2 mg Ni/kg as nickel sulfate, 5 days/week for 35 days; an increase in sperm abnormalities was also observed at 1.1 mg Ni/kg. In both studies by Pandey and associates, there were no significant alterations in the occurrence of a particular sperm abnormality; the total number of abnormalities was increased. Sobti and Gill (1989) reported increases in sperm head abnormalities in mice receiving a single gavage dose of 23, 28, or 43 mg/kg as nickel nitrate, nickel sulfate, or nickel chloride, respectively; it should be noted that this study was poorly reported and no information on number of animals tested was given.

In addition to the histological alterations and sperm alterations, alterations in fertility were observed in some studies, but not in all studies. Male-only exposure or male and female exposure to 3.6 mg Ni/kg/day as nickel chloride in drinking water resulted in decreased fertility (50% in nickel exposed rats compared to 100% in controls) in rats exposed for 28 days prior to mating (Käkelä et al. 1999). However, male rats exposed to 3.6 mg Ni/kg/day for 42 days prior to mating with unexposed females resulted in a small decrease in fertility (83 versus 100%) (Käkelä et al. 1999); suggesting regeneration of damaged tissues. Female-only exposure to concentrations as high as 13 mg/kg/day as nickel chloride in drinking water did not adversely affect fertility in rats (Käkelä et al. 1999). No adverse effects on fertility were

observed in a multigeneration study in which male and female rats exposed to doses as high as 55 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to mating (RTI 1988a, 1988b) or in a multilitter study in which female rats were exposed to doses as high as 31.6 mg Ni/kg/day (Smith et al. 1993).

The highest NOAEL value and all LOAEL values from each reliable study for reproductive effects in each species, duration category, and nickel compound are recorded in Table 3-4 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to nickel.

The available animal data on developmental toxicity provide suggestive evidence that the developing fetus and neonates are sensitive targets of nickel toxicity. The most commonly reported end point is fetal loss and decreased survival observed in the rat and mouse offspring in studies involving male-only exposure, female-only exposure, and combined male and female exposure in single generation, multilitter, and multigeneration studies. The developmental effects were often reported at maternally toxic doses. Other developmental end points that have been examined include body weights, gross necropsy for abnormalities, and neurodevelopmental toxicity.

Male-only exposure to 3.6 mg Ni/kg/day as nickel chloride in drinking water for 28 days resulted in decreases in the number of pups born alive (2.7/dam versus 10.2/dam in controls), the number of pups surviving until postnatal day 4 (56% versus 100% in controls), and litter size at postnatal day 21 (1.3 pups versus 9.2 pups in controls) (Käkelä et al. 1999). However, when the male rats were exposed to 3.6 mg Ni/kg/day for 42 days, no significant alterations in pup viability or survival were observed (Käkelä et al. 1999). A NOAEL was not identified in this study.

Several studies examined female-only exposure to nickel (Berman and Rehnberg 1983; Käkelä et al. 1999; Smith et al. 1993). An increase in spontaneous abortions was observed in female mice exposed to 160 mg Ni/kg/day as nickel chloride in drinking water on gestational days 2–17 (Berman and Rehnberg 1983); no effects were observed at 80 mg Ni/kg/day. In contrast, no effects on the average number of neonates per litter were observed when mouse dams were treated by gavage on gestation days 8–12 with 90.6 mg Ni/kg/day as nickel chloride (a dose that resulted in a significant decrease in maternal body weight) (Seidenberg et al. 1986). Exposure of rats to 13 mg Ni/kg/day as nickel chloride in drinking

water for 14 days prior to mating, during mating, gestation, and lactation resulted in a decreased pup survival from birth to postnatal day 4 (87 versus 100% in controls) and from postnatal day 4 to 21 (52 versus 90% in controls) (Käkelä et al. 1999); no significant alterations were observed at 4.0 mg Ni/kg/day. Pup mortality was also observed in a multilitter study in which rats were exposed to 0, 1.3, 6.8, or 31.6 mg Ni/kg/day as nickel chloride in drinking water for 11 weeks prior to breeding and during two successive gestation and lactation periods (Smith et al. 1993). In the first litter, the percentages of dead pups per litter at postnatal day 1 were 1.7, 3.1, 0, and 13.2% (statistically significant at the high dose only); no significant alterations were observed in the number of dead pups at postnatal day 21. In the second litter, the number of litters with dead pups at birth (2, 7, 6, and 10%; statistically significant at high dose only), the percentages of dead pups per litter at postnatal day 1 (1.0, 4.3, 4.6, and 8.8%; statistically significant at all three dose levels), and the percentage of dead pups at postnatal day 21 (12.5, 13.4, 19.4, and 29.2%; significant at high dose only) were increased.

Offspring mortality was also assessed in three studies involving combined male and female exposure (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b). Exposure of rats to 3.6–4.0 mg Ni/kg/day as nickel chloride in drinking water for 28 days prior to mating, during mating, gestation, and lactation adversely affected the litter size at postnatal day 21 (2.7/dam versus 9.2/dam in controls) and pup survival from postnatal day 4 to 21 (44 versus 90% in controls) (Käkelä et al. 1999); a NOAEL was not identified. In a multigeneration study (Ambrose et al. 1976) involving exposure of rats to 0, 22.5, 45, or 90 mg Ni/kg/day as nickel chloride in the diet for 11 weeks prior to mating, during mating, gestation, and lactation, a dose-related increase in the number of stillborn pups was observed. An independent statistical analysis of the data using the Fisher Exact Test found significant ($p<0.05$) increases in the total number pups born dead at 22.5 mg Ni/kg/day and higher for the F1a generation, 45 and 90 mg Ni/kg/day for the F1b generation, 90 mg Ni/kg/day for the F2a generation, 22.5 mg Ni/kg/day for the F2b generation, and 45 and 90 mg Ni/kg/day for the F3b generation. The study authors noted that the number of offspring (dead and alive) was progressively less with increasing nickel levels above 45 mg/kg/day (10.3, 10.6, 9.8, and 9.0 for 0, 22.5, 45, and 90 mg/kg/day, respectively); the number of offspring weaned per litter was also decreased with increasing nickel levels (8.1, 7.2, 6.8, and 6.4 for 0, 22.5, 45, and 90 mg/kg/day, respectively). The third study (RTI 1988a, 1998b) is a two-generation study in which the P0 generation was exposed to nickel chloride in drinking water for 11 weeks before mating and during gestation and lactation, and the F1b generation animals were mated to produce the F2 generations. A reduction in live litter size was observed in the F1a, F1b, and F2a offspring of rats exposed to 55 mg Ni/kg/day. Increases in mortality were also observed in the F1b rats on postnatal days 22 through 42; these increases were statistically significant in males at 30 and 55 mg Ni/kg/day and in females at 55 mg Ni/kg/day. No

adverse developmental effects were observed in the cesarean delivered F2b rats, suggesting that the nickel-induced decrease in live litter size occurred postnatally.

Decreases in pup body weights were reported in the offspring of rats exposed to 90 mg Ni/kg/day (Ambrose et al. 1976), 30, and 55 mg Ni/kg/day (RTI 1988a, 1988b). Neither the Ambrose et al. (1976) nor the RTI (1988a, 1988b) multigeneration studies found significant, nickel-related gross abnormalities in the surviving offspring of rats exposed to nickel. Käkelä et al. (1999) noted that the pups that died during lactation were runts: the heads were disproportionately large and the posteriors of the bodies were underdeveloped. No effects on figure eight maze reactive locomotor activity levels were observed in the offspring of mice treated by gavage at 45.3 mg Ni/kg/day as nickel chloride on gestation days 8–12 (Gray et al. 1986).

In summary, these data provide suggestive evidence that exposure to nickel prior to mating and during gestation and lactation results in decreased survival (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). Decreased survival was also observed in the offspring of male rats exposed prior to mating to unexposed females (Käkelä et al. 1999) and increased spontaneous abortions were observed following gestation-only exposure of mice (Berman and Rehnberg 1983). Interpretation of these data is complicated by the maternal toxicity, in particular, a decrease in maternal body weight gain, which was also observed at these dose levels (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993). Decreases in food and water intake have also been observed (RTI 1988a, 1988b; Smith et al. 1993).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species, duration category, and nickel compound are recorded in Table 3-4 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding cancer in humans after oral exposure to nickel.

In lifetime drinking water studies in rats and mice, nickel acetate (0.6 mg Ni/kg/day for rats; 0.95 mg Ni/kg/day for mice) was found to be noncarcinogenic (Schroeder et al. 1964, 1974). The incidence of tumors was comparable to that observed in controls.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to nickel.

3.2.3.2 Systemic Effects

No studies were located regarding adverse cardiovascular, gastrointestinal, musculoskeletal, or ocular effects in humans or animals after dermal exposure to nickel.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects for each species, duration category, and nickel compound are recorded in Table 3-5.

Respiratory Effects. Scratch tests and intradermal tests were performed on a patient diagnosed with nickel-related asthma (McConnell et al. 1973). Nonasthmatic controls were also tested. Testing resulted in respiratory distress in the patient but not in the controls, with a more severe response resulting from the scratch test.

No studies were located regarding adverse respiratory effects in animals after dermal exposure to nickel.

Hematological Effects. No studies were located regarding adverse hematological effects in humans after dermal exposure to nickel.

Hematocrit and hemoglobin levels were not affected in guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994). Only one dose level was used in this study.

Hepatic Effects. No studies were located regarding adverse hepatic effects in humans after dermal exposure to nickel.

Effects on the liver were observed in rats treated dermally (lateral abdominal area) with daily doses of 60 mg Ni/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). The effects included swollen

Table 3-5 Levels of Significant Exposure to Nickel - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
ACUTE EXPOSURE								
Systemic								
Human	once	Dermal	0.01 Percent (%)	0.0316 Percent (%)	(contact dermatitis in sensitive individuals)			Emmett et al. 1988 sulfate
Human	once	Dermal		0.04 Percent (%)	(allergic dermatitis in sensitive individuals)			Eun and Marks 1990 sulfate
Human	once	Dermal	0.01 Percent (%)	0.1 Percent (%)	(skin reaction in nickel sensitive individuals)			Menne and Calvin 1993 chloride
Human	once	Dermal		1 mg/cm2/week	(contact dermatitis)			Menne et al. 1987
Immuno/ Lymphoret								
Mouse (C3H:Hej)	once occluded for 7d			1 F Percent (%)	(develpoment of dermal sensitization)			Siller and Seymour 1994 sulfate
INTERMEDIATE EXPOSURE								
Systemic								
Rat (NS)	15 or 30d daily	Hepatic	40 M mg/kg/day	60 M mg/kg/day	(focal necrosis)			Mathur et al. 1977 sulfate
		Renal	100 M mg/kg/day					
		Dermal		40 M mg/kg/day	(slight hyperkeratosis)	60 M mg/kg/day	(degeneration of basal layer)	
Gn Pig (NS)	15 or 30d	Hemato	100 mg/kg/day					Mathur and Gupta 1994 sulfate
		Hepatic		100 mg/kg/day	(increased Mg2+ ATPase, acid phosphatase, and glucose-6-phosphatase activities)			

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Table 3-5 Levels of Significant Exposure to Nickel - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form
		Renal		100 mg/kg/day	(increased Mg2+ ATPase activity)			
		Endocr		100 mg/kg/day	(increased blood glucose)			
Reproductive								
Rat (NS)	30 d daily		40 M mg/kg/day			60 M mg/kg/day	(degeneration and edema of seminiferous tubules)	Mathur et al. 1977 sulfate

d = day(s); LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million

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hepatocytes and feathery degeneration after 15 days and focal necrosis and vacuolization after 30 days. In this study, there was no indication that the rats were prevented from licking the nickel from the skin; therefore, these effects could have resulted from oral exposure. Increased Mg^{2+} ATPase activity was observed in the livers of guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994). Acid phosphatase and glucose-6-phosphatase activities were increased only after 30 days of treatment.

Renal Effects. Proteinuria was not observed in electroforming industry workers exposed to nickel. No information was provided on exposure level or nickel compound (Wall and Calnan 1980).

No gross or microscopic lesions were observed in the kidneys of rats treated dermally with ≤100 mg Ni/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). In this study, there was no indication that the rats were prevented from licking the nickel from the skin; therefore, the animals could have been orally exposed. Increased Mg^{2+} ATPase activity was observed in the kidneys of guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 30 days (Mathur and Gupta 1994). No adverse effect was noted at 15 days, and dermal nickel exposure had no effect on kidney acid phosphatase or glucose-6-phosphatase activities.

Endocrine Effects. No studies were located regarding adverse endocrine effects in humans after dermal exposure to nickel.

Blood glucose levels were significantly increased in guinea pigs treated with 100 mg Ni/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994).

Dermal Effects. Allergic contact dermatitis is a commonly reported effect in humans exposed to nickel. Contact dermatitis was found in 15.5% of approximately 75,000 individuals undergoing patch tests with nickel sulfate (5% in petrolatum) (Uter et al. 2003). Smaller scale studies reported a similar frequency: 19.1% of 542 subjects (Akasya-Hillenbrand and Özkaya-Bayazit 2002), 21.2% of 1,729 subjects (Wantke et al. 1996), and 20.13% of 3,040 subjects (Simonetti et al. 1998). In the general population (a random sample of 567 people aged 15–69 years responding to a mailed screening questionnaire on respiratory allergy symptoms), 11% of the subjects had a positive reaction to nickel patch tests (Nielsen et al. 2002). Contact dermatitis in response to nickel exposure is more frequently observed in females, particularly younger females, than in males or older individuals (Uter et al. 2003; Wantke et al. 1996). This increased prevalence appears to be related to previous nickel exposure rather

than increased susceptibility. Exposure to nickel in consumer products, especially jewelry, rather than occupational exposure, is often the sensitizing exposure. An association has been observed between ear piercing and nickel sensitivity (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995; Uter et al. 2003). The prevalence of nickel allergy was 9% among girls (age 8, 11, and 15; n=960) with pierced ears compared to 1% among girls without pierced ears. Girls with more than one hole in each ear were also more likely to be sensitive to nickel than girls with only one hole in each ear (19 versus 11%) (Larsson-Stymne and Widstrom 1985). In a study in schoolchildren age 7–12, the frequency of nickel allergy was 30.8% among girls with pierced ears and 16.3% among girls who did not have pierced ears (Dotterud and Falk 1994). Similarly, 14% of females with pierced ears developed nickel allergy compared to 4% in females without pierced ears (Nielsen et al. 2002). Among a group of Swedish men (age 18–24) completing military service, 4.6% with pierced ears reacted to nickel, while 0.8% who did not have pierced ears had a positive reaction to nickel (Meijer et al. 1995). Once an individual is sensitized, even minimal contact with nickel may induce a reaction. Keczkes et al. (1982) have shown that sensitivity to nickel remains for many years. Fourteen people who tested positively for nickel sensitivity using nickel sulfate also tested positive 10 years later. However, the time interval between exposures can influence the degree of reactivity (Hindsén et al. 1997). A stronger reaction was found in nickel sensitized women when there was a 1-month period between nickel sulfate exposures compared to a 4-month period. This study also found a stronger reaction when nickel sulfate was applied to an area with previous allergic contact dermatitis.

Patch test studies in sensitive individuals using nickel sulfate have shown a dose-response relationship between the amount of nickel and the severity of the test response (Emmett et al. 1988; Eun and Marks 1990). In a study of 12 individuals, a nickel concentration of 0.0316% (316 ppm) in petrolatum resulted in dermatitis, while a concentration of 0.01% (100 ppm) did not produce adverse effects (Eun and Marks 1990). In aqueous solution, the nickel concentration of 0.0316% (316 ppm) did not result in dermatitis.

Although most patch testing is done with nickel sulfate because it is less irritating than nickel chloride, nickel alloys on the skin interact with human sweat, resulting in the release of nickel chloride. Therefore, nickel chloride is the more relevant form of nickel for examining threshold concentrations (Menne 1994). Menne and Calvin (1993) examined skin reactions to various concentrations of nickel chloride in 51 sensitive and 16 nonsensitive individuals. Although inflammatory reactions in the sweat ducts and hair follicles were observed at 0.01% and lower, positive reactions to nickel were not observed. To be scored as a positive reaction, the test area had to have both redness and infiltration, while the appearance of vesicles and/or a bullous reaction were scored as a more severe reaction. At 0.1%, 4/51 and 1/51 tested

positive with and without 4% sodium lauryl sulfate. Menne et al. (1987) examined the reactivity to different nickel alloys in 173 nickel-sensitive individuals. With one exception (Inconel 600), alloys that released nickel into synthetic sweat at a rate of <0.5 μg/cm^2/week showed weak reactivity, while alloys that released nickel at a rate of >1 μg/cm^2/week produced strong reactions.

Nickel sensitivity has been induced in guinea pigs following skin painting or intradermal injection with nickel sulfate (Turk and Parker 1977; Wahlberg 1976; Zissu et al. 1987). As discussed in Section 3.2.2.2, nickel sensitivity can also be induced in mice if oral exposure to nickel is reduced (Moller 1984; van Hoogstraten et al. 1994).

Adverse effects on the skin were observed in rats treated dermally with ≥40 mg Ni/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). The effects included distortion of the epidermis and dermis after 15 days and hyperkeratinization, vacuolization, hydropic degeneration of the basal layer, and atrophy of the epidermis at 30 days. Biochemical changes in the skin (enzymatic changes, increased lipid peroxidation, and an increase in the content of sulfhydryl groups and amino nitrogen) were observed in guinea pigs dermally exposed to nickel sulfate for up to 14 days (Mathur et al. 1988, 1992). Additive effects were observed when nickel sulfate was given in combination with sodium lauryl sulfate.

3.2.3.3 Immunological and Lymphoreticular Effects

Contact dermatitis resulting from nickel allergy is well reported in the literature (see Section 3.2.3.2 for further discussion of allergic reactions to nickel following dermal exposure). A relationship between human lymphocyte antigens (HLA) and nickel sensitivity was observed in individuals who had contact allergic reactions and positive results in the patch test (Mozzanica et al. 1990). The individuals had not been occupationally exposed to nickel. The HLA typing found a significantly greater prevalence of HLA-DRw6 antigen in the nickel-sensitive group compared to normal controls. The relative risk for individuals with DRw6 to develop a sensitivity to nickel was approximately 1:11. In individuals with allergic contact dermatitis to nickel, nickel directly bound and activated T-cells (Kapsenberg et al. 1988).

The dose-response relationship for the development of nickel sensitivity has been examined in a mouse model (Siller and Seymour 1994). The sensitization exposure involved placing a 6-mm pad containing 45 μL of a 0, 1, 5, 10, 15, or 20% nickel sulfate solution on the shaved abdominal skin of mice. This pad was left on the skin under occlusion for 7 days. Seven days after the sensitization procedure, the mice were challenged with 10 μL of a 0.4% aqueous nickel sulfate solution injected into the footpad. Saline

was injected into the opposite footpad as a control. Contact hypersensitivity, indicated by footpad swelling, was elicited at all doses, although the degree of swelling was minimal and only barely significant at 48 hours at the 1% concentration. Footpad swelling increased as the sensitizing dose increased and generally peaked between 24 and 48 hours after the challenge. In a comparison of the responses between male and female mice, males showed a weaker and more variable response than females, and the response peaked at 72 hours in males compared to 48 hours in females. The LOAEL for sensitization in mice is recorded in Table 3-5.

3.2.3.4 Neurological Effects

No studies were located regarding adverse neurological effects in humans or animals after dermal exposure to nickel.

3.2.3.5 Reproductive Effects

No studies were located regarding adverse reproductive effects in humans after dermal exposure to nickel.

Tubular degeneration of the testes was observed in rats treated dermally with nickel sulfate at 60 mg Ni/kg/day for 30 days (Mathur et al. 1977). No effects were found at 40 mg Ni/kg/day after 30 days or at doses of ≤100 mg Ni/kg/day after 15 days of treatment. In this study, there was no indication that the rats were prevented from licking the nickel sulfate from the skin; therefore, these effects could have resulted from oral exposure. Consequently, these values do not appear in Table 3-5.

3.2.3.6 Developmental Effects

No studies were located regarding adverse developmental effects in humans or animals after dermal exposure to nickel.

3.2.3.7 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to nickel.

3.3 GENOTOXICITY

The genotoxicity of nickel and compounds *in vivo* and *in vitro* is presented in Tables 3-6 and 3-7, respectively.

A significant increase, compared with controls, in the incidence of chromosomal aberrations (gaps), but not chromosomal breaks or sister chromatid exchanges, was observed in two groups of nickel refinery workers (Waksvik and Boysen 1982). A slight but significant increase in the incidence of chromosomal aberrations was observed in workers exposed to manganese, nickel, and iron (Elias et al. 1989). No correlation was found between nickel exposure levels and the incidence of aberrations. Nickel could not be identified as the sole causal agent because the workers were also exposed to other substances. The limited data indicate that nickel exposure produced genotoxic effects in humans following inhalation exposure.

The equivocal results of mutagenicity tests in bacteria probably reflect the variation in sensitivity of bacterial strains and different conditions of the studies. Results of chromosome aberration tests in cultured mammalian cells generally indicate a positive response. Most of the studies of chromosome aberrations *in vivo* indicate that nickel compounds are not clastogenic; however, one oral study (Sobti and Gill 1989) and one intraperitoneal study (Dhir et al. 1991) reported an increase in the incidence of micronuclei in the bone marrow of mice exposed to various nickel compounds. In the second study, a dose-related increase in chromosome aberrations was observed in the bone marrow cells of mice given a single intraperitoneal injection of nickel chloride (Dhir et al. 1991). The results of sister chromatid exchange studies in mammalian cells and cultured human lymphocytes are positive (Andersen 1983; Arrouijal et al. 1992; Larremendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981; Wulf 1980). Data concerning human foreskin cells, mouse embryo fibroblasts, and hamster cells indicate that nickel induces cellular transformation (Biedermann and Landolph 1987; Conway and Costa 1989; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stern 1984; Miura et al. 1989; Saxholm et al. 1981). The induction of cellular transformation by a particular nickel compound is proportional to its cellular uptake (Costa 1989; Costa and Heck 1982; Costa and Mollenhauer 1980). Crystalline nickel subsulfide, a carcinogen that induces cellular transformation, was actively phagocytized by Syrian hamster embryo cells (Costa and Heck 1982; Costa and Mollenhauer 1980). Phagocytosis and cellular transformation were negligible, however, for amorphous nickel monosulfide.

Table 3-6. Genotoxicity of Nickel *In Vivo*

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

– = negative result; + = positive result; ± = weakly positive; (ip) = intraperitoneal

Table 3-7. Genotoxicity of Nickel *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	Arlauskas et al. 1985; Biggart and Costa 1986; Marzin and Phi 1985; Wong 1988	Nickel chloride, nickel nitrate, nickel sulfate
Escherichia coli	Gene mutation	–	Green et al. 1976	Nickel chloride
E. coli	DNA replication	+	Chin et al. 1994	Nickel chloride
Cornebacterium sp.	Gene mutation	+	Pikalek and Necasek 1983	Nickel chloride
Bacillus subtilis	DNA damage	–	Kanematsue et al. 1980	Nickel oxide and trioxide
Eukaryotic organisms				
Fungi				
Saccharomayces cerevesiae	Gene mutation	–	Singh 1984	Nickel sulfate
Mammalian cells:				
CHO cells	Gene mutation	–	Hsie et al. 1979	Nickel chloride
Virus-infected mouse cells	Gene mutation	+	Biggart and Murphy 1988; Biggart et al. 1987	Nickel chloride
Mouse lymphoma cells	Gene mutation	+	Amacher and Paillet 1980; McGregor et al. 1988	Nickel chloride, nickel sulfate
Chinese hamster V79 cells	Gene mutation	+	Harwig and Beyersmann 1989; Miyaki et al. 1979	Nickel chloride
CHO cells	DNA damage	+	Hamilton-Koch et al. 1986; Patierono and Costa 1985	Crystalline NiS, nickel chloride
Human diploid fibroblasts	DNA damage	–	Hamiltion Koch et al. 1986	Nickel chloride
Human gastric mucosal cells	DNA damage	–[b]	Pool-Zobel et al. 1994	Nickel sulfate
CHO AS52 cells	Gene mutation	+	Fletcher et al. 1994	Nickel oxide (black and green); amorphous nickel sulfide; nickel subsulfide nickel chloride; nickel sulfate; nickel acetate
Human HeLa cells	DNA replication	+	Chin et al. 1994	Nickel chloride

Table 3-7. Genotoxicity of Nickel *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Hamster cells	Sister chromatid exchange	+	Andersen 1983; Larrenmendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981	Nickel sulfate, nickel chloride; crystalline NiS
Human lymphocytes	Sister chromatid exchange	+	Andersen 1983; Larrenmendy et al. 1981; Saxholm et al. 1981; Wulf 1980	Nickel sulfate, nickel sulfide
Hamster cells	Chromosome aberration	+	Conway and Costa 1989; Larremendy et al. 1981; Sen and Costa 1986b; Sen et al. 1987	Nickel sulfate, nickel chloride, nickel mono-sulfide
Human lymphocytes	Chromosome aberration	+	Larremendy et al. 1981	Nickel sulfate
Human lymphocytes	Sister chromatid exchange	+	Arrouijal et al. 1982	Nickel subsulfide
	Metaphase analysis	+		
	Micronucleus	+		
Human bronchial epithelial cells	Chromosome aberration	+	Lechner et al. 1984	Nickel sulfate
Hamster cell and C3H/10T1/2 cells	Cell transformation	+	Conway and Costa 1989; Costa and Heck 1982; Costa and Mollenhauer 1980; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stern 1984; Saxholm et al. 1981	Nickel mono-sulfide, nickel subsulfide, nickel chloride, nickel, nickel oxide or trioxide
Mouse embryo fibroblasts	Cell transformation	–	Miura et al. 1989	Nickel sulfate, nickel chloride
Mouse embryo fibroblasts	Cell transformation	+	Miura et al. 1989	Nickel subsulfide, nickel mono-sulfide, nickel oxide

Table 3-7. Genotoxicity of Nickel *In Vitro*

Species (test system)	End point	Results	Reference	Compound
Human foreskin cells	Cell transformation	+	Buedernann and Landolph 1987	Nickel subsulfide, nickel oxide, nickel sulfate, nickel acetate

[a]Metabolic activation is not an issue for nickel compounds.
[b]Nickel was genotoxic and cytotoxic at the same concentration (9.5 μmol/mL), so it was not a selective genotoxicant.

– = negative result; + = positive result; CHO = Chinese hamster ovary; DNA = dexoyribonucleic acid; NiS = nickel sulfide

The genotoxicity of nickel subsulfide was examined in human lymphocytes from nickel-sensitized individuals and from individuals not sensitized to nickel (Arrouijal et al. 1992). Compared to lymphocytes from sensitized individuals, lymphocytes from those not sensitized to nickel took up more nickel and showed a greater increase in clastogenic activity, as determined by the metaphase analysis and micronucleus tests. This study and the other *in vitro* and *in vivo* genotoxicity data indicate that if nickel can get inside the cells, it is genotoxic. Nickel has been reported to interact with DNA, resulting in crosslinks and strand breaks (Ciccarelli and Wetterhahn 1982; Patierno and Costa 1985, 1987; Robinson and Costa 1982).

A high level of mutagenicity (30–40 times background) has been found for less-soluble nickel compounds (nickel sulfide, nickel subsulfide, green and black nickel oxides) at the guanine phosphoribosyl transferase gene in the Chinese hamster G12 cell line (Klein et al. 1994). In contrast to these findings, the nickel compounds were less mutagenic (from 2 to 3 times background) in the Chinese hamster G12 cell line where the guanine phosphoribosyl gene was integrated at a different location. The soluble nickel sulfate was less mutagenic (4 times background) in either cell line. The investigators suggest that nickel mutagenesis in the G12 cells may be related to the integration of the guanine phosphoribosyl sequence into a heterochromatic region of the genome.

3.4 TOXICOKINETICS

Following inhalation exposure, about 20–35% of nickel deposited in the lungs of humans is absorbed into the bloodstream. Absorption from the respiratory tract is dependent on the solubility of the nickel compound, with higher urinary nickel levels observed in workers exposed to soluble nickel compounds (nickel chloride, nickel sulfate) than in those exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide). Following oral exposure, about 27% of the nickel given to humans in drinking water was absorbed, while only about 1% was absorbed when nickel was given with food. Nickel applied directly to the skin can be absorbed into the skin where it may remain rather than entering the bloodstream.

Autopsy data from nonoccupationally exposed individuals indicate that the highest concentrations of nickel are found in the skin, adrenal glands, and intestines. Following inhalation exposure, nickel also tends to accumulate in the lungs. The pituitary may accumulate nickel if exposure occurs during pregnancy. Nickel has been shown to cross the placenta, and nickel can accumulate in milk, resulting in exposure of the offspring. In human serum, the exchangeable pool of nickel is bound to albumin,

L-histidine, and α_2-macroglobulin. There is also a nonexchangeable pool of nickel in the serum, which is tightly bound to nickeloplasmin. Regardless of the route of exposure, absorbed nickel is excreted in the urine. Nickel that is not absorbed from the gastrointestinal tract is excreted in the feces.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Inhaled nickel particles are deposited in the upper and lower respiratory tract and are subsequently absorbed by several mechanisms. The deposition pattern in the respiratory tract is related to particle size, which determines the degree to which particles are affected by inertial impaction, sedimentation, and diffusion. Large particles (5–30 μm) deposit in the nasopharyngeal area where higher airstream velocities and airway geometry promote inertial impaction (Gordon and Amdur 1991). Smaller particles (1–5 μm) enter the trachea and bronchiolar region where they deposit principally by sedimentation. The smallest particles (<1 μm) enter the alveolar region of the lungs where diffusion and electrostatic precipitation of the particles occurs. Fractional deposition can be expected to vary considerably with age and breathing patterns.

In humans, about 20–35% of the inhaled nickel that is retained in the lungs is absorbed into the blood (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991). The remainder is either swallowed, expectorated, or remains in the respiratory tract. Nickel is detected in the urine of workers exposed to nickel (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Higher concentrations of urinary nickel were found in workers exposed to soluble nickel compounds (nickel chloride, nickel sulfate) than in those exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide), indicating that the soluble compounds were more readily absorbed from the respiratory tract (Torjussen and Andersen 1979). A man who died of adult respiratory distress syndrome 13 days after being exposed to a very high concentration of metallic nickel fume (approximately 380 mg/m^3) had very high concentrations of nickel in his urine (700 μg/L) (Rendall et al. 1994). This case report indicates that metallic nickel can be absorbed from the lungs if levels are high enough to result in lung damage.

The half-life of nickel in the lungs of rats exposed by inhalation has been reported to be 32 hours for nickel sulfate (mass median aerodynamic diameter [MMAD] 0.6 μm) (Hirano et al. 1994b), 4.6 days for nickel subsulfide ($^{63}Ni_3S_2$ activity median aerodynamic diameter [AMAD] 1.3 μm), and 120 days for

green nickel oxide (^{63}NiO, AMAD 1.3 μm) (Benson et al. 1994). Elimination half-times from the lung of rats of 7.7, 11.5, and 21 months were calculated for green nickel oxide with MMADs of 0.6, 1.2, and 4.0 μm, respectively (Tanaka et al. 1985, 1988).

Following exposure to green nickel oxide, nickel was only excreted in the feces indicating that the dominant mechanism for removing nickel oxide from the lungs is macrophage-mediated rather than dissolution-absorption (Benson et al. 1994). Following exposure to nickel subsulfide, nickel was excreted in both the urine and the feces, with greater amounts in the urine on days 6–14 post-exposure. These results indicate that dissolution-absorption plays an important role in the removal of nickel subsulfide in the lungs, and the study authors concluded that in the lungs, nickel subsulfide acts more like a soluble compound (Benson et al. 1994).

3.4.1.2 Oral Exposure

A human study using a stable nickel isotope estimated that 29–40% of the ingested label was absorbed (based on fecal excretion data) (Patriarca et al. 1997). Other human absorption studies show that 40 times more nickel was absorbed from the gastrointestinal tract when nickel sulfate was given in the drinking water (27±17%) than when it was given in food (0.7±0.4%) (Sunderman et al. 1989b). The bioavailability of nickel, as measured by serum nickel levels, was elevated in fasted subjects given nickel sulfate in drinking water (peak increase of 80 μg/L after 3 hours), but not when nickel was given with food (Solomons et al. 1982). The bioavailability of nickel increased when nickel was administered in a soft drink, but decreased when nickel was given with whole milk, coffee, tea, or orange juice. In another study (Nielsen et al. 1999) examining the relationship between nickel absorption and food intake, the highest nickel absorption (11.07–37.42% of dose), as evidenced by the amount excreted in urine, was found when the subjects were administered 12 μg Ni/kg 4 hours after ingestion of a scrambled egg meal. The lowest absorption level (2.83–5.27%) was found when nickel was administered at the same time as the meal. Ethylenediamine tetraacetic acid (EDTA) added to the diet decreased nickel bioavailability to below fasting levels (Solomons et al. 1982). These data indicate that the presence of food profoundly reduced the absorption of nickel. The observation of a decreased serum-nickel to urine-nickel ratio with increasing nickel doses in nickel-sensitive individuals suggests that at least some sensitive people adapt to increasing oral doses of nickel by reducing absorption by the gastrointestinal tract (Santucci et al. 1994). Urinary excretion of nickel following a single oral dose given to women after an overnight fast was found to decrease with increasing age, suggesting that nickel absorption may decrease with age (Hindsen et al. 1994).

Studies in rats and dogs indicate that 1–10% of nickel, given as nickel, nickel sulfate, or nickel chloride in the diet or by gavage, is rapidly absorbed by the gastrointestinal tract (Ambrose et al. 1976; Ho and Furst 1973; Tedeschi and Sunderman 1957). In a study in which rats were treated with a single gavage dose of a nickel compound (10 mg nickel) in a 5% starch saline solution, the absorption was found to be directly correlated with the solubility of the compound (Ishimatsu et al. 1995). The percentages of the dose absorbed were 0.01% for green nickel oxide, 0.09% for metallic nickel, 0.04% for black nickel oxide, 0.47% for nickel subsulfide, 11.12% for nickel sulfate, 9.8% for nickel chloride, and 33.8% for nickel nitrate. Absorption was higher for the more-soluble nickel compounds. Unabsorbed nickel is excreted in the feces.

3.4.1.3 Dermal Exposure

Human studies show that nickel can penetrate the skin (Fullerton et al. 1986; Norgaard 1955). In a study in which radioactive nickel sulfate was applied to occluded skin, 55–77% was absorbed within 24 hours, with most being absorbed in the first few hours (Norgaard 1955). It could not be determined whether the nickel had been absorbed into the deep layers of the skin or into the bloodstream. Compared to normal subjects, nickel absorption did not differ in nickel-sensitive individuals. In a study using excised human skin, only 0.23% of an applied dose of nickel chloride permeated skin after 144 hours when the skin was not occluded, while 3.5% permeated occluded skin (Fullerton et al. 1986). Nickel(II) ions from a chloride solution passed through the skin ≈50 times faster than nickel(II) ions from a sulfate solution (Fullerton et al. 1986). Application of nickel chloride in a sodium lauryl sulfate solution (0.25, 2, or 10%) to excised human skin resulted in a dose-related increase in the penetration of nickel during a 48-hour period (Frankild et al. 1995).

Studies in animals also indicate that nickel can penetrate the skin (Lloyd 1980; Norgaard 1957). Radioactive nickel sulfate was absorbed through the depilated skin of rabbits and guinea pigs after 24 hours and appeared primarily in the urine (Norgaard 1957). A small percentage of radioactive nickel chloride was absorbed through the skin of guinea pigs 4–24 hours after application, as indicated by radioactivity in the blood and urine (0.005–0.51%) (Lloyd 1980). Most of the nickel remained in the skin, primarily in the highly keratinized areas. Increased levels of nickel in the liver and kidneys in guinea pigs treated dermally with nickel sulfate for 15 or 30 days also indicate that nickel can be absorbed through the skin (Mathur and Gupta 1994).

3.4.2 Distribution

An autopsy study of individuals not occupationally exposed to nickel has shown the highest concentrations of nickel (μg/kg dry weight) in the lungs (174±94), followed by the thyroid (141±83), adrenals (132±84), kidneys (62±43), heart (54±40), liver (50±31), whole brain (44±16), spleen (37±31), and pancreas (34±25) (Rezuke et al. 1987). In an autopsy study, median levels of 0.046, 0.084, and 0.33 μg Ni/g wet weight were found in the adrenal glands, colon, and skin, respectively (Tipton and Cook 1963). The total amount of nickel found in the human body has been estimated as 6 mg or 86 μg/kg for a 70-kg person (Sumino et al. 1975).

3.4.2.1 Inhalation Exposure

Workers occupationally exposed to nickel have higher lung burdens of nickel than the general population. Dry weight nickel content of the lungs at autopsy was 330±380 μg/g in roasting and smelting workers exposed to less-soluble compounds, 34±48 μg/g in electrolysis workers exposed to soluble nickel compounds, and 0.76±0.39 μg/g in unexposed controls (Andersen and Svenes 1989). In an update of this study, Svenes and Andersen (1998) examined 10 lung samples takes from different regions of the lungs of 15 deceased nickel refinery workers; the mean nickel concentration was 50 μg/g dry weight. Nickel levels in the lungs of cancer victims did not differ from those of other nickel workers (Kollmeier et al. 1987; Raithel et al. 1989). Nickel levels in the nasal mucosa are higher in workers exposed to less-soluble nickel compounds relative to soluble nickel compounds (Torjussen and Andersen 1979). These results indicate that, following inhalation exposure, less-soluble nickel compounds remain deposited in the nasal mucosa.

Higher serum nickel levels have been found in occupationally exposed individuals compared to nonexposed controls (Angerer and Lehnert 1990; Elias et al. 1989; Torjussen and Andersen 1979). Serum nickel levels were found to be higher in workers exposed to soluble nickel compounds compared to workers exposed to less-soluble nickel compounds (Torjussen and Andersen 1979). Concentrations of nickel in the plasma, urine, and hair were similar in nickel-sensitive individuals compared to nonsensitive individuals (Spruit and Bongaarts 1977).

Following a single 70-minute inhalation exposure of rats to green nickel oxide (^{63}NiO; 9.9 mg Ni/m^3; AMAD 1.3 μm), the fraction of the inhaled material deposited in the total respiratory tract was 0.13, with 0.08 deposited in the upper respiratory tract and 0.05 deposited in the lower respiratory tract (Benson et

al. 1994). During the 180 days postexposure, nickel was not detected in extrarespiratory tract tissues. Following a single 120-minute inhalation exposure of rats to nickel subsulfide ($^{63}Ni_3S_2$; 5.7 mg Ni/m^3; AMAD 1.3 μm), the fraction of inhaled material deposited in the upper respiratory tract was similar to that observed for nickel oxide (0.14 in the total respiratory tract, 0.09 in the upper respiratory tract, and 0.05 in the lower respiratory tract). In contrast to nickel from nickel oxide, nickel from nickel subsulfide was detected in the blood, kidneys, and carcass between 4 and 24 hours after the exposure.

Data in rats and mice indicate that a higher percentage of less-soluble nickel compounds was retained in the lungs for a longer time than soluble nickel compounds (Benson et al. 1987, 1988; Dunnick et al. 1989; Tanaka et al. 1985) and that the lung burden of nickel decreased with increasing particle size (≤4 μm) (Kodama et al. 1985a, 1985b). Nickel retention was ≈6 times (mice) to 10 times (rats) greater in animals exposed to less-soluble nickel subsulfide compared to soluble nickel sulfate (Benson et al. 1987, 1988). The lung burdens of nickel generally increased with increasing exposure duration and increasing levels of the various nickel compounds (Dunnick et al. 1988, 1989). From weeks 9 to 13 of exposure, lung levels of nickel sulfate and nickel subsulfide remained constant while levels of nickel oxide continued to increase (Dunnick et al. 1989).

Slow clearance of nickel oxide from the lungs was also observed in hamsters (Wehner and Craig 1972). Approximately 20% of the inhaled concentration of nickel oxide was retained in the lungs at the end of exposure for 2 days, 3 weeks, or 3 months. The retention was not dependent on the duration of exposure or exposure concentration. By 45 days after the last exposure to nickel oxide (2-day exposure), 45% of the initial lung burden was still present in the lungs (Wehner and Craig 1972). The nickel oxide used in this study was not further identified.

The clearance of nickel compounds from the lungs was studied following intratracheal injection (Carvalho and Ziemer 1982; Valentine and Fisher 1984). Nickel subsulfide (less soluble) was cleared from the lungs of mice in two phases: 38% of the dose was cleared with a half-time of 1.2 days, and 42% was cleared with a half-time of 12.4 days. After 35 days, 10% of the dose remained in the lungs (Valentine and Fischer 1984). Soluble nickel chloride was cleared from the lungs much faster: 71% of the dose was cleared from the lungs in 24 hours, and only 0.1% remained in the lungs by day 21 (Carvalho and Ziemer 1982).

In a study that examined the effect of green nickel oxide and nickel sulfate on the clearance of nickel from the lungs, rats and mice were exposed 6 hours/day, 5 days/week, for up to 6 months and then given a

single nose-only exposure to a ^{63}Ni-labeled compound (Benson et al. 1995a). Nickel sulfate at concentrations up to 0.11 mg Ni/m^3 had no effect on lung clearance of nickel sulfate. Nickel oxide exposure did reduce the lung clearance of nickel oxide. When measured 184 days after the single exposure, a 6-month exposure of rats to nickel oxide at 0, 0.49, and 1.96 mg Ni/m^3 was found to result in the retention of 18, 33, and 96% of the dose, respectively. In mice exposed to nickel oxide at 0, 0.98, or 3.93 mg/m^3 for 6 months, 4, 20, and 62%, respectively, of the dose was retained 214 days after the single exposure to radiolabelled compound.

3.4.2.2 Oral Exposure

Serum nickel levels peaked 1.5 and 3 hours after ingestion of nickel (Christensen and Lagesson 1981; Patriarca et al. 1997; Sunderman et al. 1989b). In workers who accidentally ingested water contaminated with nickel sulfate and nickel chloride, the mean serum half-time of nickel was 60 hours (Sunderman et al. 1988). This half-time decreased substantially (27 hours) when the workers were treated intravenously with fluids.

In animals, nickel was found primarily in the kidneys following both short- and long-term oral exposure to various soluble nickel compounds (Ambrose et al. 1976; Borg and Tjalve 1989; Dieter et al. 1988; Ishimatsu et al. 1995; Jasim and Tjalve 1986a, 1986b; Oskarsson and Tjalve 1979; Whanger 1973). Substantial levels of nickel were also found in the liver, heart, lung, and fat (Ambrose et al. 1976; Dieter et al. 1988; Jasim and Tjalve 1986b; Schroeder et al. 1964; Whanger 1973) as well as in the peripheral nerve tissues and in the brain (Borg and Tjalve 1989; Jasim and Tjalve 1986a). Following a 2-year study in rats in which nickel levels were measured in bone, liver, kidneys, and fat, Ambrose et al. (1976) concluded that there were no important storage sites for nickel. In control rats, bone nickel was 0.53 ppm in female rats and <0.096 ppm in male rats. An explanation for the difference in bone nickel between male and female rats was not provided. Nickel was found to cross the placenta, as indicated by increases in the levels of nickel in the fetuses of mice given nickel during gestation (Jasim and Tjalve 1986a; Schroeder et al. 1964).

In pregnant rats not exposed to nickel, maternal and fetal blood concentrations of nickel were 3.8 and 10.6 μg/L, respectively (Szakmary et al. 1995). Twenty-four hours after a single gavage dose of 5.4, 11.3, or 22.6 mg Ni/kg as nickel chloride was given to pregnant rats (gestation day 19), nickel levels in μg/L were 18.5, 90, and 91.5, respectively, in maternal blood, 14.5, 65.5, and 70.5, respectively, in fetal blood, and 16.5, 20, and 17, respectively, in amniotic fluid. This study showed that at higher doses,

nickel reached a plateau in maternal and fetal blood, and that nickel concentrations in amniotic fluid were relatively well controlled in that they were similar at all three doses.

3.4.2.3 Dermal Exposure

No data were located regarding the distribution of nickel in humans after dermal exposure.

One hour after application of nickel chloride to the shaved skin of guinea pigs, nickel had accumulated in keratinaceous areas and in hair sacs (Lloyd 1980). After 4 hours, nickel was found in the stratum corneum and stratum spinosum. Twenty-four hours after treatment of depilated skin in rabbits and guinea pigs with nickel-57, radioactivity was detected in the blood, kidneys, and liver with the greatest amounts found in the blood and kidneys (Norgaard 1957). Quantitative data were not provided. Concentrations of nickel in the liver were 2.4±0.1 μg/g following 15 daily dermal treatments of guinea pigs with nickel sulfate at 100 mg Ni/kg/day and 4.4±0.5 μg/g following 30 days of treatment with the same dose, compared to 0.2±0.01 μg/g before treatment (Mathur and Gupta 1994). In the kidneys, nickel levels in μg/g were 0.4±0.2 before treatment, 1.5±0.12 at 15 days, and 3.52±0.42 at 30 days.

3.4.2.4 Other Routes of Exposure

Several researchers have examined the distribution of nickel in pregnant and lactating rats following its injection (Dostal et al. 1989; Mas et al. 1986; Sunderman et al. 1978). Half-lives of nickel in whole blood following intraperitoneal treatment of pregnant and nonpregnant rats were similar (3.6–3.8 hours), while the half-life for nickel in fetal blood was 6.3 hours following treatment on gestation days 12 or 19 (Mas et al. 1986). Intramuscular injection of nickel chloride (12 mg Ni/ kg/day) into pregnant and nonpregnant rats resulted in a greater accumulation of nickel in the pituitary of pregnant rats (Sunderman et al. 1978). Wet weight nickel concentrations in the pituitary were 0.13 μg/g in nonpregnant rats and 1.1 and 0.91 μg/g in pregnant rats treated on gestation days 8 and 18, respectively. Following subcutaneous exposure of lactating rats to nickel chloride, Dostal et al. (1989) found that peak nickel concentrations in the milk were reached 12 hours after treatment. Relative to treatment with a single dose, four daily subcutaneous doses of nickel resulted in higher nickel concentrations in milk, while serum nickel levels were the same as following a single dose (Dostal et al. 1989). This study suggests that nickel can accumulate in the milk, which would result in exposure of the offspring.

Using whole-body autoradiography, Ilback et al. (1992, 1994) examined the distribution of an intravenous dose of nickel given to mice with and without Coxsackie virus B3 infection. Virus infection changed nickel distribution, resulting in accumulation in the pancreas and the wall of the ventricular myocardium. The investigators suggested that the change in distribution may result from repair and immune mechanisms activated in response to the virus.

3.4.3 Metabolism

The extracellular metabolism of nickel consists of ligand exchange reactions (Sarkar 1984). In human serum, nickel binds to albumin, L-histidine, and α_2-macroglobulin. Binding in animals is similar. The principal binding locus of nickel to serum albumins is the histidine residue at the third position from the amino terminus in humans, rats, and bovines (Hendel and Sunderman 1972). Dogs do not have this binding locus, and most of the nickel (>85%) in dog serum was not bound to protein. A proposed transport model involves the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and L-histidine. The low molecular weight L-histidine nickel complex can then cross biological membranes (Sarkar 1984). In the serum, there is also a nonexchangeable pool of nickel tightly bound to nickeloplasmin, which is an α-macroglobulin (Sunderman 1986).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Absorbed nickel is excreted in the urine, regardless of the route of exposure (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). In nickel workers, an increase in urinary excretion was found from the beginning to the end of the shift, indicating a fraction that was rapidly eliminated. An increase in urinary excretion was also found as the workweek progressed, indicating a fraction that was excreted more slowly (Ghezzi et al. 1989; Tola et al. 1979). Nickel was also excreted in the feces of nickel workers, but this probably resulted from mucociliary clearance of nickel from the respiratory system to the gastrointestinal tract (Hassler et al. 1983). Among electrolysis and refinery workers exposed to soluble nickel compounds (nickel sulfate aerosols), nickel concentrations in the urine were 5.2–22.6 μg/L for those exposed to concentrations of 0.11–0.31 mg Ni/m^3, and 3.2–18 μg/L for those exposed to 0.08–0.2 mg Ni/m^3 (Chashschin et al. 1994). Higher nickel levels were found in the urine of workers exposed to soluble nickel compounds, indicating that the

soluble compounds are more readily absorbed than the less-soluble compounds (Bernacki et al. 1978; Torjussen and Andersen 1979). Although high levels of nickel were found in the urine of a man who died of adult respiratory distress syndrome 13 days after being exposed to a very high concentration of metallic nickel (Rendall et al. 1994), it is not clear if metallic nickel would be absorbed from healthy lungs.

In animals, the route of excretion following intratracheal administration of nickel depends on the solubility of the nickel compound. In rats given soluble nickel chloride or nickel sulfate, ≈70% of the given dose was excreted in the urine within 3 days (Carvalho and Zeimer 1982; Clary 1975; English et al. 1981; Medinsky et al. 1987). By day 21, 96.5% of the given dose of nickel chloride had been excreted in the urine (Carvalho and Zeimer 1982). Following intratracheal administration of less-soluble compounds (nickel oxide, nickel subsulfide), a greater fraction of the dose was excreted in the feces as a result of mucociliary clearance. Following administration of black nickel oxide to rats or nickel subsulfide to mice, approximately equal amounts of the initial dose were excreted in the urine and the feces (English et al. 1981; Valentine and Fischer 1984). A total of 90% of the initial dose of nickel subsulfide was excreted within 35 days (Valentine and Fischer 1984), and 60% of the initial dose of black nickel oxide was excreted within 90 days (English et al. 1981). This is consistent with nickel oxide being less soluble and not as rapidly absorbed as nickel subsulfide (English et al. 1981; Valentine and Fischer 1984).

3.4.4.2 Oral Exposure

In humans, most ingested nickel is excreted in the feces; however, this represents unabsorbed nickel (Patriarca et al. 1997; Sunderman et al. 1989b). However, the nickel that is absorbed from the gastrointestinal tract is excreted in the urine. Nickel administered in the drinking water was absorbed much more readily than when administered in the food (27% absorption in water versus 0.7% absorption in food, respectively) (Sunderman et al. 1989b). By 4 days post-treatment, 26% of the dose given in water was excreted in the urine and 76% in the feces, and 2% of the dose given in food was excreted in the urine and 102% in the feces (Sunderman et al. 1989b). The elimination half-time for absorbed nickel averaged 28±9 hours (Sunderman et al. 1989b). These data are consistent with a nickel tracer study that found that 51–82% of the administered label was excreted in the urine over the 5 days (Patriarca et al. 1997).

In animals, the majority of the ingested dose of nickel is excreted in the feces. One day after administration of nickel chloride in rats, 94–97% had been excreted in the feces and 3–6% had been excreted in the urine (Ho and Furst 1973). In dogs fed nickel sulfate in the diet for 2 years, only 1–3% of

the ingested nickel was excreted in the urine (Ambrose et al. 1976). Because dogs lack a major binding site in serum albumin that is found in humans (Hendel and Sunderman 1972), the relevance of dog data to humans is unclear.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of nickel in humans or animals after dermal exposure to nickel.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-

specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

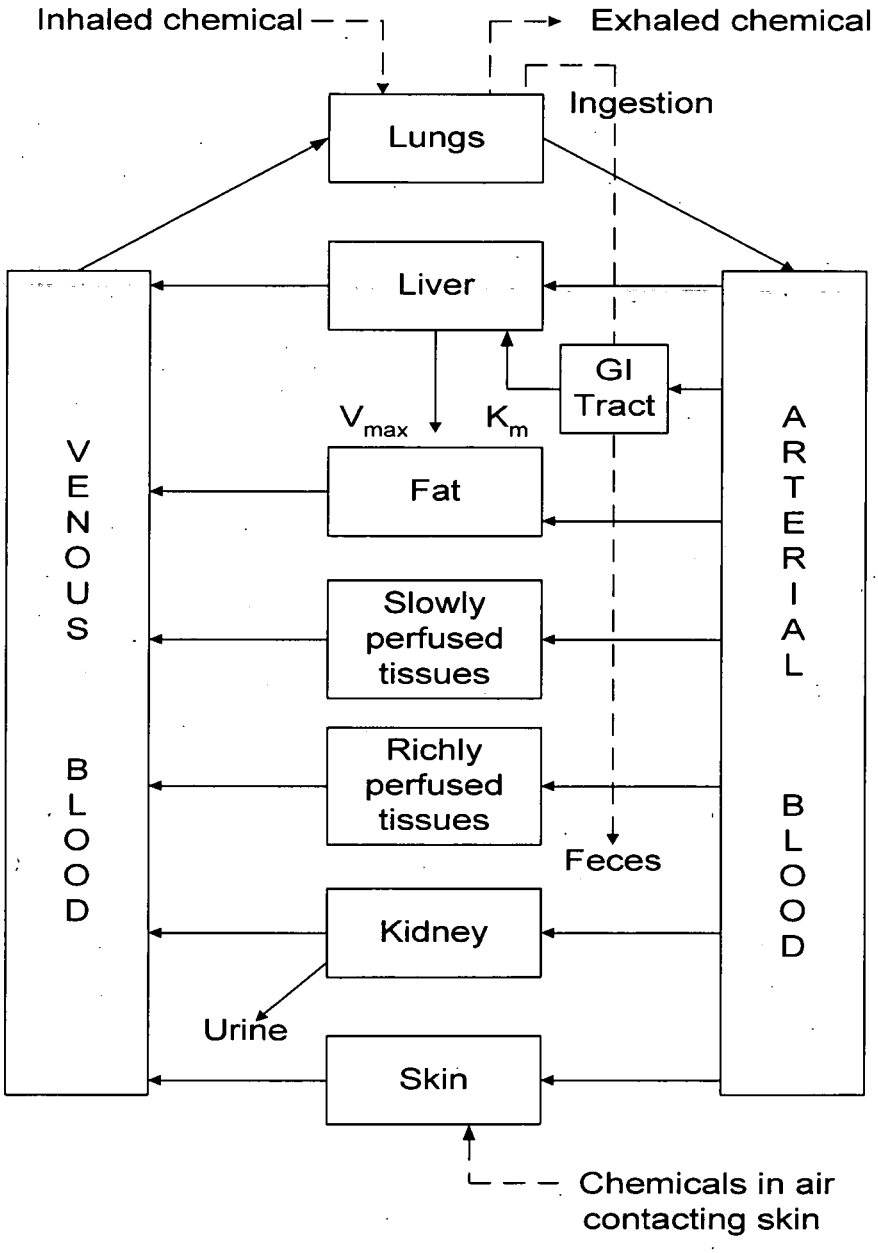
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

Sunderman et al. (1989b) Model

Description of the Model

Sunderman et al. (1989b) developed a model to predict nickel absorption, serum levels, and excretion following oral exposure to nickel in water and food. The model was developed based on two experiments in humans in which serum nickel levels and urinary and fecal excretion of nickel were monitored for 2 days before and 4 days after eight subjects were given an oral dose of nickel as nickel sulfate (12, 18, or 50 μg Ni/kg) in water (experiment 1) or in food (experiment 2). The data were then analyzed using a linear, compartmental, toxicokinetic model (Figure 3-4). Two inputs of nickel, the single oral dose, in which uptake was considered to be a first-order process, and the baseline dietary ingestion of nickel, in which uptake was considered to be a pseudo-zero order process, were included in the model. Parameters determined for the model from the two experiments are shown in Table 3-8. The only parameter that was significantly different between exposure in water and exposure in food was the fraction of nickel

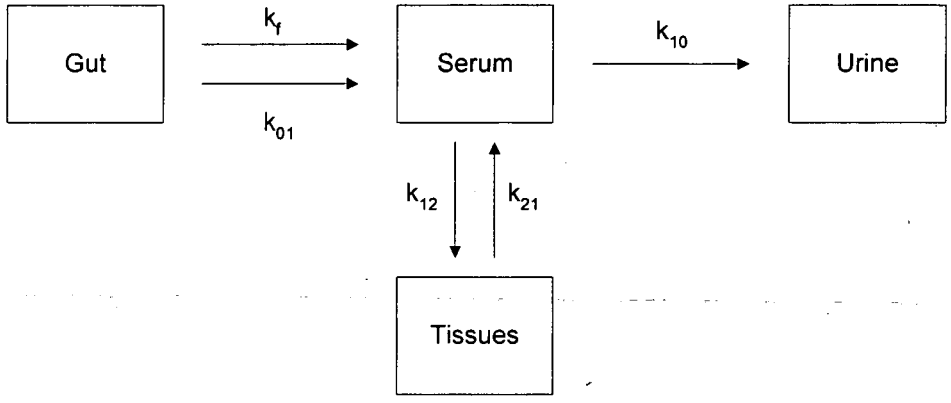
Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Figure 3-4. Diagram of the Compartmental Model of Nickel Metabolism*



*Modified from Sunderman et al. 1989b

k_f = zero-order rate constant for fractional absorption of dietary nickel
k_{01} = first-order rate constant for intestinal absorption of nickel from oral $NiSO_4$
k_{12} = first-order rate constant for nickel transfer from serum to tissues
k_{21} = first-order rate constant for nickel transfer from tissue to serum
k_{10} = first-order rate constant for nickel excretion in urine

Table 3-8. Kinetic Parameters of Nickel Sulfate Absorption, Distribution, and Elimination in Humans[a]

Parameters (symbols and units)	Experiment 1 (nickel sulfate in water)	Experiment 2 (nickel sulfate in food)
Mass fraction of nickel dose absorbed from the gastrointestinal tract (F, percent)	27±17	0.7±0.4[b]
Rate constant for alimentary absorption of nickel from the nickel dose (k_{01}, $hour^{-1}$)	0.28±0.11	0.33±0.24
Rate constant for alimentary absorption of dietary nickel intake (k_f, μg/hour)	0.092±0.051	0.105±0.036
Rate constant for nickel transfer from serum to tissues (k_{12}, $hour^{-1}$)	0.38±0.17	0.37±0.34
Rate constant for nickel transfer from tissue to serum (k_{21}, $hour^{-1}$)	0.08±0.03	–[c]
Rate constant for urinary elimination of nickel (k_{10}, $hour^{-1}$)	0.21±0.05	0.15±0.11
Rate clearance of nickel (C_{Ni}, mL/minute/1.73 mg/m^2)	8.3±2.0	5.8±4.3
Rate clearance of creatinine ($C_{creatinine}$, mL/minute/1.73 mg/m^2)	97±9	93±15
Nickel clearance as percent of creatinine clearance ($C_{Ni}/C_{creatinine}$, x100)	8.5±1.8	6.3±4.6

[a]Data (mean ± standard deviation) from Sunderman et al. 1989b
[b]$p<0.001$ relative to exposure in food computed by analysis of variance
[c]No value was determined because of the small mass of nickel absorbed from the gastrointestinal tract and transferred from the serum into the tissues.

absorbed from the gastrointestinal tract. The absorption rate constant was not different at the different doses, but the investigators indicated that the observations do not exclude the possibility that nickel absorption from the gastrointestinal tract could be saturated at higher doses. At doses low enough to be in the deficiency range, the absorption rate and percentage absorbed are probably larger.

Validation of the Model

The model has been shown to predict serum nickel and cumulative nickel levels in subjects receiving a single dose of nickel in drinking water or food. The study authors (Sunderman et al. 1989b) noted that the model was going to be analyzed using data on individuals accidentally ingesting nickel from a contaminated drinking fountain (toxicity data described in Sunderman et al. 1988); however, it does not appear that this validation of the model has been published.

Risk Assessment

Currently, there are no oral exposure MRLs for nickel. Because the model evaluates the absorption of nickel from different media (food and water), the model can be used in conjunction with MRLs during the assessment of potential health hazards associated with nickel in different environmental media (e.g., soil, water).

Target Tissues

This model was designed to predict nickel absorption. It did not measure nickel in target tissues.

Species Extrapolation

This model was designed for application to humans; the study authors noted that studies to use this model for absorption, distribution, and excretion in laboratory animals are being initiated. No publications of these data were located.

Interroute Extrapolation

This model is designed to simulate oral absorption of nickel and cannot be used for other routes of exposure.

Dosimetric Model for Lung Burden (Hsieh et al. 1999a, 1999b; Yu et al. 2001)

Description of the Model

Hsieh et al. (1999a) describe a dosimetric model of nickel deposition and clearance from the lung. This model was derived using lung burden data from the rat NTP studies of nickel sulfate (NTP 1996c), nickel subsulfide (NTP 1996b), and nickel oxide (NTP 1996a) and existing models of lung deposition. The model considers the alveolar region of the lung as a single compartment; removal of nickel from the compartment occurs via macrophage phagocytosis and migration (mechanical clearance) and/or via dissolution. For nickel sulfate and nickel oxide, dissolution and mechanical clearance, respectively, are assumed to be the primary clearance mechanisms; clearance of nickel subsulfide occurs via both mechanisms. The accumulation of nickel in the lung over time was described by the following equations:

$$(1) \qquad \frac{dM}{dt} = \dot{r} - \lambda M$$

$$(2) \qquad \dot{r} = concentration \times \eta \times MV$$

$$(3) \qquad \lambda = a \exp\left[-b\left(\frac{m_s}{m_{s0}}\right)^c\right]$$

where M is the mass burden, r is the deposition rate, λ is the total alveolar clearance rate coefficient; η is the alveolar deposition fraction, MV is the minute ventilation, a, b, c are clearance rate coefficient constants, m_s=M/S in which M is the lung mass burden and S is the total alveolar surface area (m_s=5.38x10^3 cm^2 for rats), and m_{s0}=1 mg/cm^2 is the dimensional constant introduced to normalize m_s.

The clearance rate coefficients constants in rats for the three nickel compounds examined are presented in Table 3-9.

Hsieh et al. (1999b) modified the rat model to develop a model of deposition and clearance of nickel in humans. Deposition rates were calculated for six scenarios: nose-breathing at rest, nose-breathing at light work, nose breathing at moderate work, mouth breathing at rest, mouth breathing at light work, and mouth breathing at moderate work. The clearance rate coefficient constants for humans were modified from the rat values. For nickel oxide, clearance rate coefficient constant *a* was estimated to be 1/7.6 times

Table 3-9. Clearance Rate Coefficient Constants of Nickel Compounds

Species	Nickel compound	Clearance rate coefficient constant		
		a	b	c
Rat[a]				
	Nickel sulfate	10.285	17.16	0.105
	Nickel subsulfide	0.00768	-20.135	0.266
	Nickel oxide	0.0075	300	0.95
Human[b]				
	Nickel sulfate	10.285	17.16	0.105
	Nickel subsulfide	0.00117	-20.135	0.266
	Nickel oxide	0.00099	300	0.95

[a]Data from Hsieh et al. 1999a
[b]Data from Hsieh et al. 1999b

the rat value; constants *b* and *c* were assumed to be the same as rats. For nickel subsulfide, clearance is due to mechanical transport and dissolution; the clearance rate coefficient constant *a* was estimated to be the sum of the clearance rate coefficient constant *a* for insoluble nickel (nickel oxide) and the difference between the clearance rate coefficient constant *a* for nickel oxide and for nickel subsulfide for rats. For nickel sulfate, clearance rate coefficient constants in humans were assumed to be the same as in rats. The human coefficient constants are presented in Table 3-9.

Yu et al. (2001) further expanded this human model to incorporate three additional factors: inhalability, mixed breathing mode, and clearance rate coefficient of a mixture of nickel compounds.

Validation of the Model

To validate the Hseih et al. (1999a) model, lung burdens for the nickel concentrations used by NTP were compared with measured lung burdens. In general, there was good agreement between the predicted lung burdens and measured burdens. Some differences were noted, particularly for the shorter term studies (16 days and 13 weeks). Hsieh et al. (1999a) noted that the differences may be due to assumptions used in the model (e.g., average body weight, constant respiratory parameters), using lung geometry data for Long Evans rats rather than for the Fischer rats used by NTP, or shortcomings in the experimental data.

The Hsieh et al. (1999b) model modification was not verified.

The Yu et al. (2001) modification of the model was used to predict lung burdens in nickel refinery workers; the predicted burdens were compared to measured lung burdens in deceased nickel refinery workers (Andersen and Svenes 1989). Good agreement between predicted and measured body burdens was found.

Risk Assessment

Currently, the intermediate- and chronic-duration inhalation MRLs for nickel are based on lung effects in rats. Further development of this model (Hseih et al. 1999a) and the modifications of the model (Hseih et al. 1999b; Yu et al. 2001) would allow for the model to be used to extrapolate from rats to humans with greater certainty than using the standard dosimetric approach.

Target Tissues

Based on limited human data and extensive animal data, the lung has been identified as the critical target of nickel toxicity. Further development of this model would allow nickel lung burdens to be predicted.

Species Extrapolation

The modifications of the Hsieh et al. (1999a) model allow for estimation of human lung burdens.

Interroute Extrapolation

This model is designed to simulate deposition and clearance of nickel from the lung and cannot be used for other routes of exposure.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Nickel is thought to be absorbed from the gastrointestinal tract as a lipophilic, low molecular weight compound (Kenney and McCoy 1992). The absorption of nickel from the gut is dependent on the various ligands and ions that are present. For example, food greatly decreases the absorption of nickel (Sunderman et al. 1989b). The results of an *in situ* perfusion study in rats (Arnich et al. 2000) suggest that at low concentrations (≤10 mg Ni/L), nickel is absorbed via active transport and facilitated diffusion; at higher concentrations, the carriers become saturated and nickel is absorbed via passive diffusion. These results are consistent with *in vitro* data showing that nickel is actively absorbed in the jejunum, but may cross the ileum by passive diffusion (Tallkvist and Tjalve 1994).

In the plasma, nickel is transported by binding to albumin and ultrafiltrable ligands, which include small polypeptides and amino acids; for example, histidine (Sunderman and Oskarsson 1991). The nickel binding site on albumin consists of the terminal amino group, the first two peptide nitrogen atoms at the *N*-terminus, and the imidazole nitrogen of the histidine at the third position from the *N*-terminus. Nickel competes with copper for this albumin binding site. In the plasma, nickel is also found bound to nickeloplasmin, an α-macroglobulin, but the nickel associated with nickeloplasmin is not readily exchangeable, and this protein is not thought to play a role in the transport of nickel (Sunderman and

Oskarsson 1991). An *in vitro* study of rat hepatocytes found that the calcium channels are involved in nickel uptake by the liver (Funakoshi et al. 1997). At physiological levels, no tissue significantly accumulates orally administered nickel (Nielsen 1990).

Nickel that is absorbed is excreted primarily in the urine. In the urine, nickel is primarily associated with low molecular weight complexes that have free amino acids as indicated by the ninhydrin reaction (Sunderman and Oskarsson 1991). In humans nickel is also eliminated in hair, skin, milk, and sweat.

The physiological role of nickel in animals and humans has not yet been identified. The most likely roles are as cofactors in metalloenzymes or metalloproteins, or as a cofactor that facilitates the intestinal absorption of iron (Fe^{3+} ion) (Nielsen 1982). Support for a role of nickel in enzymes comes from the identification of nickel-containing enzymes in plants and microorganisms. The types of nickel-containing enzymes that have been identified are urease, hydrogenase, methylcoenzyme M reductase, and carbon monoxide dehydrogenase (Nielsen 1990). Nickel may also have a role in endocrine gland function as suggested by its effect on prolactin levels.

3.5.2 Mechanisms of Toxicity

The mechanism of adverse respiratory effects following lung exposure of rabbits to metallic nickel or nickel chloride has been examined (Johansson and Camner 1986; Johansson et al. 1980, 1981, 1983, 1987, 1988a, 1989). In these studies, an accumulation of macrophages and granular material (primarily phospholipids) in the alveoli and an increase in volume density of alveolar type II cells were observed. The type II cells contained large amounts of lamellar bodies. Similar results were found following exposure to metallic nickel and nickel chloride, indicating that nickel ions apparently had a direct effect on type II cells (Johansson and Camner 1986). At the end of 6 months, all of the rabbits had foci of pneumonia, indicating an increased susceptibility to infection (Johansson et al. 1981). This may have been a result of the decreased function of the alveolar macrophages.

The substitution of nickel for other essential elements may also contribute to the adverse effects of nickel. Nickel can replace magnesium in certain steps in the activation of complement (McCoy and Kenney 1992). For example, the replacement of nickel for magnesium can increase the formation of C3b, Bb enzyme by 40 times, which amplifies activation of the complement pathway. Nickel has also been shown to activate calcineurin, a phosphatase that binds zinc and iron, and is usually activated by manganese.

There is some evidence that nickel may have a role in the release of prolactin from the pituitary. *In vitro* studies have shown that nickel could directly inhibit the release of prolactin by the pituitary, and it has been suggested that nickel may be part of a prolactin inhibiting factor (LaBella et al. 1973). Intravenous exposure to nickel chloride has been shown to reduce serum levels of prolactin in male rats that were pretreated with chlorpromazine, which itself produces hyperprolactinemia (LaBella et al. 1973). The effect was not observed in rats that had not been pretreated with chlorpromazine. Nickel has also been shown to accumulate more in the pituitaries of pregnant rats than nonpregnant rats (Sunderman et al. 1978), suggesting that a toxicological effect through prolactin may only be manifested during maximum prolactin production. A subcutaneous injection study has also shown that nickel can change the quality of the milk produced, resulting in increased milk solids (42%) and lipids (110%), and decreased protein (29%) and lactose (61%) (Dostal et al. 1989). Because these changes were noted in comparison to pair-fed rats, they were not considered to be a result of changes in food intake. An effect on prolactin would help explain the reproductive effects (maternal deaths during delivery, perinatal deaths) observed in multigeneration studies (Ambrose et al. 1976; RTI 1988a, 1988b; Smith et al. 1993) and the lack of dose response observed in these studies. The reproductive effects may be a result of physiological changes induced by nickel through changes in prolactin levels rather than a direct effect of nickel.

Costa (1989) reviewed potential mechanisms of nickel carcinogenesis. Soluble nickel compounds, although genotoxic *in vitro*, are rapidly cleared *in vivo* and are therefore not carcinogenic *in vivo* (Kasprzak et al. 1983; Sunderman and Maenza 1976). Particle solubility is not the only property that determines the genotoxic potential of nickel compounds; the physical form of the nickel particles is also important. Costa and Mollenhauer (1980) found that crystalline but not amorphous nickel subsulfide transformed Syrian hamster embryo cells *in vitro* and was phagocytized by cells that were transformed. The crystalline particles had a greater negative charge than the amorphous particles, which allowed the crystalline particles to be phagocytized. Once inside the phagosomes, the crystalline nickel subsulfide is dissolved through acidification of vacuoles by lysozymes. The nickel II ions released in this process are then delivered to the nucleus, where they interact with DNA or DNA protein complexes (Costa 1995). In contrast, soluble nickel compounds are taken into the cytosol and are not delivered to the nucleus, which prevents the interaction of nickel ions with DNA.

Most DNA damage induced by nickel ions is thought to occur during the late S phase of the cell cycle when heterochromatic DNA is replicating (Costa 1989). Evidence suggests that nickel may alter gene expression by enhanced DNA methylation and compaction (Lee et al. 1995). Methylation of DNA may result in critical genes becoming incorporated into heterochromatin where they can no longer be

expressed (Costa 1995). There is also evidence that nickel ions inhibit DNA repair (Hartwig et al. 1994). Nickel enhances the genotoxicity of ultraviolet light, x-rays, *cis*- and *trans*-platinum, and mitomycin C. *In vitro* studies in HeLa cells suggest that nickel inhibits the incision step in excision repair (Hartwig et al. 1994), while studies using Chinese hamster ovary cells suggest that nickel inhibits the ligation step of excision repair (Lee-Chen et al. 1994). The underlying mechanism of how nickel affects DNA repair is unclear. Sunderman and Barber (1988), Sunderman (1989b), and Hartwig et al. (1994) suggest that nickel ions may compete with zinc ions for binding to zinc-finger DNA binding proteins, resulting in structural changes in DNA that prevent repair enzymes from binding. Nickel may also directly interact with enzymes required for DNA repair (Hartwig et al. 1994).

3.5.3 Animal-to-Human Extrapolations

The available data on the toxicity of inhaled nickel provide strong evidence that the respiratory tract, in particular the lung, is the most sensitive target of nickel toxicity in humans and animals. There are limited exposure-response data for noncarcinogenic effects in humans; several well-designed animal studies (Benson et al. 1995a, 1995b; NTP 1996a, 1996b, 1996c) provide good exposure-response data that can be used to predict the thresholds of toxicity. One of these studies (NTP 1996c) was used to derive intermediate- and chronic-duration inhalation MRLs for nickel. A PBPK model (Hsieh et al. 1999a, 1999b) of lung deposition and clearance of inhaled nickel found a higher deposition of nickel in the alveolar region of humans compared to rats; however, adjustment for differences in lung weights resulted in a lower alveolar deposition of nickel in humans than in rats. This model, as described in more detail in Section 3.4.5, allows for prediction of human lung burdens. A cancer bioassay in rats and mice conducted by NTP (1996c) did not find significant increases in the occurrence of lung tumors. However, numerous occupational exposure studies have reported increases in the occurrence of nasal and lung tumors in workers exposed to soluble nickel compounds, primarily nickel sulfate and nickel chloride (Anttila et al. 1998; Grimsrund et al. 2001, 2002; International Committee on Nickel Carcinogenesis in Man 1990). It is not known if the apparent species differences are due to differences in carcinogenic potential, co-exposure to other nickel compounds or other metals, or differences in exposure concentrations.

The available data on the oral toxicity of nickel are insufficient for comparing sensitive targets of toxicity and dose-response relationships between humans and laboratory animals. With the exception of dogs, the toxicokinetic properties of nickel did not differ between species. In dogs, the serum albumin lacks the histidine residue at the third position from the amino terminus (Hendel and Sunderman 1972); thus, dogs

would not be a good model for the disposition of nickel in humans. In the absence of data to the contrary, it is assumed that most laboratory animals are a good model for humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

There is no evidence to suggest that nickel disrupts the normal functioning of the neuroendocrine axis. However, nickel-induced endocrine effects have been observed in laboratory animals. Several studies

have found decreases in prolactin levels in lactating animals following oral (Smith et al. 1993), subcutaneous (Dostal et al. 1989), or intravenous (LaBella et al. 1973) administration.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to adverse health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the

child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are limited data on the toxicity of nickel in children. Several surveys of nickel-induced dermatitis found higher incidences of nickel sensitivity among young girls (Uter et al. 2003; Wantke et al. 1996). This apparent age-related increase in nickel-induced dermatitis is likely the result of increased nickel exposure in this segment of the population rather than an increase in sensitivity. For most of the general population, the sensitizing exposure is through consumer products, particularly jewelry. The higher prevalence of ear piercing in young women probably results in a higher prevalence of nickel sensitivity (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995; Uter et al. 2003). With the exception of nickel sensitization, there are limited toxicity data on age-related differences in toxicity in humans or animals. Zhang et al. (2000) found that elderly rats (aged 20 months) were more susceptible to the proinflammatory effects in the lungs of inhaled ultrafine nickel as compared to juvenile rats (aged 2 months).

A number of inhalation and oral exposure studies in rats and mice provide strong evidence that the fetus and neonate are sensitive targets of nickel toxicity. Increases in spontaneous abortions and stillbirths and decreases in neonatal survival have been observed in rats (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993) and mice (Berman and Rehnberg 1983) following oral exposure to nickel. Decreases in pup body weight have also been observed in rats following inhalation (Weischer et al. 1980) or oral (Ambrose et al. 1976; RTI 1988a, 1988b) exposure.

No human or animal data on the toxicokinetic properties of nickel in children or immature animals or studies examining possible age-related differences in the toxicokinetics of nickel were located. Studies with other metals, notably lead and cadmium (Bhattacharyya 1983), have found higher absorption rates in suckling animals, as compared to adults; it is not known if this is also true for nickel. Parenteral administration studies in rats and mice demonstrate that water-soluble nickel compounds are transferred across the placenta (Olsen and Jonsen 1979) and via maternal milk (Dostal et al. 1989). Subsequent sections of this chapter (Sections 3.8, 3.10, and 3.11) discuss the available information on biomarkers, interactions, and methods for reducing toxic effects. The available information is from adults and mature animals; no child-specific information was identified. It is likely that this information will also be applicable to children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to nickel are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health

impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by nickel are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible".

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Nickel

Biological monitoring data are available primarily from occupational settings. Determination of nickel in the urine, feces, serum, hair, and nasal mucosa has been used to demonstrate human exposure to nickel compounds (Angerer and Lehnert 1990; Bencko et al. 1986; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Based on an extensive review of biological monitoring data, Sunderman et al. (1993) concluded that serum and urine nickel levels were the most useful biomarkers of nickel exposure. Levels of nickel in urine and serum can provide the most information about levels of nickel exposure if the route, sources, and duration of exposure are known, if the chemical identities and physical-chemical properties of the nickel compounds are known, and if physiological information (e.g., renal function) of the exposed population is known (Sunderman 1993). In the general population, average nickel concentrations in serum and urine are 0.2 and 1–3 μg/L, respectively (Templeton et al. 1994).

Significant correlations have been found between occupational exposure to less-soluble nickel compounds (breathing zone samples) and the levels of nickel in the urine and serum in various groups of workers (Morgan and Rouge 1984). Nickel levels in urine and serum of workers inhaling nickel powder, alloys, or slightly soluble compounds reflect the combined influences of long-term accumulation and recent exposures (Sunderman et al. 1986). Correlations between exposure concentration and levels in the urine and serum were found only in groups and not in individual workers. A relationship between exposure concentrations of soluble nickel compounds and levels of nickel in the urine and serum has also

been reported (Bernacki et al. 1980). Urine and serum levels of nickel in workers inhaling soluble nickel compounds reflect the amount of nickel absorbed in the previous 1 or 2 days (Sunderman et al. 1986). With respect to monitoring nickel following exposure to soluble compounds, the best correlations between exposure concentration and urine levels were found with "end-of-shift" urine sampling (Bernacki et al. 1980) or "next morning" urine sampling (Tola et al. 1979). A correlation was found between urinary nickel and plasma nickel in workers, with nickel levels in urine being about 8-fold higher than plasma levels (Angerer and Lehnert 1990; Bernacki et al. 1978). Bavazzano et al. (1994) did not find significant correlations between urinary nickel concentrations in nickel electroplating workers and air concentrations of soluble nickel compounds. Among nickel refinery workers, there was a significant correlation between urinary nickel levels (unadjusted or adjusted for creatinine levels) and soluble nickel concentrations in air; the correlation coefficients were approximately 0.35 and 0.55 for unadjusted and adjusted urine (Werner et al. 1999). Adding insoluble nickel air concentrations into the regression analysis as a predictor value resulted in a neglible change; the correlation coefficient increased by <0.05. Similarly, Oliveira et al. (2000) found significant correlations between postshift urinary nickel levels (adjusted for creatinine excretion) and nickel concentrations in the air among workers at a galvanizing facility exposed to soluble nickel compounds. A lower correlation coefficient was found for the relationship between preshift adjusted urinary levels and airborne nickel concentrations.

Higher concentrations of nickel in the urine and the plasma and lower concentrations of nickel in the nasal mucosa were observed in workers exposed to soluble nickel compounds when compared to workers exposed to less-soluble compounds (Bernacki et al. 1978; Torjussen and Andersen 1979). Less-soluble nickel compounds tended to remain in the nasal mucosa (half-life of ≈3.5 years); therefore, urinary and plasma levels were relatively low (Torjussen and Andersen 1979).

In workers exposed to nickel at a battery factory, a positive correlation was also found between air concentrations of nickel and concentrations of nickel in the feces (Hassler et al. 1983). High concentrations of nickel were found in the feces of workers exposed to nickel dusts containing large particles (as a result of greater mucociliary clearance from the lungs to the gastrointestinal tract) (Hassler et al. 1983).

It has been questioned whether or not levels of nickel in urine or serum are indicators of specific adverse health effects in humans. After reviewing monitoring data in occupationally exposed workers, Sunderman (1993) concluded that with the exception of nickel carbonyl, a relationship between nickel levels in body fluids and a specific health risk could not be established.

Exposure to nickel has also been monitored by assessing the content of nickel in the hair (Bencko et al. 1986). Analysis of the nickel content of hair provides evidence of past exposure and not changes in recent exposure to nickel. Correlations between exposure concentration and the level of nickel in hair were not reported.

Sensitization to nickel causes changes in serum antibodies (an increase in IgG, IgA, and IgM and a decrease in IgE) that may be monitored to determine if exposure to nickel has occurred (Bencko et al. 1983, 1986; Novey et al. 1983). These changes were found in both sensitized (Novey et al. 1983) and nonsensitized (Bencko et al. 1983, 1986) individuals. Information regarding the exposure concentration of nickel needed to cause serum antibody changes was not reported.

3.8.2 Biomarkers Used to Characterize Effects Caused by Nickel

Antibodies to hydroxymethyl uracil, an oxidized DNA base, were determined in workers exposed to nickel and cadmium, and in welders (Frenkel et al. 1994). Compared to controls, a significant increase in these antibodies was noted in the most highly exposed workers. Personal monitoring of 12 workers exposed to nickel and cadmium showed correlation coefficients between exposure concentrations and the antibodies of 0.4699 for cadmium and 0.7225 for nickel. Antibodies to hydroxymethyl uracil were not increased among welders. The levels of antibodies in the control populations for the nickel cadmium workers and for the welders were different, indicating the importance of determining the distribution of a new biomarker in controls for each population that is studied. This preliminary study suggests that antibodies to oxidized DNA products may be useful biomarkers for nickel and other metals that induce oxidative stress.

A preliminary study using imaging cytometry of nasal smears obtained from nickel workers indicates that this method may be useful to detect precancerous and cancerous lesions (Reith et al. 1994). With this method in which the cells were obtained by brushing the inside of the nose, the investigators were able to distinguish between nickel-exposed workers with non-dysplastic normal and suspicious mucosa smears and those with dysplastic lesions.

Although increases in oxidized DNA products and precancerous and cancerous lesions in the nose have been associated with nickel exposure, these effects are not specific to nickel. There are no specific biomarkers for nickel adverse health effects.

3.9 INTERACTIONS WITH OTHER CHEMICALS

A number of interactions of nickel with other chemicals are reported in the literature. The toxicity of nickel has been mitigated by treatment with chelating agents (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). Chelation treatment stimulates the excretion of nickel, thereby mitigating its toxicity. Lipophilic chelating agents, such as triethylenetetramine (TETA) and Cyclam (1,4,8,11-tetraazacyclotetradecane), were more effective than hydrophilic chelating agents such as EDTA, cyclohexanediamine tetraacetic acid (CDTA), diethylenetriamine pentaacetic acid (DTPA), and hydroxyethylenediamine triacetic acid (HEDTA) (Misra et al. 1988). The higher efficacy of the lipophilic agents may be due to their ability to bind to nickel both intracellularly and extracellularly, while the hydrophilic agents can only bind extracellularly.

A cross-reactivity between nickel and cobalt in sensitive individuals has been noted. For example, eight patients with asthma resulting from cobalt exposure also developed asthma when challenged with nickel sulfate (Shirakawa et al. 1990).

Nickel has also been found to interact with other metals such as iron, chromium, magnesium, manganese, zinc, and cadmium. The toxicity of nickel was mitigated by treatment with zinc (Waalkes et al. 1985) and magnesium (Kasprzak et al. 1986). The data suggest that magnesium, but not zinc, acted by altering the pharmacokinetics of nickel. The mechanism of action for zinc could not be determined from the study (Waalkes et al. 1985). Nickel absorption is increased during iron deficiency (Müller-Fassbender et al. 2003; Talkvist and Tjälve 1997), suggesting that iron deficiency may result in increased nickel toxicity. Coadministration of magnesium and nickel resulted in increased urinary excretion of nickel and decreased deposition of nickel in the lung, liver, and kidney (Kasprzak et al. 1986). Manganese dust inhibited nickel subsulfide-induced carcinogenesis following simultaneous intramuscular injection of the two compounds (Sunderman and McCully 1983). The inhibition by manganese was a local and not a systemic effect.

Pretreatment of animals with cadmium 1 week before nickel treatment enhanced the nephrotoxicity and hepatotoxicity of nickel (Khandelwal and Tandon 1984). The mechanism of interaction could not be determined from these studies. Pretreatment of mice with cadmium 24 hours before nickel treatment has also been shown to decrease nickel-induced lethality and lipid peroxidation in the liver (Srivastava et al.

1995). The investigators suggested that a cadmium-induced production of ceruloplasmin, which prevented a nickel-induced reduction of ceruloplasmin, provided the protection against nickel toxicity.

More severe respiratory effects (increases in lung weight, in the accumulation of alveolar macrophages, and in the density of type II cell volumes) were observed in rabbits exposed by inhalation to both nickel and trivalent chromium than in rabbits exposed to nickel only (Johansson et al. 1988b).

In iron-deficient rats, nickel enhanced the absorption of iron (Nielsen 1980; Nielsen et al. 1980, 1984). This effect of nickel was only observed when ferric sulfate was given. No interaction was observed when iron was given as a 60% ferric/40% ferrous sulfate mixture. It has been proposed that nickel facilitates the passive diffusion of ferric ions by stabilizing the transport ligand (Nielsen 1980).

Veien and Menne (1990) have suggested that vasoactive substances found in food can enhance nickel sensitivity reactions. Foods that they suggested that nickel-sensitive people should avoid include beer, wine (especially red wine), herring, mackerel, tuna, tomatoes, onions, carrots, apples, and citrus fruits. The vasoactive substances may increase the amount of nickel that is able to reach the skin.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to nickel than will most persons exposed to the same level of nickel in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of nickel, or compromised function of organs affected by nickel. Populations who are at greater risk due to their unusually high exposure to nickel are discussed in Section 6.7, Populations with Potentially High Exposures.

Individuals sensitized to nickel may be unusually susceptible because exposure to nickel by any route may trigger an allergic response. Epidemiology studies indicate that African-Americans have a higher nickel sensitivity than Caucasians and that women of both racial groups have higher reaction rates than men (Nethercott and Holness 1990; North American Contact Dermatitis Group 1973; Prystowsky et al. 1979). The incidence of reactions may be higher in women because they generally wear more metal jewelry than men. Further studies are required to determine if there are true gender and racial differences in nickel sensitivity, or if it is indeed a difference in exposure.

A relationship between HLA and nickel sensitivity was observed in patients who had a contact allergy and positive results in a patch test for nickel (Mozzanica et al. 1990). The nickel-sensitive group had a significant elevation in HLA-DRw6 antigen, compared to normal controls. The relative risk for patients with DRw6 to develop a sensitivity to nickel was approximately 1:11. The presence of DRw6 may be monitored to determine the potential risk of individuals to become sensitized to nickel.

Nickel that has been absorbed into the blood stream is primarily excreted in the urine. Therefore, individuals with kidney dysfunction are likely to be more sensitive to nickel. The increased sensitivity of persons with kidney dysfunction is also suggested by increased serum concentrations of nickel in dialysis patients (Hopfer et al. 1989). Because diabetics often have kidney damage, and because of the hyperglycemic effects of nickel observed in animal studies, the sensitivity of diabetics to nickel is also likely to be increased.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to nickel. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to nickel. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to nickel:

Bronstein AC, Currance PL. 1988. Emergency care for hazardous material exposure. Washington, DC: The CV Mosby Company, 147-148.

Gosselin RE, Smith RP, Hodge HC. 1984. Clinical toxicology of commercial products, 5th ed. Baltimore, MD: Williams & Wilkins, II, 145.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries--a handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 218-219.

3.11.1 Reducing Peak Absorption Following Exposure

General recommendations for reducing absorption of nickel following acute inhalation exposure have included moving the patient to fresh air and monitoring for respiratory distress (HSDB 2003). About 20–35% of less-soluble nickel deposited in the lungs is absorbed into the blood from the respiratory tract (see Section 3.4.1.1). The nickel that is not absorbed into the blood is removed by mucociliary action and is

expectorated or swallowed. Since the oral toxicity of metallic nickel is low, treatment with fluid and electrolyte replacement has been considered necessary only in cases with severe vomiting and diarrhea (HSDB 2003), which can occur as a result of nickel-induced gastrointestinal irritation (Sunderman et al. 1988). Thus, further induction of emesis is seldom necessary. EDTA added to the diet of humans decreased the bioavailability of orally administered nickel (Solomons et al. 1982). The presence of food in the stomach also reduced the gastrointestinal absorption of nickel (Christensen and Lagesson 1981). Oral administration of water or milk helps to dilute caustic nickel compounds in the stomach (Bronstein and Currance 1988; Stutz and Janusz 1988). In cases of dermal or ocular exposure, the skin or eyes should be thoroughly washed to prevent absorption by the skin or irritation of the eyes (Bronstein and Currance 1988; Stutz and Janusz 1988). Topical application of chelating agents and barrier creams have also been used to reduce dermal absorption in nickel-sensitive subjects (Gawkrodger et al. 1995). The most effective topical ligand for nickel yet described is 5-chloro-7-iodoquinolin-8-ol, but its use may be limited by its toxicity. Propylene glycol, petrolatum, and lanolin have been shown to reduce the dermal absorption of nickel.

3.11.2 Reducing Body Burden

Once absorbed into the blood, nickel has been found to distribute to the kidneys, liver, heart, fat, peripheral nervous tissues, and brain of animals (see Section 3.4.2). A mean serum half-time of nickel of 60 hours was measured in humans after oral exposure to nickel sulfate and nickel chloride (Sunderman et al. 1988).

A number of methods to decrease the body burden of nickel have been used or suggested. As discussed in Section 3.9, chelation treatment with a number of agents has been helpful (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). Lipophilic chelating agents such as TETA and Cyclam were more effective than hydrophilic chelating agents such as EDTA, CDTA, DTPA, and HEDTA (Misra et al. 1988). This may reflect differences in the distribution of hydrophilic and lipophilic agents between the intracellular and extracellular compartments. The use of diethyldithiocarbamate (DDC) as a chelating agent has been suggested as the preferred agent (Goldfrank et al. 1990; HSDB 2003). Disulfiram, which is metabolized to two molecules of DDC, might also be effective if DDC is not available. Penicillamine has also been used as a chelating agent for nickel. Intravenous infusion of fluids reduced the half-time for serum clearance of nickel from 60 to 27 hours in humans accidentally exposed to nickel sulfate and nickel chloride in water (Sunderman et al. 1988). The use of chelating agents over the long term to reduce nickel body burden in nickel-sensitive individuals is not recommended because it would also result in the

reduction of other essential metals (Veien and Menne 1990). A nickel-restricted diet is useful in some sensitive adults for reducing nickel dermatitis, but this diet must be used with caution in nickel-sensitive children because it may not provide sufficient levels of nutrients for growth (Veien and Menne 1990).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Many toxic effects of both soluble nickel and some relatively less-soluble (in water) nickel compounds, which slowly dissolve in serum and cytosol, are due to nickel ions (Sunderman and Oskarsson 1991). In addition to reducing body burden of nickel, chelating agents may effectively mitigate toxicity by binding to nickel ions before toxic effects can be produced. For example, contact dermatitis is a prevalent allergic response to nickel, and disulfiram has been shown to be effective in clearing up cases of nickel dermatitis (Goldfrank et al. 1990; HSDB 2003).

In human serum, nickel binds to albumin, L-histidine, and α_2-macroglobulin (Sarkar 1984). The principal binding locus of nickel to serum albumin is the histidine residue at the third position from the amino terminus (Hendel and Sunderman 1972). A proposed transport model involves the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and L-histidine. The low molecular weight L-histidine nickel complex can cross biological membranes (Sarkar 1984). How nickel gets inside of cells may determine the effects of the nickel compounds. If nickel ions are taken into the cytosol and bind to protein, they are not delivered to the nucleus, which prevents the interaction of nickel ions with DNA. Crystalline nickel compounds are phagocytized and nickel ions are delivered to the nucleus where they interact with DNA or DNA protein complexes (Costa 1995).

Inhalation exposure to nickel or nickel compounds (along with other metals) in the workplace has resulted in such adverse respiratory effects as chronic bronchitis, emphysema, reduced vital capacity, and asthma (see Section 3.2.1.2). Studies in animals have indicated that the effects of nickel compounds on the respiratory system (chronic inflammation, fibrosis, macrophage hyperplasia) depend on the solubility of the compounds rather than on lung burden. Nickel oxide (low solubility) was less toxic than the soluble nickel sulfate but resulted in a higher lung burden. Nickel compounds have been shown to have effects on lung macrophages of animals, including accumulation of macrophages and granular material in the alveoli and an increase in volume density of alveolar type II cells. A decrease in alveolar macrophage activity was observed in animals after exposure to nickel compounds, and the more-soluble compounds had the greatest effect (Haley et al. 1990). The relationship between the effects on alveolar macrophages

and respiratory toxicity is unknown, but since soluble nickel compounds appear to have greater effects, the involvement of the nickel ion is implicated.

Nickel subsulfide produced erythrocytosis in animals by increasing renal production of erythropoietin (Hopfer and Sunderman 1978; Hopfer et al. 1984). The mechanism for increased production of erythropoietin is unclear, but coadministration of manganese inhibited the erythrocytosis. Furthermore, nickel has also been found to have a role in the absorption of the ferric ion, resulting in increased hemoglobin levels and hematocrit (Nielsen 1980; Nielsen et al. 1980, 1984). Whether these mechanisms of increased erythropoiesis are related is not clear. Short-term restriction of dietary intake of iron until chelation therapy is started has been shown to be useful to prevent the increase in hemoglobin and hematocrit in a group of individuals who drank water heavily contaminated with nickel (Sunderman et al. 1988).

In conclusion, it appears that the toxicity of nickel and nickel compounds involves the binding of nickel ions to biological macromolecules. Chelation therapy appears to be effective both in reducing the body burden of nickel and interfering with the mechanism by which nickel exerts toxic effects by competing with the binding sites on biological molecules.

3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of nickel is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of nickel.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Nickel

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to nickel are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of nickel. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Humans have been exposed to nickel in nickel mines and processing plants, and numerous epidemiology studies have been performed to assess the cause of death in these workers. Accidental ingestion of nickel also has been documented in a small child and in electroplating workers. Nickel dermatitis is the most prevalent effect of nickel in humans.

Several chronic inhalation and oral studies and acute dermal studies in animals are reported in the literature. These studies exposed several species of animals to both soluble and less-soluble nickel compounds. The target organs were found to be the respiratory system for inhalation exposure and the respiratory system, gastrointestinal tract, hematological system, and kidneys for oral exposure at high levels. Reproductive and developmental effects were observed in animals after inhalation exposure and after oral exposure to nickel. Nickel sensitivity and dermatitis were also observed.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Data on the acute toxicity of nickel come from case reports of individuals exposed to nickel via inhalation, ingestion, or dermal contact, studies of patch testing in

Figure 3-5. Existing Information on Health Effects of Nickel

	Death	Acute	Intermediate	Chronic	Systemic: Immunologic/Lymphoretic	Systemic: Neurologic	Systemic: Reproductive	Systemic: Developmental	Systemic: Genotoxic	Cancer
Inhalation	●			●	●		●	●	●	●
Oral	●	●	●		●	●				
Dermal		●			●					

Human

	Death	Acute	Intermediate	Chronic	Systemic: Immunologic/Lymphoretic	Systemic: Neurologic	Systemic: Reproductive	Systemic: Developmental	Systemic: Genotoxic	Cancer
Inhalation	●	●	●	●	●		●	●		●
Oral	●		●	●	●	●	●	●	●	●
Dermal		●	●				●			

Animal

● Existing Studies

humans, and animal inhalation, oral, and dermal exposure studies. Human inhalation data are limited to a study of a worker dying due to respiratory tract injury following a 90-minute exposure to a very high concentration of metallic nickel with a small particle size (Rendall et al. 1994). Adverse gastrointestinal and neurological effects were observed in workers who ingested drinking water contaminated with nickel and boric acid (Sunderman et al. 1988). The contribution of boric acid to these effects is not known. Patch testing and oral nickel challenge testing have been done on individuals with contact dermatitis to determine if an allergy to nickel exists (Christensen and Moller 1975; Cronin et al. 1980; Eun and Marks 1990; Gawkrodger et al. 1986; Jordan and King 1979; Kaaber et al. 1978; Nielsen et al. 1990; Sjovall et al. 1987; Veien et al. 1987). With the exception of nickel sensitivity following dermal contact, the available human data are not sufficient for identifying the most sensitive targets of nickel toxicity.

Acute inhalation studies in animals of nickel sulfate, nickel subsulfide, and nickel oxide indicate that nickel sulfate as the most toxic of the three compounds tested (NTP 1996a, 1996b, 1996c). The most sensitive target of nickel toxicity in animals appears to be the respiratory tract. Alveolitis, chronic lung inflammation, alveolar macrophage hyperplasia, and atrophy of the nasal olfactory epithelium have been observed in rats exposed to nickel sulfate (Evans et al. 1995; NTP 1996c) or nickel subsulfide (Benson et al. 1995b; NTP 1996b), and active lung inflammation has been observed in rats exposed to nickel oxide (NTP 1996a). Chronic lung inflammation was also observed in mice acutely exposed to nickel sulfate (NTP 1996c) or nickel subsulfide (NTP 1996b). In addition to the respiratory effects, adverse immunological effects have been observed in mice exposed to nickel chloride (Adkins et al. 1979; Graham et al. 1978) or nickel sulfate (Adkins et al. 1979). Although the available acute-duration inhalation data are sufficient for identifying the critical target of nickel toxicity, the data were not considered adequate for derivation of an inhalation MRL because a serious LOAEL was identified at the lowest concentration tested in a study examining the respiratory tract (NTP 1996c). Although a NOAEL was identified for immunological effects; this study (Graham et al. 1978) was not suitable for MRL derivation due to the uncertainty of whether the NOAEL concentration would also be a no effect level for respiratory effects. A study involving exposure to low concentrations of a soluble nickel compound in which the respiratory tract was examined is needed to derive an acute-duration inhalation MRL.

Acute oral studies in animals are limited to LD_{50} studies (Haro et al. 1968; Mastromatteo 1986), a mouse study reporting increases in the occurrence of sperm head abnormalities (Sobti and Gill 1989), and a developmental toxicity screening study in mice that did not find adverse developmental effects (Seidenberg et al. 1986). Because of the limited number of end points examined, these studies do not provide sufficient information for identifying the most sensitive target of nickel toxicity following acute oral exposure, and are thus inadequate for MRL derivation. Acute oral exposure studies that examine a

number of end points, including reproductive and development toxicity, would help to identify the most sensitive target of toxicity. Studies utilizing a number of doses would be useful for establishing the dose-response relationships for ingested nickel.

The development of nickel sensitivity in mice has been shown to be related to both the concentration of the nickel solution applied to the skin and the duration of exposure (Siller and Seymour 1994). Male mice showed a weaker response than females, and further studies regarding the gender difference in the development of nickel sensitivity would be useful. Additionally, dermal exposure studies examining a number of potential end points would be necessary for identifying the most sensitive target of nickel toxicity following dermal exposure.

Intermediate-Duration Exposure. Intermediate-duration inhalation studies in humans were not located. Several studies examining the relationship between nickel ingestion and contact dermatitis were identified (Jordan and King 1979; Santucci et al. 1994; Sjovall et al. 1987). These studies are not useful for identifying the critical target of nickel toxicity or the threshold of toxicity in nonsensitized individuals. No human studies examining the toxicity of nickel following dermal contact for an intermediate duration were located.

A number of adverse health effects have been observed in laboratory animals exposed to airborne nickel; the effects occurred in the respiratory tract (Benson et al. 1995a; Bingham et al. 1972; Horie et al. 1985; Johansson and Camner 1986; NTP 1996a, 1996b, 1996c; Tanaka et al. 1988), blood glucose levels (Weischer et al. 1980), immune and lymphoreticular system (Haley et al. 1990; Johansson et al. 1980, 1987, 1988a, 1989; Morimoto et al. 1995; NTP 1996a, 1996b, 1996c; Spiegelberg et al. 1984), reproductive system (NTP 1996a), and the developing organism (Weischer et al. 1980). The available inhalation data provide strong evidence that the respiratory tract is the most sensitive target of nickel toxicity following intermediate-duration exposure. Chronic active lung inflammation was the most sensitive respiratory effect and a NOAEL for this effect (NTP 1996c) was used to derive an intermediate-duration inhalation MRL.

A number of animal studies have assessed the toxicity of nickel following intermediate-duration oral exposure. Observed effects include decreases in body weight (American Biogenics Corporation 1988; Dieter et al. 1988; RTI 1988a, 1988b; Weischer et al. 1980; Whanger 1973), kidney damage (Dieter et al. 1988), adverse lung effects (American Biogenics Corporation 1988; RTI 1988b), adverse reproductive effects (Käkelä et al. 1999; Pandey and Srivastava 2000; Pandey et al. 1999) and decreases in fetal/neonatal survival (Ambrose et al. 1976; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993).

These data provide suggestive evidence that the developing organism may be the most sensitive target of nickel toxicity following intermediate-duration exposure. Decreases in pup survival were observed at the lowest adverse effect level (Smith et al. 1993); this end point is inadequate for derivation of an intermediate-duration oral MRL because it is a serious adverse effect. As discussed in the sections on data needs for Reproductive Effects and Developmental Effects, additional studies are needed to confirm the identification of these effects as sensitive targets of nickel toxicity. Additional intermediate-duration studies would be useful for identifying sensitive targets of systemic toxicity and establishing dose-response relationships.

Dose-response data for dermal exposure of humans or animals to nickel were not identified. Dermal exposure studies would be useful for identifying sensitive targets of toxicity and establishing exposure-response relationships.

Chronic-Duration Exposure and Cancer. A number of epidemiology studies examining the inhaled toxicity of nickel in workers at nickel mines or nickel processing plants have been identified (Bencko et al. 1983, 1986; Cornell 1984; Cornell and Landis 1984; Enterline and Marsh 1982; Godbold and Tompkins 1979; Kilburn et al. 1990; Muir et al. 1993; Pedersen et al. 1973; Polednak 1981; Redmond et al. 1994; Shannon et al. 1991; Sunderman and Horak 1981). In general, these studies were mortality studies and did not provide nickel monitoring data. Additionally, Chashschin et al. (1994) examined the potential of nickel to induce reproductive and developmental effects in female nickel workers. Chronic oral toxicity data in humans are limited to a study on nickel sensitized individuals (Panzani et al. 1995), which examined the occurrence of contact dermatitis. Three studies examined the occurrence of contact dermatitis in individuals chronically exposed to nickel via dermal contact (Lee and Lee 1990; Meijer et al. 1995; Wall and Calnan 1980).

The toxicity of nickel sulfate (NTP 1996c), nickel subsulfide (NTP 1996b; Ottolenghi et al. 1974), and nickel oxide (NTP 1996a; Takenaka et al. 1985, 1988) following chronic inhalation exposure has been investigated in a number of studies in laboratory animals. The results of these studies provide strong evidence that the lung is the most sensitive target of toxicity; inflammatory changes were observed in the lung at the lowest adverse effect levels. Other effects that have been observed include damage to the nasal olfactory epithelium (NTP 1996b, 1996c), decreases in body weight gain (Ottolenghi et al. 1974; Takanaka et al. 1985), and hyperplasia of the bronchial lymph nodes (NTP 1996a, 1996b, 1996c). A chronic-duration inhalation MRL was derived from the NTP (1996c) rat study of nickel sulfate. Data on the chronic toxicity of ingested nickel in laboratory animals are limited to a 2-year study in rats and dogs

(Ambrose et al. 1976). The observed effects included decreases in body weight gain, lung damage, and adverse kidney effects. A chronic-duration oral MRL was not derived from this study because intermediate-duration studies provide suggestive evidence that the developing organism and possibly the reproductive system are sensitive targets of toxicity; these end points were not examined in chronic-duration studies. Additional oral exposure studies are necessary to identify the critical targets of toxicity for ingested nickel; studies which examined the systemic toxicity of nickel would be useful in assessing whether the developing organism and/or the reproductive system are most sensitive targets. No chronic-duration dermal studies in laboratory animals were located. Studies by the dermal route of exposure are necessary for identifying the most sensitive targets of toxicity and establishing exposure-response relationships

A number of occupational exposure studies have examined the carcinogenic potential of nickel. In general, these studies have found increased risks of lung and/or nasal cancer in workers exposed to less-soluble nickel compounds (Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; International Committee on Nickel Carcinogenesis in Man 1990; Magnus et al. 1982; Pedersen et al. 1973; Sunderman et al. 1989a) or soluble nickel compounds (Anttila et al. 1998; Grimsrund et al. 2002, 2003; International Committee on Nickel Carcinogenesis in Man 1990). No studies have examined the carcinogenicity of nickel in humans following oral or dermal exposure. A series of bioassays conducted by NTP (1996a, 1996b, 1996c) and Ottolenghi et al. (1974) examined the carcinogenic risk of inhaled nickel. Significant increases in the occurrence of lung tumors following exposure to nickel oxide (NTP 1996a) and nickel subsulfide (NTP 1996b; Ottolenghi et al. 1974), but not after nickel sulfate (NTP 1996c), were found. No additional inhalation studies in laboratory animals are needed at this time. Data on the carcinogenicity of ingested nickel are limited to a rat and mouse study conducted by Schroeder and associates (Schroeder and Mitchener 1975; Schroeder et al. 1974); no increases in the occurrence of malignant tumors were observed. These studies are inadequate for assessing carcinogenic potential because very low doses, below the MTD, were administered. Additional oral exposure carcinogenicity studies are needed to assess whether increased exposure to nickel could lead to an increased risk of developing cancer. Carcinogenicity studies using animals dermally exposed to nickel were not located. Cancer has been observed, however, after parental administration of less-soluble nickel compounds (e.g., nickel oxide, nickel subsulfide), but not soluble nickel compounds (Gilman 1962; Kasprzak et al. 1983; Lumb and Sunderman 1988; Smialowicz et al. 1985; Sunderman and Maenza 1976; Sunderman and McCully 1983).

Genotoxicity. Investigators conducting epidemiology studies have reported a higher incidence of chromosomal aberrations in nickel workers compared to controls (Elias et al. 1989; Waksvik and Boysen

1982). Both *in vitro* and *in vivo* studies in mammals indicate that nickel is genotoxic (Andersen 1983; Biedermann and Landolph 1987; Conway and Costa 1989; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stern 1984; Larramendy et al. 1981; Miura et al. 1989; Ohno et al. 1982; Saxholm et al. 1981; Sobti and Gill 1989; Wulf 1980), and the mechanism of action of nickel on cellular DNA has been studied (Ciccarelli and Wetterhahn 1982; Patierno and Costa 1985, 1987; Robinson and Costa 1982). Additional studies regarding the genotoxicity of nickel compounds are not needed at this time.

Reproductive Toxicity. An increase in the abortion rate has been reported among women who worked in a nickel hydrometallurgy refining plant in the Arctic region of Russia (Chashschin et al. 1994). The contribution of heavy lifting and possible heat stress to this effect is not known. A number of oral exposure studies suggest that nickel can result in testicular and epididymal damage (Käkelä et al. 1999; Pandey et al. 1999) and decreases in sperm motility, count, and sperm abnormalities (Pandy and Srivastava 2000; Pandey et al. 1999; Sobti and Gill 1999). Other oral studies have not found histological alterations in male or female reproductive tissues following 90 days or 2 years of exposure (Ambrose et al. 1976; American Biogenics Corporation 1988; Obone et al. 1999; RTI 1988a, 1988b). Although testicular effects were also observed following inhalation exposure, the investigators (NTP 1996b, 1996c) considered the testicular effects to be secondary to emaciation. Some oral exposure studies have also found significant alterations in fertility (Käkelä et al. 1999; Pandey et al. 1999) in male rats mated with unexposed female rats or with exposed females; fertility was not adversely affected in a multigeneration study (RTI 1988a, 1988b). Additional studies examining potential adverse effects in male reproductive tissues and on fertility would be useful for establishing whether the reproductive system is a sensitive target of nickel toxicity. Nickel treatment of rats during lactation has also been shown to change the quality of the milk (Dostal et al. 1989). Further studies concerning the role of physiological levels, as well as toxic levels, of nickel in the release of prolactin from the pituitary could provide useful information on potential reproductive and developmental effects of nickel.

Developmental Toxicity. An increase in structural malformations was observed in infants of women who worked in a nickel hydrometallurgy refining plant in the Arctic region of Russia (Chashschin et al. 1994). The contribution of heavy lifting and possible heat stress to this effect is not known. Decreased fetal body weight was observed in offspring of rats exposed to high levels of nickel via inhalation during gestation (Weischer et al. 1980). Developmental effects such as increased pup mortality, decreased pup survival, and decreased pup body weight were observed in oral exposure single-generation studies involving male-only, female-only, or male and female exposure to nickel (Käkelä et al. 1999), multigeneration studies in rats (Ambrose et al. 1976; RTI 1988a, 1988b), and multilitter studies in rats

(Smith et al. 1993). Although the available studies have consistently found decreases in pup survival, decreases in maternal body weight, food consumption, and water consumption often occur at the same dose levels. Thus, it is not known if the effects are due to nickel-induced damage to the offspring or are secondary to the maternal toxicity. Studies that controlled for maternal food intake and water consumption would be useful in understanding the mechanism of nickel toxicity. Additionally, the available studies do not clearly define the NOAEL/LOAEL boundary for developmental toxicity; a considerable amount of overlap between NOAEL and LOAEL values has been found. Developmental toxicity studies utilizing a number of dose levels would provide useful information in establishing the dose-response relationships for nickel. Studies assessing the developmental effects following dermal exposure were not located. Developmental effects have also been observed in animals following parental administration of nickel (Chernoff and Kavlock 1982; Lu et al. 1979; Sunderman et al. 1978).

Immunotoxicity. Human exposure to a large dose of nickel can result in sensitization manifested as contact dermatitis. Although there are limited data for the inhalation route, there are extensive data for the oral and dermal routes. Three studies examined immunological end points following inhalation exposure; two of these studies (Bencko et al. 1983, 1986) measured immunoglobulin levels in nickel workers and found significant alterations. The third study (Shirakawa et al. 1990) found positive results in patch tests of workers with hard metal lung disease. In nickel-sensitized individuals, oral exposure to fairly low doses of nickel can result in contact dermatitis; this has been tested in several acute-duration studies (Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Veien et al. 1987) and two intermediate-duration studies (Jordan and King 1979; Sjovall et al. 1987). There is extensive information on the immunotoxicity of nickel in humans following dermal exposure. In general, the dermal exposure studies fall into two main categories: patch testing in individuals with contact dermatitis (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Cavelier et al. 1988; Emmett et al. 1988; Eun and Marks 1990; Keczkes et al. 1982; Meijer et al. 1995; Menne et al. 1987; Simonetti et al. 1998; Uter et al. 2003; Wantke et al. 1996) and studies designed to assess the occurrence of nickel sensitivity in the general population (Dotterud and Falk 1994; Larsson-Stymme and Widstrom 1985; Menne and Holm 1983; Nielsen et al. 2002).

Animal studies demonstrate that nickel can induce immunological effects in nonsensitized individual. Alterations in nonspecific immunity (e.g., macrophage activity) (Adkins et al. 1979; Haley et al. 1990; Johansson et al. 1980) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) (Adkins et al. 1979; Graham et al. 1978; Morimoto et al. 1995; Spiegelberg et al. 1984) has been observed in animals following inhalation exposure. Similarly, oral

exposure to nickel has resulted in alterations in natural killer cells (Ilback et al. 1994) and humoral and cell mediated immunity (e.g., resistance to bacterial infection, response to foreign substances) (Dieter et al. 1988; Ilback et al. 1994). One dermal exposure study in mice examined the exposure-response relationship for nickel sensitization in mice (Siller and Seymour 1994). Studies designed to assess the dose-response relationship for contact dermatitis and oral dose are needed; the results of these studies should be considered during the derivation of oral MRLs for nickel. Additionally, studies that examined whether tolerance to nickel can develop and that assess cross sensitization of nickel with other metals would also be useful.

Neurotoxicity. No studies on the neurotoxicity of nickel in humans following inhalation or dermal exposure were located. Neurological effects (giddiness, weariness) were reported in individuals accidentally exposed to nickel and boric acid in drinking water (Sunderman et al. 1988). Temporary blindness in half of each eye occurred shortly after one person took a 0.05-mg/kg dose of nickel as nickel sulfate in drinking water (Sunderman et al. 1989b). There is limited information on the neurotoxicity of nickel in laboratory animals. No histological alterations were observed in the central nervous system following inhalation (NTP 1996a, 1996b, 1996c) or oral exposure (Ambrose et al. 1976; Obone et al. 1999). Although histological damage to the nasal olfactory epithelium was observed in animals following inhalation exposure to nickel sulfate or nickel subsulfide (Evans et al. 1995; NTP 1996b, 1996c), functional changes were not noted (Evans et al. 1995). Neurological signs (lethargy, ataxia, prostration) were observed in dying rats treated with nickel for 3 months; however, these effects were probably associated with overall toxicity (American Biogenics Corporation 1988). No animal dermal exposure studies examined neurological end points. The human data provide suggestive evidence that exposure to nickel may result in neurological effects; additional animal studies examining neurobehavioral performance would provide valuable information on the neurotoxic potential of nickel.

Epidemiological and Human Dosimetry Studies. A number of epidemiology studies regarding nickel toxicity are available in the literature. Most of these studies have focused on the carcinogenicity of inhaled nickel (Anttila et al. 1998; Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; Grimsrund et al. 2002, 2003; International Committee on Nickel Carcinogenesis in Man 1990; Magnus et al. 1982; Pedersen et al. 1973; Sunderman et al. 1989a) or nickel sensitivity following oral (Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Jordan and King 1979; Sjovall et al. 1987; Veien et al. 1987) or dermal (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Cavelier et al. 1988; Dotterud and Falk 1994; Emmett et al. 1988; Eun and Marks 1990; Keczkes et al. 1982; Larsson-Stymme and Widstrom 1985; Meijer et al. 1995; Menne and Holm 1983; Menne et al. 1987; Nielsen et al. 2002;

Simonetti et al. 1998; Uter et al. 2003; Wantke et al. 1996) exposure. As nickel exposure levels in the occupational environments have been reduced, continued health monitoring of populations occupationally exposed to nickel would be useful to determine if more subtle adverse health effects occur in humans at lower concentrations. Continued monitoring of nickel sensitization in the general population is needed to assess whether the increased popularity of body piercing will result in increased occurrences of nickel sensitivity. Additional studies on the dose-response relationship of ingested nickel dose and contact dermatitis would be useful. Animal data provide some suggestive evidence that nickel may be a reproductive toxicant and maternal exposure may result in increases in neonatal mortality. Inclusion of these end points in occupational exposure studies may provide valuable information on whether these would also be end points of concern for humans.

Biomarkers of Exposure and Effect.

Exposure. Nickel is a naturally occurring component of the diet and can be detected in hair, blood, urine, and feces (Angerer and Lehnert 1990; Bencko et al. 1986; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). In persons exposed to nickel above background levels, positive qualitative correlations have been found between air concentrations of nickel and nickel levels in the feces (Hassler et al. 1983) and urine (Angerer and Lehnert 1990; Bavazzano et al. 1994; Bernacki et al. 1978, 1980; Morgan and Rouge 1984; Oliveira et al. 2000; Sunderman et al. 1986; Tola et al. 1979; Torjussen and Andersen 1979; Werner et al. 1999). Additional studies examining the relationship between levels of nickel in the urine and body burden levels and studies associating urinary nickel levels and the manifestation of adverse health effects would be useful in establishing biological exposure indices for nickel.

Effect. A relationship between human lymphocyte antigens and nickel sensitivity exists and predicts that individuals with this antigen have a relative risk of approximately 1 in 11 of developing nickel sensitivity (Mozzanica et al. 1990). Antibodies to hydroxymethyl uracil, an oxidized DNA base, have also been shown to be increased in some nickel-exposed workers (Frenkel et al. 1994). A preliminary study using imaging cytometry of nasal smears obtained from nickel workers indicates that this method may be useful to detect precancerous and cancerous lesions (Reith et al. 1994). Studies that identify nickel-specific biomarkers may be helpful in alerting health professionals to nickel exposure before serious toxicological effects occur.

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetic studies in humans indicate that nickel is absorbed through the lungs (Bennett 1984; Grandjean 1984; Sunderman and

Oskarsson 1991), gastrointestinal tract (Nielsen et al. 1999; Patriarca et al. 1997; Sunderman et al. 1989b), and skin (Fullerton et al. 1986; Norgaard 1955). Food greatly decreases the absorption of nickel from the gastrointestinal tract (Sunderman et al. 1989b). Following absorption from the lungs and the gastrointestinal tract, nickel is excreted in the urine (Angerer and Lehnert 1990; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Sunderman et al. 1989b; Torjussen and Andersen 1979). Increased levels of nickel were found in the lungs, nasal septum, liver, and kidneys of workers inhaling nickel (Andersen and Svenes 1989; Kollmeier et al. 1987; Raithel et al. 1988; Rezuke et al. 1987; Sumino et al. 1975; Svenes and Andersen 1998; Torjussen and Andersen 1979). Animal data indicate that after inhalation, nickel particles can remain in the lungs (nickel oxide) or be absorbed and then excreted in the urine (nickel sulfate). High levels of nickel have been found in the liver, kidneys, and spleen of animals after inhaling high levels of nickel (Benson et al. 1987, 1988, 1994, 1995a; NTP 1996a, 1996b, 1996c; Tanaka et al. 1985). Nickel that has been absorbed after oral exposure is primarily distributed to the kidneys before being excreted in the urine. High levels of nickel were also found in the liver, heart, lungs, fat, peripheral nervous tissue, and brain (Ambrose et al. 1976; Borg and Tjalve 1989; Dieter et al. 1988; Jasim and Tjalve 1986a, 1986b; Oskarsson and Tjalve 1979; Whanger 1973). Studies examining the bioavailability of nickel from soil following oral exposure would be useful for determining the absorbed dose from nickel-contaminated soil at a hazardous waste site. Further verification of the toxicokinetic models developed by Hsieh et al. (1999a, 1999b) and Sunderman et al. (1989b) would improve the ability to predict the absorbed dose following inhalation or oral exposure.

Comparative Toxicokinetics. Studies that examine the toxicokinetics of nickel in humans after occupational exposure, ingestion of nickel from food and water, and dermal exposure are available (Bennett 1984; Fullerton et al. 1986; Grandjean 1984; Norgaard 1955; Sunderman and Oskarsson 1991; Sunderman et al. 1989b). The toxicokinetics of both inhaled and ingested nickel have been examined in several species of animals (rats, mice, dogs, hamsters) (Ambrose et al. 1976; Benson et al. 1987, 1988; Borg and Tjalve 1989; Dieter et al. 1988; Jasim and Tjalve 1986a, 1986b; NTP 1996a, 1996b, 1996c; Oskarsson and Tjalve 1979; Tanaka et al. 1985; Whanger 1973). Dermal studies have been performed in guinea pigs and rabbits (Lloyd 1980; Norgaard 1957). The limited human data correlate well with the toxicokinetics observed in animals. Studies that compare the toxicokinetics of humans and animals using the same experimental protocol would be helpful in determining which species of animal is the best model for assessing the effects of nickel in humans.

Methods for Reducing Toxic Effects. Approximately 20–35% of inhaled less-soluble nickel is absorbed through the lungs (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991). Methods

that would enhance the clearance of nickel from the lung, thus preventing or reducing the severity of lung damage (inflammation or fibrosis), would be useful. The administration of EDTA in food (Solomons et al. 1982) and the presence of food in the stomach (Christensen and Lagesson 1981) decrease the amount of nickel that is absorbed through the gastrointestinal tract. Several chelating agents (e.g., TETA, Cyclam, EDTA) have been shown to be effective in reducing the body's nickel burden (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). It is not known if other methods, such as dialysis, would be more effective in reducing the body burden. The mechanism of nickel toxicity involves the binding of nickel ions to macromolecules; chelating agents have been shown to bind to the nickel ions, thus mitigating the toxicity. Studies designed to determine if other methods would be more effective in binding nickel ions would be useful.

Children's Susceptibility. There are limited data on the toxicity of nickel in children. Several patch testing studies have included children (Akasya-Hillenbrand and Özkaya-Bayazit 2002; Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995;Uter et al. 2003; Wantke et al. 1996), the results of which suggest that children may be more susceptible than adults. However, the increases sensitive is probably due to potential for exposure (via ear piercing) than increased sensitivity; additional studies are needed to verify this assumption. Studies in laboratory animals provide evidence that the fetus and neonates are sensitive targets of nickel toxicity following inhalation or oral exposure (Ambrose et al. 1976; Berman and Rehnberg 1983; Käkelä et al. 1999; RTI 1988a, 1988b; Smith et al. 1993; Weischer et al. 1980). As noted in the Developmental Toxicity section, additional studies are needed to verify this apparent sensitivity. No human or animal data on the toxicokinetic properties of nickel in children or immature animals or studies examining possible age-related differences in the toxicokinetics of nickel were located. Studies with other metals, notably lead and cadmium (Bhattacharyya 1983), have found higher absorption rates in suckling animals, as compared to adults; it is not known if this is also true for nickel. Additional studies that examine potential age-related differences in nickel would provide valuable information on the susceptibility of children to nickel toxicity.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Information on ongoing studies cited in Table 3-10 was obtained from FEDRIP (2003).

Table 3-10. Ongoing Studies on Nickel Health Effects

Investigator	Institute	Research area
Costa, M	New York University, School of Medicine	Examination of the epigenetic mechanisms of nickel carcinogenesis
Klein, JN	University of Iowa	
Merchant, JA	University of Iowa	
Reynolds, SJ	University of Iowa	
Lynch, CF	University of Iowa	
Schnoor, J	University of Iowa	
Hunninghake, GW	University of Iowa	
Sprince, NL	University of Iowa	
Leikauf, GD	University of Cincinnati	Genetic determinants on nickel-induced toxicity
Benoff, SH	North Shore University Hospital	Mechanism of nickel-induced sperm effects
Erhlrich, A	Department of Veterans Affairs, Medical Center, Kansas City	Relationship between body piercing and nickel sensitivity
Rokita, SE	University of Maryland	Mechanisms of nickel carcinogenicity

Source: FEDRIP 2003

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Nickel is a transition metal in group VIII of the Periodic Table following iron and cobalt (Cotton and Wilkinson 1980). Its outer shell of electrons has a $4s^2 3d^8$ configuration. While nickel can exist in oxidation states -1, 0, +2, +3, and +4, its only important oxidation state is nickel(+2) under normal environmental conditions.

Nickel forms useful alloys with many metals. It is added to metals to increase their hardness, strength, and corrosion resistance. The most familiar nickeliferous alloys are stainless steel and coinage metal.

Nickel oxide also comes in a black crystalline form that has a slightly higher oxygen content than its formula, NiO (Antonsen 1981). The nickel content of black nickel oxide is 76–77% compared with 78.5% for the more stable green nickel oxide. Nickel ammonium sulfate, nickel sulfate, nickel chloride, and nickel nitrate usually exist as hexahydrates, while nickel acetate, nickel cyanide, and nickel sulfamate are in the form of a tetrahydrate.

Information regarding the chemical identity of nickel and nickel compounds is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Metallic nickel is a hard, lustrous, silvery white metal, which, in its bulk form, is resistant to attack by air and water at ordinary temperatures. However, powdered nickel is reactive in air and may spontaneously ignite.

Nickel has typical metallic properties; it can be readily rolled, drawn into wire, forged, and polished. It is also ferromagnetic and a good conductor of both heat and electricity. Nickel is positioned after hydrogen in the electrochemical series and slowly displaces hydrogen ions from dilute hydrochloric and sulfuric acids. It reacts more rapidly with nitric acid. Nickel is highly resistant to attack by strong alkalis (Hawley 1981). Black nickel oxide readily yields nickel salts.

Table 4-1. Chemical Identity of Nickel and Compounds[a]

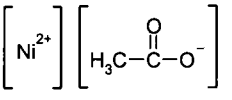
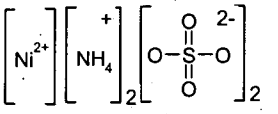
Characteristic	Nickel	Nickel acetate	Nickel ammonium sulfate
Synonyms	CI 77775; Nickel 200; Nickel 201; Nickel 205; Nickel 270; Alnico[b]; NP 2[b]	Acetic acid, nickel(2+) salt; nickel diacetate; nickelous acetate; nickel(II) acetate	Ammonium nickel sulfate; sulfuric acid, ammonium nickel(2+) salt; ammonium disulfatonickelate(II)
Registered trade name(s)	Monel[b]; Iconel[b]; Icoloy[b]; Raney nickel[c]; Nimonic[d]; Hastelloy[d]; Udimet[d]; Mar M[d]; René 41[d]; Waspaloy[d]	No data	No data
Chemical formula	Ni	$Ni(CH_3CO_2)_2$	$Ni(NH_4)_2(SO_4)_2$
Chemical structure	Ni		
Identification numbers:			
CAS registry	7440-02-0	373-02-4	15699-18-0
NIOSH RTECS	QR5950000[d]	QR6125000	WS6050000[d]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/ IMCO shipping	No data	No data	No data
HSDB	1096	1029	1241
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Nickel and Compounds[a]

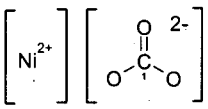
Characteristic	Nickel carbonate	Nickel chloride	Nickel cyanide
Synonyms	CI 77779; Carbonic acid, nickel(2+) salt; nickel (II) carbonate; nickelous carbonate; nickel monocarbonate	Nickel(II) chloride; nickel dichloride; nickelous chloride	Nickel(II) cyanide; nickel dicyanide; dicyanonickel
Registered trade name(s)	No data	No data	No data
Chemical formula	$NiCO_3$	$NiCl_2$	$Ni(CN)_2$
Chemical structure		Cl – Ni – Cl	NC– Ni – CN
Identification numbers:			
CAS registry	3333-67-3	7718-54-9	557-19-7
NIOSH RTECS	QR6200000[d]	QR6475000[d]	QR6495000[d]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/ IMCO shipping	No data	No data	UN1653
HSDB	1662	860	1185
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Nickel and Compounds[a]

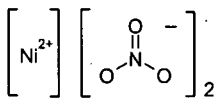
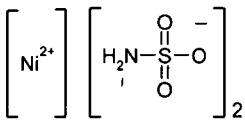
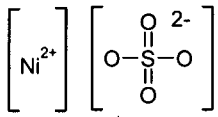
Characteristic	Nickel oxide	Nickel nitrate	Nickel subsulfide
Synonyms	Bunsenite; CI 77777; green nickel oxide; mononickel oxide; nickel(II) oxide; nickelous oxide; nickel monoxide[b]; nickel oxide sinter 75[b]; nickel protoxide; mononickel	Nitric acid, nickel(2+) salt, nickelous nitrate; nickel dinitrate; nickel(II) nitrate	Trinickel disulfide[b]; nickel sulfide; Heazlewoodite; nickel sesquisulfide[b]; khislevudite[b]; nickel tritadisulfide
Registered trade name(s)	Nickel oxide	No data	No data
Chemical formula	NO	$Ni(NO_3)_2$	Ni_3S_2
Chemical structure	Ni – O		No data
Identification numbers:			
CAS registry	1313-99-1	13138-45-9	12035-72-2
NIOSH RTECS	QR8400000[d]	QR7200000[d]	QR9800000[d]
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/ IMCO shipping	No data	UN 27525; IMO 5.1	No data
HSDB	1664	1829	2965
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Nickel and Compounds[a]

Characteristic	Nickel sulfamate	Nickel sulfate
Synonyms	Sulfamic acid, nickel(2+) salt[d]; Nickel amidosulfate[e]; Nickel (II) sulfamate[e]; Aeronikl 250[d]; Aeronikl 400[d]; Aeronikl 575[d]	Nickel monosulfate; nickelous sulfate; nickel(II) sulfate; sulfuric acid nickel salt[b]
Registered trade name(s)	No data	No data
Chemical formula	$Ni(NH_2SO_3)_2$	$NiSO_4$
Chemical structure		
Identification numbers:		
CAS registry	13770-89-3[d]	7786-81-4
NIOSH RTECS	QR9275000[d]	QR9350000[d]
EPA hazardous waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/ IMCO shipping	No data	ID8027
HSDB	No data	1114
NCI	No data	NCI-C60344[d]

[a]All information obtained from HSDB 2003 except where noted.
[b]Czerczak and Gromiec 2001
[c]Tien and Howson 1981; Windholz 1983. Names refer to alloys of nickel. Generally, there is a series of alloys with the same trade name (e.g., Monel alloy K-400, Monel alloy K-500).
[d]RTECS 2003
[e]Laschelles and Nicholls 1991

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; Ni = nickel; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Information regarding the physical and chemical properties of nickel and 10 of its compounds is located in Table 4-2.

Table 4-2. Physical and Chemical Properties of Nickel and Compounds[a]

Property	Nickel	Nickel acetate	Nickel ammonium sulfate	Nickel carbonate
Molecular weight	58.69	176.80	286.90	118.70
Color	Silvery	Green	Blue-green	Green
Physical state	Solid	Solid	Solid	Solid
Melting point	1,455 °C	Decomposes	No data	Decomposes
Boiling point	2,730 °C	16.6 °C	No data	No data
Density	8.91 g/cm^3	1.798 g/cm^3	1.923 g/cm^3	4.39 g/cm^3
Odor	Odorless	Acetic odor	Odorless	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	1.13 mg/L at 37 °C[b]	17 weight% at 68 °C	104 g/L at 20 °C	93 mg/L at 25 °C
Organic solvents	No data	Insoluble in alcohol	Insoluble in alcohol	No data
Partition coefficients:				
K_{ow}	No data	No data	No data	No data
K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 1,810 °C	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	Nonflammable	Nonflammable
Flashpoint	No data	No data	Nonflammable	Nonflammable
Flammability limits	No data	No data	Nonflammable	Nonflammable
Conversion factor	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Nickel and Compounds[a]

Property	Nickel chloride	Nickel cyanide	Nickel oxide	Nickel nitrate
Molecular weight	129.60	110.73	74.69	182.72
Color	Golden yellow	Yellow brown	Green or black	Green
Physical state	Solid	Solid	Solid	Solid
Melting point	1,001 °C	>200 °C	1,955 °C	56.7 °C[b]
Boiling point	Sublimes at 973 °C	Decomposes	No data	136.7 °C[b]
Density	3.55 g/cm^3	2.393 g/cm^3	6.72 g/cm^3	2.05 g/cm^3[c]
Odor	None	Weak almond odor	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	642 g/L at 20 °C	Insoluble	1.1 mg/L at 20 °C	2,385 g/L at 0 °C[c]; 48.5 weight% at 20 °C[c]
Organic solvents	Soluble in ethanol; 180 g/L at 20 °C in ethylene glycol	No data	No data	Insoluble in alcohol[b]; soluble in alcohol[c]
Partition coefficients:				
K_{ow}	No data	No data	No data	No data
K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 671 °C	No data	No data	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	Nonflammable	Nonflammable	No data	No data
Flashpoint	Nonflammable	Nonflammable	No data	No data
Flammability limits	Nonflammable	Nonflammable	No data	No data
Conversion factor	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Nickel and Compounds[a]

Property	Nickel subsulfide	Nickel sulfamate	Nickel sulfate
Molecular weight	240.212	322.94[e,f]	154.75
Color	Pale yellowish[d]	No data	Greenish-yellow
Physical state	Solid	Solid	Solid
Melting point	787 °C	No data	840 °C
Boiling point	No data	No data	Decomposes at 840 °C
Density	5.87 g/cm^3	No data	4.01 g/cm^3
Odor	No data	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	517 mg/L at 37 °C[b]	No data	293 g/L at 0 °C
Organic Solvents	No data	No data	Insoluble in ether and acetone; 0.2 g/L at 35 °C in ethanol; 0.9 g/L at 35 °C in methanol
Partition coefficients:			
K_{ow}	No data	No data	No data
K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	Nonflammable
Flashpoint	No data	No data	Nonflammable
Flammability limits	No data	No data	Nonflammable
Conversion factor	No data	No data	No data
Explosive limits	No data	No data	No data

[a]All information obtained from HSDB 2003 except where noted.
[b]Ishimatsu et al. 1995.
[c]Data are for the hexahydrate.
[d]IARC 1990
[e]Data are for the tetrahydrate.
[f]Laschelles and Nicholls 1991

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Nickel ranks 24th in order of abundance in the earth's crust, with an average concentration of 0.0086%. Its crustal concentration varies from ≤0.0001 to >0.3%. Economically exploitable ore deposits typically contain 1–3% nickel. The concentration of nickel increases towards the center of the earth, and nickel is estimated to comprise 0.22% of the earth's mantle and 5.8% of its core (Duke 1980a). Overall, it is the fifth most abundant element on Earth after iron, oxygen, magnesium, and silicon. Nickel is found combined with iron in meteorites; the nickel content ranges from 5 to 50% (Duke 1980a; Mastromatteo 1986). It is also found in sea floor nodules (Mastromatteo 1986).

Nickel ores are of two general types: magmatic sulfide ores, which are mined underground, and lateritic hydrous nickel silicates or garnierites, which are surface mined (Duke 1980a; Warner 1984).

The most important nickel sulfide-arsenide deposits are in hydrothermal veins associated with mafic (i.e., rich in magnesium and iron) and ultramafic igneous rock. These ores typically contain 1–3% nickel. Pentlandite $(Ni,Fe)_9S_8$ is the principle ore. Pentlandite often occurs along with the iron mineral pyrrhotite and the copper mineral chalcopyrite, and part of the smelting and refining process separates the copper and iron from the nickel. The ore is concentrated by physical means (i.e., flotation and magnetic separation) after crushing. One of the largest sulfidic nickel deposits is in Sudbury, Ontario, Canada. Nickeliferous sulfide deposits are also found in Thompson, Manitoba, Canada; South Africa; Russia (primarily Siberia); Finland; western Australia; and Minnesota (Ademec and Kihlgren 1967; Duke 1980a).

The lateritic hydrous nickel silicate ores are formed by the weathering of rocks rich in iron and magnesium in humid tropical areas. The repeated processes of dissolution and precipitation lead to a uniform dispersal of the nickel that is not amenable to concentration by physical means; therefore, these ores are concentrated by chemical means such as leaching. Lateritic ores are less well defined than sulfide ores. The nickel content of lateritic ores is similar to that of sulfide ore and typically ranges from 1 to 3% nickel. Important lateritic deposits of nickel are located in Cuba, New Caledonia, Indonesia, Guatemala, the Dominican Republic, the Philippines, and Brazil. Fossil nickeliferous laterite deposits are found in Oregon, Greece, and the former Soviet Union, where humid, tropical climates prevailed in the

past. Lateritic deposits constitute the largest nickel reserves (Ademec and Kihlgren 1967; Antonsen and Springer 1967; Duke 1980a). Thirty-five percent of known nickel reserves are in Cuba (Kirk 1988b).

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

Lateritic ore is processed by pyrometallurgical or hydrometallurgical processes. In the pyrometallurgical process, sulfur is generally added to the oxide ore during smelting, usually as gypsum or elemental sulfur, and an iron-nickel matte is produced. The smelting process that does not include adding sulfur produces a ferronickel alloy, containing ≤50% nickel, which can be used directly in steel production. Hydrometallurgical techniques involve leaching with ammonia or sulfuric acid, after which the nickel is selectively precipitated (Duke 1980b; IARC 1990; Tien and Howson 1981; Warner 1984). Alloys, such as stainless steels, are produced by melting primary metals and scrap in large arc furnaces and adjusting the carbon content and concentration of alloying metals to the desired levels. More information on the mining, smelting, and refining of nickel can be found in Duke (1980b), Tien and Howson (1981), and Warner (1984).

Domestic primary nickel production in the United States ceased in 1986 (Chamberlain 1985; Kirk 1988a) with the closing of the Hanna mine and smelter in Riddle, Oregon, and the AMAX refinery in Braithwaite, Louisiana. However, Glenbrook Nickel Company purchased the Riddle, Oregon, facility in 1989 and had reactivated the mining and smelting operation, but then decommissioned both the mining and smelting operations in 2000. World mine production of nickel in 2001 was estimated at 1,330,000 metric tons (Kuck 2001). Secondary nickel production from scrap is a major source of nickel for industrial applications. In 1988, an estimated 59,609 and 3,700 short tons of nickel were produced from ferrous and nonferrous scrap, respectively. Nickel recovery from scrap is estimated by using the gross weight of the scrap and a weighted average nickel content (e.g., 7.5% for stainless steel). The secondary recovery from ferrous scrap was considerably higher and the recovery from nonferrous scrap was considerably lower than for the previous 7 years in which the annual recovery of nickel from ferrous and nonferrous scrap ranged from 30,034 to 389,265 short tons and from 8,392 to 19,776 short tons,

respectively. The production of refined nickel in 1993 has been estimated as 220,700, 346,800, 176,200, 52,100, and 96,300 short tons for North America, Europe, Asia, Africa, and Australia, respectively (ABMS 1994). In 1994, the world distribution of refined nickel production was 21%, Russia (Commonwealth of Independent States); 17%, Western Europe; 14%, Japan; 13%, Canada; 13%, Australia/New Caledonia; 6%, Africa; 4%, Dominican Republic; 4%, China; and 8%, Brazil, Columbia, Cuba, Eastern Europe, Indonesia, and the United States (Anderson 1995). The reported world consumption of refined nickel was 1,150,800 metric tons in 2001, up from 997,800 metric tons in 1997 (ABMS 2002).

Tables 5-1 and 5-2 list the facilities that produced, imported, processed, or used nickel and its compounds, respectively, in 2001 according to reports made to the EPA under the requirements of Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986, which were subsequently published in the Toxic Chemical Release Inventory (TRI) (TRI01 2003). Companies were required to report if they produced, imported, or processed ≥75,000 pounds of nickel and its compounds or used >10,000 pounds. Also included in Tables 5-1 and 5-2 are the maximum amount of nickel and its compounds, respectively, that these facilities had on site and whether nickel was produced, processed, or used by the facility.

5.2 IMPORT/EXPORT

In 2001, the United States imported 144,000 metric tons of nickel, including 110,000 metric tons of unwrought metal, 8,310 metric tons of powder and flakes, 11,600 metric tons of ferronickel, 5,580 metric tons of nickel waste and scrap, 3,180 metric tons stainless steel scrap, 1,350 metric tons of oxide and oxide sinter, and 3,200 metric tons of nickel salts (Kuck 2001). In 2001, Canada supplied the largest share of primary nickel, 60,700 metric tons (42%). Norway was the second largest exporter of primary nickel to the United States with 18,900 metric tons (13%) followed by Australia and Russia with 17,200 and 9,280 metric tons, respectively. The 144,000 metric tons of nickel imported in 2001 was down from the 158,000 and 167,000 metric tons imported in 1996 and 2000, respectively (Kuck 1997, 2001). From 1980 to 1985, nickel imports as a percentage of consumption ranged from 68 to 76%. This is comparable to the figures for 2000 and 2001 of 84 and 72%, respectively (Kuck 2001).

The amount of exported nickel dropped sharply in 1986 to 15,217 short tons from 35,245 short tons the previous year (Kirk 1988a), which coincided with the cessation of primary nickel production in the United States. The nickel content of exported primary and secondary nickel in 2001 was 57,000 metric tons, most of which was in the form of unwrought metal (Kuck 2001).

Table 5-1. Facilities that Produce, Process, or Use Nickel Metal

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	42	100	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
AR	28	100	999,999	1, 7, 8, 11, 12, 13
AZ	17	0	9,999,999	1, 4, 5, 7, 8, 9, 10, 11, 12
CA	91	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
CO	11	1,000	999,999	2, 3, 4, 6, 7, 8, 11, 12
CT	47	100	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
DE	1	10,000	99,999	8
FL	20	0	499,999,999	7, 8, 10, 11
GA	30	0	999,999	1, 2, 3, 5, 7, 8, 10, 11, 12, 14
IA	43	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	1	100,000	999,999	1, 3, 12
IL	111	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
IN	128	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	17	100	999,999	8, 9, 11, 12, 14
KY	42	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 14
LA	20	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 10, 13, 14
MA	43	1,000	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12
MD	5	10,000	999,999	2, 4, 8, 9
ME	9	1,000	9,999,999	1, 3, 7, 8, 12
MI	105	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MN	36	1,000	999,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14
MO	37	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 10, 12
MS	19	1,000	9,999,999	2, 3, 7, 8, 12
MT	1	100	999	6, 11
NC	50	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
ND	6	10,000	999,999	2, 3, 7, 8, 9, 12
NE	15	100	999,999	1, 2, 3, 5, 8, 9, 11
NH	9	100	99,999	8
NJ	19	1,000	49,999,999	1, 2, 3, 4, 7, 8, 9, 11, 13
NM	5	100	999,999	2, 3, 6, 7, 8, 10, 11
NV	4	10,000	99,999	1, 5, 8, 12
NY	58	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12
OH	173	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	47	1,000	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
OR	17	1,000	999,999	1, 2, 3, 4, 7, 8, 9, 11, 12
PA	198	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	2	1,000	99,999	8, 12
RI	7	100	999,999	2, 3, 7, 8, 9
SC	40	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13
SD	6	1,000	999,999	1, 5, 8

Table 5-1. Facilities that Produce, Process, or Use Nickel Metal

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	45	100	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	103	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	14	1,000	999,999	1, 3, 4, 7, 8, 11, 12
VA	15	100	999,999	1, 4, 5, 6, 7, 8, 9, 12, 13, 14
VT	3	1,000	99,999	2, 4, 8, 11
WA	13	0	999,999	2, 3, 7, 8, 9
WI	136	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
WV	13	100	999,999	2, 3, 6, 7, 8, 9, 12
WY	3	1,000	99,999	1, 4, 8, 9, 12

Source: TRI01 2003

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite Use/Processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Table 5-2. Facilities that Produce, Process, or Use Nickel Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	4	10,000	9,999,999	1, 2, 3, 5, 7, 10, 11, 12
AL	28	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	13	10,000	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
AZ	12	100	99,999,999	1, 2, 3, 4, 5, 6, 8, 9, 11, 12, 13, 14
CA	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	9	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
CT	24	100	999,999	1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13
DC	1	10,000	99,999	1, 3, 11
DE	7	1,000	999,999	1, 2, 3, 5, 6, 7, 9, 10, 12, 13
FL	20	0	999,999	1, 2, 3, 4, 5, 6, 8, 9, 12, 13, 14
GA	22	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
HI	1	1,000	9,999	1, 5, 12
IA	16	100	9,999,999	1, 3, 5, 7, 8, 9, 10, 12, 13, 14
ID	3	100,000	999,999	1, 5, 8
IL	82	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	76	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	13	0	999,999	1, 5, 7, 8, 9, 10, 11, 12, 13
KY	41	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	30	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
MA	15	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12
MD	11	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
ME	3	100	99,999	1, 5, 8, 11, 13
MI	66	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	23	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
MO	32	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	15	1,000	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
MT	6	0	9,999,999	1, 2, 3, 4, 5, 6, 12, 13, 14
NC	25	0	999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
ND	4	1,000	9,999	1, 5, 12, 13, 14
NE	8	100	999,999	1, 3, 4, 5, 7, 8, 9, 10, 12, 13
NH	5	100	99,999	1, 5, 7, 8, 9
NJ	15	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
NM	6	10,000	999,999	1, 3, 4, 5, 9, 11, 12, 13
NV	10	100	10,000,000,000	1, 5, 6, 9, 10, 12, 13, 14
NY	26	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OH	84	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	16	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	10	1,000	9,999,999	1, 5, 7, 8, 11, 12
PA	104	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Nickel Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PR	5	100	99,999	1, 2, 5, 10, 13
RI	6	100	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11
SC	29	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
SD	1	10,000	99,999	1, 5, 9, 13
TN	37	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
TX	81	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	8	10,000	49,999,999	1, 2, 3, 4, 5, 7, 9, 11, 12, 13, 14
VA	21	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VI	1	100,000	999,999	10
WA	6	10,000	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13
WI	41	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WV	17	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
WY	3	100	99,999	1, 5, 9, 12, 13

Source: TRI01 2003

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite Use/Processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

5.3 USE

Nickel is primarily used in alloys because it imparts to a product such desirable properties as corrosion resistance, heat resistance, hardness, and strength. Nickel alloys are often divided into categories depending on the primary metal with which they are alloyed and their nickel content. Copper-nickel alloys (e.g., Monel alloys) are used for industrial plumbing, marine equipment, petrochemical equipment, heat exchangers, pumps, and electrodes for welding. Coinage metal contains 75% copper and 25% nickel. Nickel-chromium alloys (e.g., Nichrome) are used for heating elements. Nickel-iron-chromium alloys (e.g., Inconel) provide strength and corrosion resistance over a wide temperature range. Hastelloy alloys, which contain nickel, chromium, iron, and molybdenum, provide oxidation and corrosion resistance for use with acids and salts. Nickel-based superalloys have the required high-temperature strength and creep and stress resistance for use in gas-turbine engines. Nickel silvers, and nickel alloys with zinc and copper, have an attractive white color and are used for coatings on tableware and as electrical contacts. Raney nickel, 50% aluminum and 50% nickel, is used as a catalyst in hydrogenation reactions. Large amounts of nickel are alloyed with iron to produce alloy steels, stainless steels, and cast irons. Stainless steel may contain as much as 25–30% nickel, although 8–10% nickel is more typical. Alloy steels generally contain 0.3–5% nickel. In addition to imparting characteristics such as strength, toughness, corrosion resistance, and machinability, some applications make use of nickel's magnetic characteristics. Most permanent magnets are made of alloys of iron and nickel (Tien and Howson 1981).

Nickel salts are used in electroplating, ceramics, pigments, and as catalysts. Sinter nickel oxide is used as charge material in the manufacture of alloy steel and stainless steel. Nickel is also used in alkaline (nickel-cadmium) batteries.

The distribution of nickel consumption by use in 2001 was as follows: stainless and heat-resistant steel, 60%; nonferrous alloys, excluding superalloys, 4%; nickel-copper, copper-nickel and other nickel alloys, 6%; electroplating, 6%; superalloys, 9%; and other, 10%. Other uses include cast iron; chemicals and chemical use; electric, magnet, expansion alloys; steel alloys, other than stainless steel; batteries; and ceramics. Eighty-six percent of nickel consumption was for the production of nickel metal and alloys (Kuck 2001).

5.4 DISPOSAL

Little information concerning the disposal of nickel and its compounds is found in the literature. Much of the nickel used in metal products (e.g., stainless steel, nickel plate, various alloys) is recycled, which is evident from the fact that 48% of nickel consumption in 2001 was derived from secondary scrap (Kuck 2001). According to the 2001 TRI, 95.3% of the 56,119,316 pounds (25,478,169 kg) of nickel and nickel compounds released on-site is released to land (see Section 6.1) (TRI01 2003). In addition, >21 million pounds of nickel were transferred to off-site locations that year with about 90% being recycled. Steel and other nickel-containing items discarded by households and commercial establishments are generally recycled, landfilled, or incinerated along with normal commercial and municipal trash.

Nickel is removed from electroplating wastes by treatment with hydroxide, lime, and/or sulfide to precipitate the metal (HSDB 2003). Adsorption with activated carbon, activated alumina, and iron filings is also used for treating nickel-containing waste water. Ion exchange is also used for nickel removal and recovery.

Nickel and its compounds have been designated as toxic pollutants by EPA pursuant to Section 307(a)(1) of the Federal Water Pollution Control Act (40 CFR 401.15). As such, permits are issued by the states under the National Pollutant Discharge Elimination System (NPDES) for discharges of nickel that meet the applicable requirements (40 CFR 401.12).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Nickel has been identified in at least 862 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for nickel is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 855 are located within the United States, 5 are located in the Commonwealth of Puerto Rico, and 2 are located in the Territory of Guam (the Commonwealth of Puerto Rico and the Territory of Guam are not shown).

Nickel and its compounds are naturally present in the earth's crust, and releases to the atmosphere occur from natural discharges such as windblown dust and volcanic eruptions, as well as from anthropogenic activities. It is estimated that 8.5 million kg of nickel are emitted into the atmosphere from natural sources such as windblown dust, volcanoes, and vegetation each year. Five times that quantity is estimated to come from anthropogenic sources. The burning of residual and fuel oil is responsible for 62% of anthropogenic emissions, followed by nickel metal refining, municipal incineration, steel production, other nickel alloy production, and coal combustion (Bennett 1984; Schmidt and Andren 1980). Table 6-1 lists releases from facilities in the United States that produced, processed, or used nickel in 2001, according to TRI (TRI01 2003). These releases, which totaled 2,904,982 pounds (1,318,862 kg), were distributed as follows: 85.4% to land, 11.0% to air, 0.7% to water, and 0.8% to underground injection. Table 6-2 lists releases from facilities in the United States that produced, processed, or used nickel compounds in 2001, according to TRI (TRI01 2003). These releases, which totaled 53,214,334 pounds (24,159,307 kg), were distributed as follows: 95.8% to land, 1.9% to air, 0.5% to water, and 1.8% to underground injection. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

The general population is exposed to low levels of nickel in ambient air, water, and food. Exposure also occurs from smoking. The general population takes in most nickel through food. The average daily dietary nickel intake for U.S. diets is 69–162 μg (O'Rourke et al. 1999; Pennington and Jones 1987; Thomas et al. 1999). These values agree with those from European studies. Typical average daily intakes of nickel from drinking water and air are approximately 8 and 0.04 μg, respectively. The highest general population exposures to nickel are typically observed in nickel refineries. This is reflected, for example,

Figure 6-1. Frequency of NPL Sites with Nickel Contamination

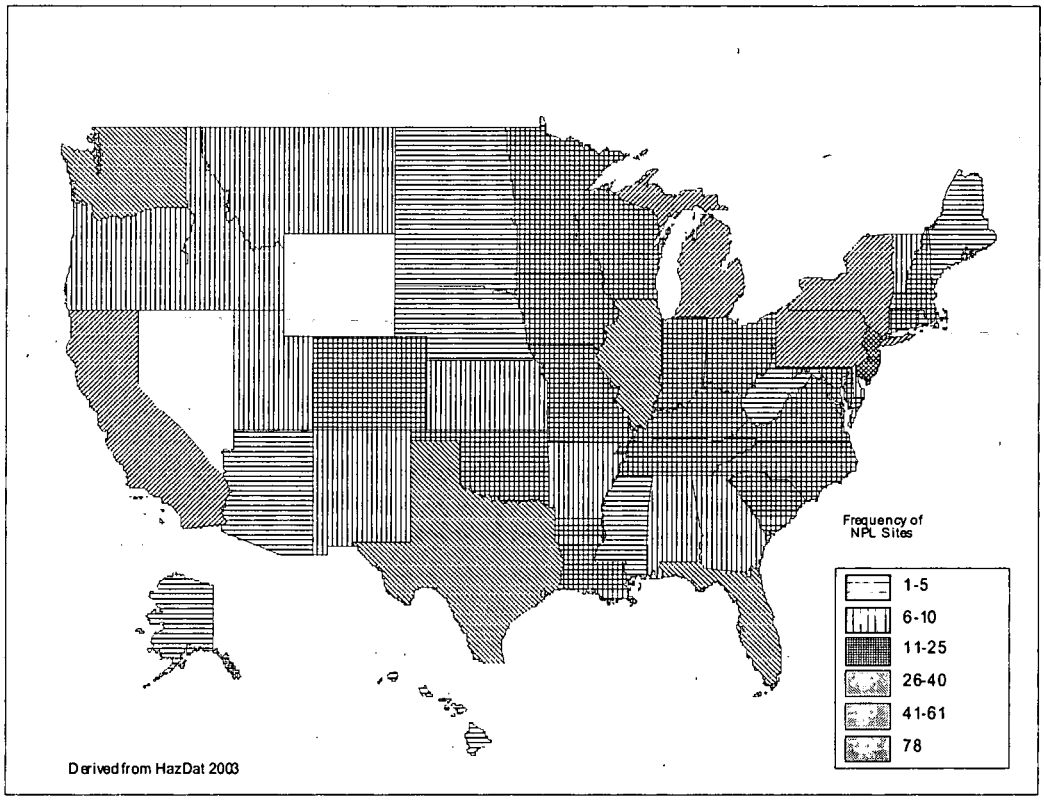

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Nickel

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AL	51	4,267	815	0	292	5,374	64,086	69,460
AR	34	15,870	20	0	2,920	18,810	16,512	35,322
AZ	21	1,052	No data	0	621,654	622,706	5,340	628,046
CA	103	2,538	579	0	661,818	664,935	32,720	697,655
CO	14	564	5	0	10,255	10,824	8,209	19,033
CT	51	2,641	1,037	0	0	3,678	198,750	202,428
DE	1	0	No data	0	0	0	250	250
FL	22	1,293	58	3,375	0	4,726	32,333	37,059
GA	39	5,262	408	0	142	5,812	10,782	16,594
IA	54	3,083	1,036	0	399	4,518	42,706	47,224
ID	3	65	No data	0	232,200	232,265	No data	232,265
IL	131	11,559	2,448	0	174,167	188,174	142,179	330,353
IN	142	38,719	517	0	5,676	44,912	3,765,019	3,809,931
KS	21	2,051	0	0	10	2,061	2,382	4,443
KY	54	103,156	95	4,766	38,290	146,307	56,547	202,854
LA	24	966	614	0	16,803	18,383	38,609	56,992
MA	46	4,285	428	0	416	5,129	81,259	86,388
MD	13	2,300	No data	0	0	2,300	1,949	4,249
ME	12	336	305	0	0	641	7,236	7,877
MI	117	17,594	1,337	0	4,395	23,326	244,455	267,781
MN	43	1,303	5	0	0	1,308	108,685	109,993
MO	50	5,418	275	0	39,049	44,742	47,671	92,413

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Nickel

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
MS	23	2,439	20	0	910	3,369	1,888	5,257
MT	1	60	No data	0	238,000	238,060	No data	238,060
NC	61	10,827	334	0	260	11,421	181,954	193,375
ND	6	35	3	0	3	41	2,427	2,468
NE	20	2,199	93	0	5	2,297	15,250	17,547
NH	15	945	9	0	0	954	28,642	29,596
NJ	21	5,908	1	0	0	5,909	13,009	18,918
NM	5	892	1	0	255	1,148	313	1,461
NV	5	6,432	0	0	250	6,682	1,000	7,682
NY	67	34,043	384	0	7,798	42,225	76,020	118,245
OH	217	30,038	2,662	0	49,305	82,005	617,283	699,288
OK	67	5,191	204	0	108,736	114,131	28,430	142,561
OR	19	3,654	150	0	30,389	34,193	41,940	76,133
PA	218	24,168	1,297	0	7,016	32,481	546,197	578,678
PR	3	0	No data	0	250	250	0	250
RI	8	511	5	0	0	516	5,733	6,249
SC	43	2,511	387	0	9,321	12,219	261,771	273,990
SD	6	262	No data	0	0	262	338	600
TN	52	4,321	267	0	66,508	71,096	66,463	137,559
TX	130	7,022	3,401	14,523	81,007	105,953	368,361	474,314
UT	18	623	0	0	8,600	9,223	3,342	12,565
VA	21	1,742	383	0	5	2,130	8,945	11,075
VT	6	0	No data	0	0	0	608	608

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Nickel

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
WA	17	1,766	809	0	6,987	9,562	45,213	54,775
WI	146	10,807	565	0	16,264	27,636	147,976	175,612
WV	14	332	5	5	21,308	21,650	1,512	23,162
WY	3	48	0	0	18,590	18,638	10	18,648
Total	2258	381,098	20,962	22,669	2,480,253	2,904,982	7,372,304	10,277,286

Source: TRI01 2003

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Nickel Compounds

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
AK	5	63	147	43,000	1,229,689	1,272,899	262	1,273,161
AL	30	8,937	7,182	0	895,880	911,999	134,786	1,046,785
AR	15	12,780	1,014	0	946,777	960,571	71,175	1,031,746
AZ	13	6,610	0	0	750,699	757,309	13,968	771,277
CA	70	5,062	1,485	0	845,882	852,429	203,254	1,055,683
CO	9	1,450	6	0	29,179	30,635	20,236	50,871
CT	24	1,803	3,879	0	0	5,682	291,645	297,327
DC	1	0	No data	0	0	0	11	11
DE	7	33,951	1,975	0	70,147	106,073	73,990	180,063
FL	26	175,369	4,204	0	631,991	811,564	208,053	1,019,617
GA	25	8,657	10,221	0	537,378	556,256	18,571	574,827
HI	1	42,500	5	0	0	42,505	250	42,755
IA	17	92,848	32,851	0	124,030	249,729	158,889	408,618
ID	3	1,421	5	0	56,557	57,983	0	57,983
IL	94	28,661	1,556	0	538,247	568,464	504,405	1,072,869
IN	78	31,156	8,139	250	1,453,416	1,492,961	630,254	2,123,215
KS	13	2,567	0	0	70,315	72,882	20,295	93,177
KY	41	18,395	32,400	0	982,983	1,033,778	155,386	1,189,164
LA	33	8,644	6,923	2,850	194,728	213,145	456,795	669,940
MA	19	20,322	585	0	23,531	44,438	163,504	207,942
MD	12	45,799	3,139	533	24,452	73,923	110,054	183,977
ME	3	935	470	0	0	1,405	7,205	8,610

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Nickel Compounds

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
MI	72	26,240	1,553	0	4,133,770	4,161,563	2,238,774	6,400,337
MN	22	14,202	330	0	79,480	94,012	187,510	281,522
MO	33	10,367	4,922	0	576,710	591,999	123,946	715,945
MS	15	24,966	1,342	62,000	93,266	181,574	274,472	456,046
MT	7	1,382	1	227,070	432,045	660,498	106,064	766,562
NC	29	7,143	2,248	0	517,317	526,708	3,263	529,971
ND	4	4,174	11	0	72,800	76,985	50,683	127,668
NE	9	453	30	0	95,515	95,998	3,981	99,979
NH	5	344	5	0	860	1,209	8,903	10,112
NJ	17	4,401	8,542	0	14,283	27,226	54,906	82,132
NM	5	452	1	0	435,293	435,746	0	435,746
NV	11	2,744	687	6	24,369,117	24,372,554	1,247	24,373,801
NY	28	9,796	38,067	0	99,968	147,831	271,609	419,440
OH	96	19,524	9,013	606,600	861,928	1,497,065	2,790,023	4,287,088
OK	16	7,677	719	0	73,310	81,706	48,301	130,007
OR	11	2,392	250	0	51,263	53,905	2,181	56,086
PA	114	99,552	11,377	0	465,609	576,538	2,773,485	3,350,023
PR	8	87,442	971	0	0	88,413	60,338	148,751
RI	6	253	261	0	250	764	3,719	4,483
SC	37	3,314	2,581	0	164,531	170,426	94,780	265,206
SD	1	216	No data	0	20,000	20,216	0	20,216
TN	38	3,618	10,581	0	512,229	526,428	204,563	730,991
TX	96	18,977	6,515	38,380	498,227	562,099	740,460	1,302,559

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Nickel Compounds

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Under-ground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on and off-site release
UT	10	2,117	6,300	0	6,969,075	6,977,492	881	6,978,373
VA	23	55,238	3,095	0	311,312	369,645	67,020	436,665
VI	1	196	0	0	1,773	1,969	4,925	6,894
WA	7	1,117	840	0	75,227	77,184	1,933	79,117
WI	44	3,941	2,385	0	2,804	9,130	126,143	135,273
WV	17	41,463	16,033	0	518,525	576,021	266,001	842,021
WY	3	3,063	0	0	131,737	134,800	0	134,800
Total	1324	1,004,693	244,846	980,689	50,984,105	53,214,334	13,753,100	66,967,434

Source: TRI01 2003

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

in the intakes of nickel from water and air reported in Sudbury, Ontario, Canada, of 140 and 15 μg/day, respectively. However, this source of exposure to nickel is not a concern for U.S. populations, due to the absence of refinery operations in the United States. Other potential sources of nickel exposure are from contaminated intravenous fluids, dialysis, and leaching and corrosion of nickel from prostheses.

Occupational exposure to nickel may occur by dermal contact or by inhalation of aerosols, dusts, fumes, or mists containing nickel. Dermal contact may also occur with nickel solutions, such as those used in electroplating, nickel salts, and nickel metal or alloys. Nickel-containing dust may be ingested where poor work practices exist or where poor personal hygiene is practiced. A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimates that 727,240 workers are potentially exposed to some form of nickel metal, alloys, salts, or inorganic nickel compounds in the United States (NIOSH 1990). The forms of nickel that these workers were probably exposed to and the levels of exposure for different industries and operations were reviewed by Warner (1984) and IARC (1990).

Information on nickel exposure from hazardous waste sites is lacking. The most probable route of exposure from hazardous waste sites would be from consumption of contaminated drinking water, inhalation of dust, dermal contact with bath/shower water, soil, or dust, and ingestion of nickel-contaminated soil. Groundwater contamination may occur where the soil has a coarse texture and where acid waste, such as waste from plating industries, is discarded. However, there is no information linking this source of nickel contamination in groundwater to levels of nickel in drinking water that would be of concern (>50 μg/L).

Nickel releases to the atmosphere are mainly in the form of aerosols that cover a broad spectrum of sizes. Particulates from power plants tend to be smaller than those from smelters (Cahill 1989; Schroeder et al. 1987). Atmospheric aerosols are removed by gravitational settling and dry and wet deposition. Submicron particles may have atmospheric half-lives as long as 30 days (Schroeder et al. 1987). Monitoring data confirm that nickel can be transported far from its source (Pacyna and Ottar 1985). Average ambient air nickel concentrations in the United States measured during 1977–1982 ranged between 7 and 12 ng/m^3 (EPA 1986a). A recent estimate of ambient nickel concentrations in the United States based on data collected in 1996 is 2.22 ng/m^3 (EPA 2003u). Nickel concentrations in air particulate matter in remote, rural, and U.S. urban areas have been found in the ranges from 0.01–60, 0.6–78, and 1–328 ng/m^3, respectively (Schroeder et al. 1987). Nickel concentrations in indoor air are typically <10 ng/m^3.

The form of nickel emitted to the atmosphere varies according to the type of source. Nickel species associated with combustion, incineration, and metals smelting and refining are often complex nickel oxides, nickel sulfate, and metallic nickel, and in more specialized industries, the species commonly found are nickel silicate, nickel subsulfide, and nickel chloride (EPA 1985a).

Uncontaminated freshwater and seawater generally contain about 0.300 μg/L of nickel (Barceloux 1999). Concentrations of nickel in drinking water commonly range between 0.55 and 25 μg/L and average between 2 and 4 μg/L. The concentration of nickel in rain has been reported as ≤1.5 μg/L (1.5 ppb). Concentrations of nickel in snow in Montreal, Canada, ranged from 2 to 300 ppb (Landsberger et al. 1983).

Nickel is a natural constituent of soil; levels vary widely depending on local geology and anthropogenic input. The typical concentrations of nickel reported in soil range from 4 to 80 ppm. Nickel may be transported into streams and waterways from the natural weathering of soil as well as from anthropogenic discharges and runoff. This nickel accumulates in sediment. Nickel levels in surface water are low. In some studies, nickel could not be detected in a large fraction of analyzed samples. Median nickel concentrations in rivers and lakes range from ≈0.5 to 6 μg/L. Levels in groundwater appear to be similar to those in surface water. Levels in seawater are typically 0.1–0.5 μg/L.

The speciation and physicochemical state of nickel is important in considering its behavior in the environment and availability to biota. For example, the nickel incorporated in some mineral lattices may be inert and have no ecological significance. Most analytical methods for nickel do not distinguish the form of nickel; the total amount of nickel is reported, but the nature of the nickel compounds and whether they are adsorbed to other material is not known. This information, which is critical in determining nickel's lability and availability, is site specific. Therefore, it is impossible to predict nickel's environmental behavior on a general basis.

Little is known concerning the chemistry of nickel in the atmosphere. The probable species present in the atmosphere include soil minerals, nickel oxide, and nickel sulfate (Schmidt and Andren 1980). In aerobic waters at environmental pHs, the predominant form of nickel is the hexahydrate $Ni(H_2O)_6^{2+}$ ion (Richter and Theis 1980). Complexes with naturally occurring anions, such as OH^-, SO_4^{2-}, and Cl^-, are formed to a small degree. Complexes with hydroxyl radicals are more stable than those with sulfate, which in turn are more stable than those with chloride. $Ni(OH)_2^0$ becomes the dominant species above pH 9.5. In

anaerobic systems, nickel sulfide forms if sulfur is present, and this limits the solubility of nickel. In soil, the most important sinks for nickel, other than soil minerals, are amorphous oxides of iron and manganese. The mobility of nickel in soil is site specific depending mainly on soil type and pH. The mobility of nickel in soil is increased at low pH. At one well-studied site, the sulfate concentration and the surface area of soil iron oxides were also key factors affecting nickel adsorption (Richter and Theis 1980).

6.2 RELEASES TO THE ENVIRONMENT

Most analytical methods for nickel in environmental samples do not distinguish between compounds of nickel or the nature of its binding to soil and particulate matter. It is generally impossible to say with certainty what forms of nickel are released from natural and anthropogenic sources, what forms are deposited or occur in environmental samples, and to what forms of nickel people are exposed. The form of nickel has important consequences as far as its transport, transformations, and bioavailability are concerned.

6.2.1 Air

Nickel and its compounds are naturally present in the earth's crust, and releases to the atmosphere occur from natural processes such as windblown dust and volcanic eruption, as well as from anthropogenic activities. These latter releases are mainly in the form of aerosols. It is important to consider the background levels that are due to natural sources and distinguish them from levels that may result from anthropogenic activities. It is estimated that 8.5 million kg of nickel are emitted into the atmosphere from natural sources each year (Bennett 1984; Schmidt and Andren 1980). Based on this value, sources of nickel have been estimated as follows: windblown dust, 56%; volcanoes, 29%; vegetation, 9%; forest fires, 2%; and meteoric dust, 2%. A more recent and higher estimate of 30 million kg/year has been given for emission of nickel into the atmosphere from natural sources (Duce et al. 1991; Giusti et al. 1993). Anthropogenic sources of atmospheric nickel include nickel mining, smelting, refining, production of steel and other nickel-containing alloys, fossil fuel combustion, and waste incineration.

Emissions factors (i.e., kg of nickel emissions per unit consumption or production) have been estimated for various source categories, and these have been used to estimate worldwide emissions (Nriagu and Pacyna 1988). According to Schmidt and Andren (1980), annual anthropogenic emissions are estimated to contain 43 million kg of nickel (median value), 1.4 times the natural emission rate of 30 million

kg/year. Nriagu and Pacyna (1988) estimate annual anthropogenic emissions as 55.6 million kg. The nickel emission factor for burning residual and fuel oil is estimated to be 0.03 kg/ton, yielding nickel emissions of 26.7 million kg/year or 62% of the total anthropogenic emissions (Schmidt and Andren 1980). The estimated contributions of other anthropogenic sources of nickel are nickel metal and refining, 17%; municipal incineration, 12%; steel production, 3%; other nickel-containing alloy production, 2%; and coal combustion, 2% (Bennett 1984; Schmidt and Andren 1980). Wood combustion is also an important source of nickel emissions (Nriagu and Pacyna 1988).

Table 6-1 lists the air releases from facilities in the United States that produce, process, or use nickel, according to the 2001 TRI (TRI01 2003). These releases, totaling 381,098 pounds (173,018 kg), constitute 11.0% of the environmental releases reported for nickel in the TRI. Table 6-2 lists the air releases from facilities in the United States that produce, process, or use nickel compounds, according to the 2001 TRI (TRI01 2003). These releases, totaling 1,004,693 pounds (456,130 kg), constitute 1.9% of the environmental releases reported for nickel compounds in the TRI. The TRI data listed in Tables 6-1 and 6-2 should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Based on data contained in EPA's 1996 National Toxics Inventory (NTI) which is compilation of emissions data obtained from TRI, state and local databases, and other studies required by the Clean Air Act (CAA), it is estimated that emissions of nickel compounds into air totaled 1,330 tons per year in the United States (EPA 2000). Of this total, 1,196 tons of nickel compounds per year were derived from urban sources, with the major contributors coming from stationary sources that release 10 or more tons of nickel compounds per year. Onroad mobile sources, such as cars, motorcycles, trucks, and buses, accounted for only 10 tons per year of nickel released to air, whereas nonroad mobile sources, such as airplanes, boats, and lawn mowers, accounted for a release of 66 tons of nickel compounds per year.

Deposition of metals around large smelter complexes is a significant local problem. For example, at the Copper Cliff smelter in Sudbury, Ontario, it is estimated that 42% of nickel particulates emitted from the 381-m stack are deposited within a 60-km radius of the smelter (Taylor and Crowder 1983). The Copper Cliff smelter, one of three large nickel sources in the Sudbury area, emits 592 pounds (269 kg) of nickel per day. In another example, the soils in the 4,000 km^2 area surrounding the Severonickel Smelter Complex located on the Kola Peninsula, Russia, contain nickel at concentrations that range between 6 and 1,500 times the European background levels of nickel in soils (Barcan 2002). Concentrations of 9,000 mg of nickel per kg of soil (0.9%) have been measured near the smelter. It has been estimated that

110,000 tons of nickel have been emitted from the smelter into the atmosphere since 1962, with current (2001) emissions of 1,212 tons/year or 3,320 kg/day.

A typical, modern, coal-fired power plant emits ≈25 μg nickel per Megajoule (MJ) of power produced, compared with 420 μg/MJ for an oil-fired plant (Hasanen et al. 1986). The nickel concentration in stack emissions from a modern coal-fired power plant with an electrostatic precipitator was 1.3 $\mu g/m^3$ (Lee et al. 1975). In a case study of the emissions of metals from an average sized coal-burning electric power plant (650 MW at a capacity factor of 67%) equipped with an electrostatic precipitator (ESP), 100 kg/year of nickel is emitted into air (Rubin 1999). These nickel emissions are reduced to 16 kg/year for plants that are fitted with a wet lime/limestone flue gas desulfurization system downstream from the ESP. High-sulfur eastern coal has a higher nickel content than low-sulfur western coal, so power plants using eastern coal emit more nickel than those using western coal (QueHee et al. 1982).

It is estimated that in 1999, 570,000 tonnes of nickel were released from the combustion of fossil fuels worldwide (Rydh and Svärd 2003). Of this, 326 tonnes are released from electric utilities (Leikauf 2002).

From a public health point of view, the concentration of nickel associated with small particles that can be inhaled into the lungs is of greatest concern. The nickel content of aerosols from power plant emissions is not strongly correlated with particle size (Hansen and Fisher 1980). In one coal plant, 53 and 32% of nickel in emissions were associated with particles <3 and <1.5 μm in diameter, respectively (Sabbioni et al. 1984). Other studies found that only 17–22% of nickel emissions from coal-fired power plants were associated with particles of >2 μm, and that the mass medium diameter (MMD) of nickel-containing particles from a plant with pollution control devices was 5.4 μm (Gladney et al. 1978; Lee et al. 1975). In one study, 40% of the nickel in coal fly ash was adsorbed on the surface of the particles rather than being embedded in the aluminosilicate matrix (Hansen and Fisher 1980). Surface-adsorbed nickel would be more available than embedded nickel.

Nickel emissions from municipal incinerators depend on the nickel content of the refuse and the design and operation of the incinerator. By comparing the nickel content of particles emitted from two municipal incinerators in Washington, DC, with that of atmospheric particulate matter, Greenberg et al. (1978) concluded that refuse incineration is not a major source of nickel in the Washington area. The average nickel concentrations in suspended particles from these incinerators ranged from 170 to 200 ppm. Nickel is not primarily associated with very fine or coarse particles. In tests performed under the Canadian National Incinerator Testing and Evaluation Program, 1.0 g nickel/ton refuse was emitted under

normal operating conditions; when the combustion chamber operated at low and high combustion temperatures, nickel emissions increased to ≤2.2 g nickel/ton (Hay et al. 1986). These emissions can be compared with a factor of 0.33 g nickel/ton refuse obtained in a European study (Pacyna 1984). The European study also obtained an emission factor of 1.0 g nickel/ton for sewage sludge incineration.

An increase in nickel emissions over presettlement levels was assessed by dating and analyzing peat cores from a fen located in northern Indiana, which is downwind from the city of Chicago and the industrial complexes of Gary and East Chicago, areas that contain a large steel mill and a coal-fired power plant. The peak accumulation rate was 7.73 mg nickel/m^2/year for 1970–1973, a factor of 21 greater than the accumulation rate in presettlement times (A.D. 1339–1656) (Cole et al. 1990).

Some work has been performed to determine the species of nickel present in air emissions from different source categories (EPA 1985a). This has been determined from analyses of dust by x-ray diffraction, scanning electron microscopy, and energy dispersive x-ray analysis or by an assessment of the reactions and transformations possible for the material present and the process conditions. Nickel resulting from oil combustion is primarily nickel sulfate with lesser amounts of complex metal oxides and nickel oxide. Approximately 90% of nickel in fly ash from coal combustion consists of complex (primarily iron) oxides. Nickel silicate and iron-nickel oxides would be expected from the mining and smelting of lateritic nickel ore, whereas nickel matte refining would produce nickel subsulfide and metallic nickel. The primary nickel species from secondary nickel smelting and steel and nickel alloys production is iron-nickel oxide.

6.2.2 Water

Nickel is a natural constituent of soil and is transported into streams and waterways in runoff either from natural weathering or from disturbed soil. Much of this nickel is associated with particulate matter. Nickel also enters bodies of water through atmospheric deposition.

Emission factors have been estimated for the release of trace metals to water from various source categories and these have been used to estimate inputs of these metals into the aquatic ecosystem. The global anthropogenic input of nickel into the aquatic ecosystem for 1983 is estimated to be between 33 and 194 million kg/year with a median value of 113 million kg/year (Nriagu and Pacyna 1988).

Table 6-1 presents releases of nickel to water from facilities that produced, processed, and used nickel in 2001 in the United States. These releases, totaling 20,962 pounds (9,517 kg) of nickel, constitute 0.8% of environmental releases reported to TRI (TRI01 2003). Table 6-2 lists the releases of nickel compounds to water from facilities in the United States that produce, process, or use nickel compounds, according to the 2001 TRI (TRI01 2003). These releases, totaling 244,846 pounds (111,161 kg), constitute 0.5% of the environmental releases reported for nickel compounds in the TRI. The TRI data listed in Tables 6-1 and 6-2 should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

A survey of raw and treated waste water from 20 industrial categories indicated that nickel is commonly found in some waste waters. Those industries with mean effluent levels of >1,000 μg/L in raw waste water were inorganic chemicals manufacturing (20,000 μg/L), iron and steel manufacturing (1,700 μg/L), battery manufacturing (6,700 μg/L), coil coating (1,400 μg/L), metal finishing (26,000 μg/L), porcelain enameling (19,000 μg/L), nonferrous metal manufacturing (<91,000 μg/L), and steam electric power plants (95,000 μg/L) (EPA 1981). Those industries with mean effluent levels >1,000 μg/L in treated waste water were porcelain enameling (14,000 μg/L) and nonferrous metal manufacturing (14,000 μg/L) (EPA 1981). The maximum levels in treated discharges from these industries were 67,000 and 310,000 μg/L, respectively. In addition, four other industrial categories had maximum concentrations in treated discharges >1,000 μg/L. These were inorganic chemicals manufacturing (1,400 μg/L), iron and steel manufacturing (7,800 μg/L), aluminum forming (20,000 μg/L), and paint and ink formulation (80,000 μg/L).

Domestic waste water is the major anthropogenic source of nickel in waterways (Nriagu and Pacyna 1988). Concentrations of nickel in influents to 203 municipal waste water treatment plants (9,461 observations) ranged from 2 to 111,400 μg/L; the median value was ≈300 μg/L (Minear et al. 1981). From a study of influent streams of a waste water treatment plant in Stockholm, Sweden, it was determined that the waste streams from households (e.g., drinking water) and businesses (e.g., drinking water, car washes, chemical uses) account for 29% of nickel in influent streams (Sörme and Lagerkvist 2002). Another 31% of the nickel in influent streams is added at the waste water treatment plant through the addition of water treatment chemicals. Storm water accounts for between 1 and 5% of the nickel in influent streams. Concentrations in treated effluents were not reported. However, nickel may be removed by chemical precipitation or coagulation treatment in publicly owned treatment works, which reduces nickel releases (EPA 1981). For example, improvements in sewage treatment facilities have attributed to

a reduction in the flux of nickel in waste water effluents into the Hudson River estuary, decreasing from 518 kg/day in 1974 to 43 kg/day in 1997 (Sañudo-Wilhelmy and Gill 1999)

Effluent water generated from mining and smelting operations comes from seepage, runoff from tailing piles, or from utility water used for mine operations. These discharges consist mostly of less-soluble silicates and sulfides and readily settle out. Tailing effluents from sulfidic ores are acidic due to the bacterial generation of sulfuric acid from the sulfidic minerals in the tailings, and very high concentrations of soluble nickel sulfate may be released. Tailing waters from the Onaping and Sudbury areas of Ontario, Canada, have an average nickel content of 42,500 μg/L, a factor of 8,300 greater than that found in river water (Mann et al. 1989). Since there is presently no nickel mining of sulfidic ore in the United States, nickel-containing waste water is not generated by this activity. However, past nickel mining may have contributed to nickel entering our waterways and accumulating in sediment. Old tailing piles may contribute to runoff for decades.

In the EPA-sponsored National Urban Runoff Program, in which 86 samples of runoff from 15 cities throughout the United States were analyzed, nickel was found in 48% of runoff samples, at concentrations of 1–182 μg/L (Cole et al. 1984). The geometric mean nickel concentration in runoff water from the cities studied was between 5.8 and 19.1 μg/L. In a more recent study of nickel concentrations in storm runoff water samples taken from different urban source areas (Table 6-3), the arithmetic means of the concentrations for dissolved nickel ranged from <1 to 87 μg/L, and from 17 to 55 μg/L for nickel that also included the metal associated with particulates (Pitt et al. 1995).

One of the potentially dangerous sources of chemical release at waste sites is landfill leachate. In a study that looked at leachate from three municipal landfills in New Brunswick, Canada, the results were conflicting. Average nickel concentrations in the three leachates (control) were 28 (45) μg/L, 33 (not detectable) μg/L, and 41 (23) μg/L (Cyr et al. 1987). Sediment at three sites below the leachate outfalls contained 11.9, 37.4, and 71.2 ppm of nickel (dry weight).

6.2.3 Soil

Most of the nickel released to the environment is released to land. Emission factors for nickel released to soil have been estimated for various industries (Nriagu and Pacyna 1988). These factors can be used to estimate industrial nickel releases to land. Excluding mining and smelting releases to land, 66% of estimated anthropogenic environmental releases or 325 million kg/year (median) are to soil (Nriagu and

Table 6-3. Concentrations of Nickel Measured in Sheetflow Samples taken from Different Urban Source Areas in Birmingham, Alabama[a]

Source area	Filtering[b]	Concentrations (μg/L)		
		Mean	Maximum	Minimum
Roof areas	NF	16	70	2.6
	F	<1	<1	<1
Parking areas	NF	45	130	4.2
	F	5.1	13	1.6
Storage areas	NF	55	170	1.9
	F	87	–[c]	–[c]
Street runoff	NF	17	70	1.2
	F	<1	<1	<1
Loading docks	NF	6.7	8.1	4.2
	F	1.3	–[c]	–[c]
Vehicle service area	NF	42	70	7.9
	F	31	–[c]	–[c]
Landscaping areas	NF	53	130	21
	F	2.1	–[c]	–[c]
Urban creeks	NF	29	74	<1
	F	2.3	3.6	<1
Detention ponds	NF	24	70	1.5
	F	3.0	6.0	<1

[a] Pitt et al. 1995
[b] Nickel measured in either dissolved form (filtered, F) or associated with particulates (nonfiltered, NF).
[c] Nickel was detected in only one sample.

Pacyna 1988). Some important sources of nickel released to soil are coal fly ash and bottom ash, waste from metal manufacturing, commercial waste, atmospheric fallout, urban refuse, and sewage sludge. Tables 6-1 and 6-2, which show the range of releases from industries listed in the TRI that produce, process, or use nickel, indicates that the bulk of nickel and nickel compounds is released to land. In 2001, 85.4% of the release of nickel or 2,480,253 pounds (1,126,034 kg) was to land (TRI01 2003). For nickel compounds, a higher percentage, 95.8% or 50,984,105 pounds (23,146,784 kg), was released to land in 2001 according to TRI (TRI01 2003). Underground injection accounted for 0.8% or 22,669 pounds (10,292 kg) of nickel and 1.8% or 980,689 pounds (445,233 kg) of nickel compounds released to the environment (TRI01 2003). Since not all facilities are required to report to the TRI, the list of facilities releasing nickel to land is not complete.

Based on 1999 production data, the equivalent of 0.6–3.3% of the nickel that was mined that year was used in the manufacture of portable batteries (Rydh and Svärd 2003). This amounts to approximately 17–31 ktons of nickel. Although current battery recycling programs in Europe claim success rates of upwards of 55%, the global recycling rates are typically lower, ranging between 5 and 50%. Therefore, on a global level, more than half of the nickel used in battery production will be disposed of in landfills and other waste sites.

6.3 ENVIRONMENTAL FATE

It is not always possible to separate the environmental fate processes relating to transport and partitioning from those relating to transformation for a metal and its various compounds and complexes. Because of analytical limitations, investigators rarely identify the form of a metal present in the environment. A change in the transport or partitioning of a metal may result from a transformation. For example, complexation may result in enhanced mobility, while the formation of a less-soluble sulfide would decrease its mobility in water. Adsorption may be the result of strong bonds being formed (transformation) as well as weak ones. Separating data relating to strong and weak adsorption in different sections is awkward and may not always be possible. Section 6.3.1 covers deposition and general adsorption of nickel, and Section 6.3.2 examines areas of environmental fate in which speciation occurs.

6.3.1 Transport and Partitioning

Nickel is released to the atmosphere in the form of particulate matter or adsorbed to particulate matter. It is dispersed by wind and removed by gravitational settling (sedimentation), dry deposition (inertial

impaction characterized by a deposition velocity), washout by rain (attachment to droplets within clouds), and rainout (scrubbing action below clouds) (Schroeder et al. 1987). The removal rate and distance traveled from the source depends on source characteristics (e.g., stack height), particle size and density, and meteorological conditions.

Gravitational settling governs the removal of large particles (>5 μm), whereas smaller particles are removed by other forms of dry and wet deposition. The partitioning between dry and wet deposition depends on the intensity and duration of precipitation, the element in question and its form in the particulate matter, and particle size. The importance of wet deposition relative to dry deposition generally increases with decreasing particle size. Removal of coarse particles may occur in a matter of hours. Small particles within the size range of 0.3–0.5 μm may have an atmospheric half-life as long as 30 days and, therefore, have the potential to be transported over long distances (Schroeder et al. 1987). Evidence for the long-range transport of nickel is provided by the fact that emission sources in North America, Greenland, and Europe are responsible for elevated atmospheric nickel concentrations in the Norwegian Arctic during both the summer and winter (Pacyna and Ottar 1985).

Available studies indicate that nickel is broadly distributed among aerosol size groups. It has been concluded, based on the chemical and physical properties of atmospheric particles, that the concentrations of nickel in large particles (>1 μm diameter) that are commonly associated with particulates derived from natural sources are less than concentrations in smaller particles (<1 μm diameter) that are typically derived from anthropogenic sources (Giusti et al. 1993; Scudlark et al. 1994). For example, in a study to determine the size distribution of nickel-containing aerosols in clean, marine air was performed on an island in the German Bight (Stoessel and Michaelis 1986). The concentration of nickel in six size fractions increased with decreasing size from ≈0.3 ng/m^3 for particles >7.2 μm to ≈1.5 ng/m^3 for particles <0.5 μm. However, experiments in Ontario showed that nickel is associated with relatively large particles, 5.6±2.4 μm (Chan et al. 1986). A 1970 National Air Surveillance Network study of the average nickel size distribution in six American cities indicated that the mass median diameter (MMD) is ≈1.0 μm in all six cities (Lee et al. 1972). Although the sampling procedure used in this study may have underestimated large particles (Davidson 1980), it represents one of the few studies involving the size distribution of nickel aerosols in U.S. cities.

Metal deposition is characterized by large temporal and spatial variability. Deposition can be associated with precipitation (wet deposition) or result from processes such as gravitational settling of dust (dry deposition). Estimated nickel deposition rates range from 0.01 to 0.5 kg/hectare/year (1–50 mg/m^2/year)

and from 0.1 to 5.95 kg/hectare/year (10–595 mg/m^2/year) in rural and urban areas, respectively (Schroeder et al. 1987). In the Florida Atmospheric Mercury Study (FAMS) conducted during 1993–1994, bulk deposition rates for nickel varied between 1.700 and 4.130 mg/m^2/year, depending on local/regional anthropogenic activity (Landing et al. 1995). Nickel deposition from 1980 to 1981 in an industrial area of England where a number of ferrous and nonferrous metal smelting and manufacturing works were concentrated had a mean value of 8,800 ng/cm^2/year (88 mg/m^2/year), a factor of 8–25 above nonurban deposition rates (Pattenden et al. 1982). Wet deposition accounted for half of the deposition. Eighty-one percent of the nickel in rain was dissolved. Schroeder et al. (1987) reported the same percent of dry to wet deposition for nickel, whereas Chan et al. (1986) found that 2.2 times as much wet deposition as dry deposition occurred in Ontario in 1982 with little variability in the ratio across the province. The mean dry deposition rates for southern, central, and northern Ontario in 1982 were 0.25, 0.28, and 0.18 mg/m^2/year, respectively. In southern Ontario, Canada, where the average concentration of nickel in rain was 0.557 ppb during 1982, 0.5 mg of nickel was deposited annually per square meter as a result of wet deposition (Chan et al. 1986). For central and northern Ontario, the mean concentrations of nickel in rain were 0.613 and 0.606 ppb, respectively, and the annual wet depositions averaged 0.5 and 0.4 mg/m^2. Wet and dry deposition of particulates emitted from the Claremont Incinerator in Claremont, New Hampshire, were measured within an area between 2 and 15 km from the incinerator. Wet deposition rates varied between 0.50 and 8.87 μg/m^2/day (0.0005–0.00887 mg/m^2/day) with a mean value of 3.0 μg/m^2/day (0.003 mg/m^2/day) and depended on distance from the incinerator and wind weight. The mean wet deposition rate of 3.0 μg/m^2/day (0.003 mg/m^2/day) was a factor of approximately 19 greater than the mean dry deposition rate of 0.16 μg/m^2/day (0.00016 mg/m^2/day), which had been calculated from values ranging from 0.067 to 0.29 μg/m^2/day (0.000067–0.00029 mg/m^2/day) (Feng et al. 2000).

Atmospheric deposition of nickel in coastal waters has been reported. Bulk and wet deposition of nickel into Massachusetts Bay was determined to be 7,200 and 3,000 μg/m^2/year (Golomb et al. 1997), respectively, whereas a lower wet deposition rate of 257 μg/m^2/year was measured for nickel in Chesapeake Bay (Scudlark et al. 1994). In Europe, a bulk deposition rate of 335 μg/m^2/year was determined for nickel in the Severn Estuary in England (Golomb et al. 1997; Harrison et al. 1993) and a wet deposition rate of 880 μg/m^2/year over the Dutch Delta (Nguyen et al. 1990). Atmospheric input of nickel into the Great Lakes has been estimated to average 160–590 ng/m^2/year (Nriagu et al. 1996).

Wet and dry deposition of nickel into the world's oceans is estimated to be 8–11 and 14–17 gigagrams (10^9 grams) per year, respectively (Duce et al. 1991). However, atmospheric deposition is only a minor contributor to the flow of nickel into the oceans and coastal waterways as compared to riverine and fluvial

input of nickel. The nickel that is carried into oceans in both dissolved and particulate forms through riverine input is rated at 1,411 gigagrams per year, which is a factor of approximately 50 greater than the sum of the wet and dry deposition of nickel of 22–28 gigagrams per year (Duce et al. 1991). In an example of nickel input into Chesapeake Bay, the fluvial input of nickel of 98,700 kg/year (0.0987 gigagrams/year) is 25 times greater than bulk deposition of nickel from the atmosphere (Scudlark et al. 1994). However, for the Great Lakes the atmospheric input of nickel accounts for 60–80% of the total anthropogenic input of nickel into Lake Superior, and 20–70% of the total inputs into Lakes Erie and Ontario (Nriagu et al. 1996).

The fate of heavy metals in aquatic systems depends on partitioning between soluble and particulate solid phases. Adsorption, precipitation, coprecipitation, and complexation are processes that affect partitioning. These same processes, which are influenced by pH, redox potential, the ionic strength of the water, the concentration of complexing ions, and the metal concentration and type, affect the adsorption of heavy metals to soil (Richter and Theis 1980).

Much of the nickel released into waterways as runoff is associated with particulate matter; it is transported and settles out in areas of active sedimentation such as the mouth of a river. Additionally, when a river feeds into an estuary, the salinity changes may affect absorptivity due to complexation and competition for binding sites (Bowman et al. 1981). During a 4-month study of Lake Onondaga in Syracuse, New York, 36% of the nickel in the lake was lost to sediment (Young et al. 1982). Seventy-five percent of the nickel load into the polluted lake was soluble and remained in the lake. The soluble nickel is not likely to be as the Ni(II) ion, but is expected to exist as a complex. For example, in an analysis of the speciation of nickel in waste water effluents and runoff discharging into San Francisco Bay, it was found that approximately 20% of soluble nickel was complexed to moderately strong complexing agents, such as humic acid and biopolymers from activated sludges (Sedlak et al. 1997). However, a larger proportion of the nickel, 75% in waste water effluent and 25% in runoff, is found strongly complexed with stability constants that are similar to those found for synthetic chelating agents such as EDTA, DTPA, and phosphonates. Nickel is strongly adsorbed at mineral surfaces such as oxides and hydrous oxides of iron, manganese, and aluminum (Evans 1989; Rai and Zachara 1984). Such adsorption plays an important role in controlling the concentration of nickel in natural waters.

Nickel is strongly adsorbed by soil, although to a lesser degree than lead, copper, and zinc (Rai and Zachara 1984). There are many adsorbing species in soil, and many factors affect the extent to which nickel is adsorbed, so the adsorption of nickel by soil is site specific. Soil properties such as texture, bulk

density, pH, organic matter, the type and amount of clay minerals, and certain hydroxides, as well as the extent of groundwater flow, influence the retention and release of metals by soil (Richter and Theis 1980).

Amorphous oxides of iron and manganese, and to a lesser extent clay minerals, are the most important adsorbents in soil. In alkaline soils, adsorption may be irreversible (Rai and Zachara 1984), which limits nickel's availability and mobility in these soils. For example, in recent studies of nickel speciation in ferromanganese nodules from loess soils of the Mississippi Basin, nickel is found to have a higher partition in the soil nodules than in soil clay matrices (Manceau et al. 2003). This is due to the selective sequesterization of nickel by finely divided iron and manganese oxides in goethite and lithiophorite minerals present in the soils. Cations such as Ca^{2+} and Mg^{2+} have been reported to reduce adsorption due to competition for binding sites, whereas anions like sulfate reduce adsorption as a result of complexation. Nickel adsorption depends strongly on metal concentration and pH (Giusti et al. 1993). For each mole of nickel adsorbed by iron and manganese oxide, ≈1–1.5 moles of hydrogen ions are released (Rai and Zachara 1984). For aluminum oxide, as many as 2.3 moles H^+ are released. Mustafa and Haq (1988) found that the adsorption of nickel onto iron oxide at pH 7.0 was rapid and increased with increasing temperature. They found that two hydrogen ions are released into a solution when nickel is adsorbed. These studies indicate that while Ni^{2+} is the predominant species in solution, $NiOH^+$ is preferentially adsorbed, and that both mono- and bidentate complexes may be formed with the iron/manganese/aluminum oxides.

Batch equilibrium studies were performed using seven soils and sediments spiked with varying concentrations of nickel to assess the potential mobility of nickel in contaminated subsoil (LaBauve et al. 1988). The range of Freundlich parameters K(1/n), an adsorption constant, ranged from 739 (0.92) to 6,112 (0.87). One-, two-, and three-parameter models were used to evaluate the relation of soil properties and nickel retention. In the one-parameter model, pH was the best predictor. Cation exchange capacity (CEC) and iron oxide were the best predictors in the two-parameter models, and CEC, iron oxide, and percent clay were the best predictors in the three-parameter models. Nickel was more mobile in the soils than lead, cadmium, and zinc. The retention of nickel to two of the test subsoils diminished in the presence of synthetic landfill leachate, possibly because of complex formation. In another study in which batch adsorption experiments were conducted with a mixture of cadmium, cobalt, nickel, and zinc, and 38 different agricultural soils, taken from three depths at 13 sites, the adsorption constants ranged from 10 to 1,000 L/kg (Anderson and Christensen 1988). Soil pH, and to a lesser extent clay content and the amount of hydrous iron and manganese oxides, most influenced nickel sorption.

In 12 New Mexican soils from agricultural areas and potential chemical waste disposal sites, Freundlich parameters K (1/n) ranged from 8.23 to 650 (0.87–1.18); the median K was 388 (Bowman et al. 1981). The soil with the K of 8.23 was essentially unweathered rock that was not expected to have good adsorbing properties. The study concluded that most soils have an extremely high affinity for nickel and that once sorbed, nickel is difficult to desorb, which indicates covalent bond formation. Sadiq and Enfield (1984b) observed nickel ferrite formation following adsorption. Bowman et al. (1981) found that when nickel levels were >10 ppm, adsorption decreased. High concentrations of chloride decreased adsorption, but not as much as calcium ions, which indicates that calcium competition for sorbing sites is more important than chloride complexation for reducing adsorption. The presence of complexing agents, such as EDTA, dramatically lowers nickel adsorption, which has important implications at waste disposal sites if liquid nickel waste containing chelating agents is released to soil. Chelating agents that are added to soil containing adsorbed nickel appear to have a lesser effect.

The capacity of soil to remove nickel and the nature of the bound nickel were evaluated for 10 mineral and 3 organic soils from the southeastern United States (King 1988). Some soil samples were taken from the subsoil as well as the surface. The amount of adsorbed nickel ranged from 13 to 95%; the low value was found in subsoil, and the high value was found in soil high in organic matter. When extracted with potassium chloride, 5–87% of the nickel was nonexchangeable. Soil pH was the most important factor affecting sorbed and nonexchangeable nickel in all soil horizons. Both King (1988) and Tyler and McBride (1982) found much stronger nickel adsorptivity in organic soil than in mineral soils. Adsorption was improved by the quality and quantity of humus in the soil (Hargitai 1989). Nickel was enriched in humic and fulvic acids from Lake Ontario sediment (Nriagu and Coker 1980). It was estimated that 5–10% of the nickel in this sediment was bound to organic matter.

The leachability of nickel from some soils does not necessarily correlate with the total concentration of nickel in the soil. In an extraction study of soils sampled from the mining and smelting regions of Sudbury, Ontario, the percentage of nickel that is most easily extractable (in acetic acid) varied between 12 and 31% of the total nickel content (220–455 mg/kg) among the different sampling sites (Adamo et al. 1996). The remaining nickel was found in less extractable forms: 6–11% was found to be associated with manganese oxides and easily reducible iron oxides, 6–20% either bound to readily oxidizable organics or sulfides, and the remainder (55–73%) was associated with sulfides as separate grains or inclusions, iron oxide phases, carbon particles, and silicate spheroids. Similarly, in soils that are naturally enriched in heavy metals sampled from the Port MacQuaire region in Australia, the amount of nickel that can be easily extracted from soil samples is only a small fraction of the total nickel content (Lottermoser

2002). Extraction of these soils with EDTA or acetic acid yielded leachable nickel which amounted to between <0.1–4.1 and <0.01%, respectively, of the total nickel concentrations in the soil samples. Use of stronger extraction methods, for example hydrochloric acid, yielded only leachable nickel in percentages (0.1–2.4%) equivalent to those found for EDTA. The low amount of acetic acid extractable nickel indicates negligible leaching of this metal from these soils into groundwater and surface waters (Lottermoser 2002).

Amendment of soils with exogenous humic acid reduces mobility of dissolved nickel in soil and also increases the bioavailability of this nickel to plants. Halim et al. (2003) showed that humic acid in soils from nickel-humic acid complexes results in the removal of dissolved and exchangeable nickel from soil water. The extractability of nickel increased with the aging time of the organic material. The increased bioavailability of nickel bound to humic acid is temporary and is thought to occur mainly as the result of preventing nickel from undergoing a transformation into insoluble species in soil.

Nickel (II) is poorly removed from waste water in the activated sludge process because of its high solubility (Stephenson et al. 1987). Only 30–40% of nickel was removed in a pilot activated sludge plant. Nickel removal in activated sludge plants is best correlated with effluent suspended solids (Kempton et al. 1987). Nickel is predominantly soluble in the effluent and is found complexed to humic acid, biopolymers, and other chelating agents (Sedlak et al. 1997).

In order to evaluate the potential of elements to leach from land-spread sewage sludge, Gerritse et al. (1982) studied the adsorption of elements to sandy and sandy loam top soils from water, salt solutions, and sludge solutions. They used metal levels that occurred in the solution phase of sewage sludge, 100–1,000 ppb in the case of nickel. The results indicated that nickel is fairly mobile in these soils; the adsorption constants were ≈10–100 in the sandy soil and a factor of ≈10 higher in the sandy loam soil. The presence of sludge increases the mobility of nickel, particularly in sandy and sandy loam soils, which may be because of complexation with dissolved organic compounds (Kaschl et al. 2002) or increased ionic strength (Gerritse et al. 1982). However, land application of nickel-contaminated sludge did not give rise to increased levels of nickel in groundwater (Demirjian et al. 1984). Higher doses and repeated application of nickel-containing sewage sludge did not result in a proportional increase in nickel mobility (Hargitai 1989).

As part of EPA's National Runoff Program in Fresno, California, the soil water and groundwater at depths ≤26 m beneath five urban runoff retention/recharge basins were monitored during a 2-year study

(Nightingale 1987). The results indicated that there were no significant downward movements of nickel with the recharge water.

Saline sediments from estuaries often contain pyrite and other readily oxidizable sulfur compounds. When these sediments are oxidized, such as when dredged sediment is exposed to oxygen, sulfuric acid may be produced, which may overwhelm the buffering capacity of the sediment, lower the pH (to pH 3.1 in a laboratory experiment), and dissolve the ferric oxides and hydroxides that entrap heavy metals (DeLaune and Smith 1985). As a result, significant amounts of nickel may be released from the dredged sediments. An analogous pH decrease following exposure to oxygen was not observed in freshwater sediment.

The presence of iron-(di)sulfides in wetland sediments has been associated with increased mobilization of nickel into groundwater during periods of drought in Holland (Lucassen et al. 2002). Dessication of sediments leads to oxidation of iron-(di)sulfides and subsequent acidification of the sediments. When the S/(Ca + Mg) ratios in these sediments rise above 2/3, mobilization of heavy metals like nickel occurs, leading to groundwater concentrations of nickel that exceeded the Dutch signal level of 50 ppb for nickel in 50% of the monitoring locations.

It has been reported that nickel is not accumulated in significant amounts by aquatic organisms (Birge and Black 1980; Zaroogian and Johnson 1984). The concentration of nickel in a major carnivorous fish in New York state, the lake trout, was the lowest, and the concentration did not increase appreciably with the age of the fish (Birge and Black 1980). The mean bioconcentration factor (BCF) for three carnivorous fish was 36. The concentration of nickel in mussels and oysters treated with 5 μg nickel/kg of seawater for 12 weeks averaged 9.62 and 12.96 μg nickel/g, respectively, on a dry weight basis (Zaroogian and Johnson 1984). When these data are adjusted for controls and the nickel concentration in tissue is expressed on a wet weight basis, the BCF for the mussels and oysters is ≈100. After 2 weeks in flowing seawater, 58 and 38% of the tissue nickel was lost from the mussel and oyster, respectively. No significant loss of nickel occurred during the remainder of the 28-week depuration period. The content of acid volatile sulfide (AVS) in sediment helps determine the bioavailability of metals (Ankley et al. 1991). In studies of nickel and cadmium, the metals were toxic to an amphipod (*Hyallela azteca*) and an oligocheate (*Lumbriculus variegatus*) when the extracted metals/AVS ratio was >1.

In the work of McGeer et al. (2003), bioconcentration factors (BCF) for nickel in various aquatic organisms (e.g., algae, arthropods, mollusks, and fish) was assessed based on whole-body metal

concentrations and exposure concentrations that were obtained from the literature. For exposure concentrations within the range of 5–50 μg/L nickel in water, mean BCF values of 106±53 (1 standard deviation [SD]) were obtained. When the authors also included data for exposure concentrations outside the range of 5–50 μg/L, a BCF value of 157±135 was obtained. The authors noted that the BCF values were inversely correlated with the exposure concentrations, where the highest BCF values were obtained at the lowest exposure concentrations. There was no evidence that nickel biomagnifies in aquatic food webs and, in fact, there is evidence to indicate that the nickel concentrations in organisms decrease with increasing trophic level (McGeer et al. 2003; Suedel et al. 1994).

As part of the U.S. Geological Survey National Water-Quality Assessment (NAWQA) Program, there was no statistically significant correlation between nickel concentrations in bed-sediments collected from streams and rivers in both the Northern Rockies Intermontane Basin study area and the New Jersey study area, and nickel concentrations measured in liver and fillet samples taken from fish collected in the same study areas (USGS 2000a, 2000b). Also, nickel concentrations in fish liver and fillet samples were at or below the detection limits (<0.1–0.3 μg/g, dry weight) for nickel in these studies and are much lower than the concentrations of nickel measured in bed-sediments, which ranged from 12 to 43 μg/g (wet weight).

Uptake and accumulation of nickel into various plant species is known to occur. For example, Peralta-Videa et al. (2002) report the accumulation of nickel in alfalfa grown from soils contaminated with a mixture of four metals (e.g., Cd(II), Cu(II), Ni(II), and Zn(II)) at a loading of 50 mg/kg for each metal. Concentration ratios of nickel in plant versus soil (based on dry weights) ranged between 22 and 26 over a pH range of 4.5–7.1. As with most plant species that hyperaccumulate metals, the alfalfa actively removes and translocates heavy metals, like nickel, from the roots to the shoots.

Two studies concerning levels in voles and rabbits living on sludge-amended land did not indicate any accumulation of nickel in these herbivores or in the plants they fed upon (Alberici et al. 1989; Dressler et al. 1986). The lack of significant bioaccumulation of nickel in aquatic organisms, voles, and rabbits indicates that nickel is not biomagnified in the food chain.

6.3.2 Transformation and Degradation

Analytical methods do not generally allow identification of the precise form of nickel present in environmental samples or an assessment of the transformations that may occur. Sequential extraction techniques are sometimes employed to determine how tightly nickel is bound to particles or in

environmental matrices. Using different and progressively stronger extracting agents, the fractions of a sample that are exchangeable, adsorbed, easily reducible, moderately reducible, or organically bound carbonates, sulfides, and residual can be determined (Rudd et al. 1988; Rybicka 1989).

6.3.2.1 Air

Little is known about the chemical forms and physical and chemical transformations of trace elements in the atmosphere primarily because analytical methods provide information concerning the metal content rather than the specific compounds or species. In the absence of specific information, it is generally assumed that elements of anthropogenic origin, especially those emanating from combustion sources are present as the oxide, and nickel oxide has been identified in industrial emissions (Schroeder et al. 1987). Windblown dust particles may contain nickel in mineral species, which often contain nickel as the sulfide. Increases in the concentration of nickel in Sequoia National Park in California during rain coming from the south correlated with a sharp (7–13 times greater concentration) increase in sulfate (Cahill 1989). Nickel sulfate is a probable atmospheric species resulting from the oxidation of nickel in the presence of sulfur dioxide (Schmidt and Andren 1980).

The form of nickel in particles from different industries varies. The mineralogical composition, chemical content, and form of dusts from nine industries in Krakow, Poland, were examined (Rybicka 1989). The chemical form of a particle-associated heavy metal that was assessed by a five-step extraction scheme classified the metal as exchangeable, easily reducible (manganese oxides, partly amorphous iron oxyhydrates and carbonates), moderately reducible (amorphous and poorly crystallized iron oxyhydrates), organically bound or sulfidic, and residual. Dusts from power plants had a silicate characteristic with quartz and mullite predominant. Approximately 90% of the nickel from these facilities was in the residual fraction. Only 40–60% of the nickel from metallurgical, chemical, and cement plants was in the residual fraction. Essentially none of the nickel from any of the industries was in an organic/sulfidic fraction. Dusts from metallurgical, chemical, and cement plants contained between 0 and 10% (typically 5%) of the nickel in the relatively mobile, cation-exchangeable fraction. Thirty percent of the nickel in dust from a slag processing facility was in this form.

6.3.2.2 Water

In natural waters, nickel primarily exists as the hexahydrate. While nickel forms strong, soluble complexes with OH^-, SO_4^{2-}, and HCO_3^-, these species are minor compared with hydrated Ni^{2+} in surface

water and groundwater with pH <9 (Rai and Zachara 1984). Under anaerobic conditions, such as may exist in deep groundwater, nickel sulfide would reduce free aqueous nickel concentrations to low levels.

Precipitation can remove soluble nickel from water. In aerobic waters, nickel ferrite is the most stable compound (Rai and Zachara 1984). Nickel may also be removed by coprecipitation with hydrous iron and manganese oxides. Nickel removed by precipitation and coprecipitation settles into the sediment.

Nickel in sediment may be strongly bound or present in a removable form. A metal's form in soil or sediment and its availability are determined by measuring the extractability of the metal with different solvents. Sediment samples from western Lake Ontario were analyzed in regard to the compositional associations of nickel by a series of sequential extractions (Poulton et al. 1988). The mean nickel percentages in the various fractions were as follows: exchangeable, 0.7±1.4; carbonate, 0.0; iron or manganese oxide-bound, 0.0; organic-bound, 7.4±4.1; and residual, 91.9±4.5. The nickel concentration in 450 uncontaminated estuarine and coastal marine sites in the southeastern United States covaried significantly with the aluminum concentration, suggesting that natural aluminosilicates are the dominant natural metal-bearing phase in some aquatic systems (Windom et al. 1989). In 13 random samples of bottom sediment from the highly industrialized Meuse River in The Netherlands, between 0 and 88% (median 33%) of the nickel was removable at low pH, showing the great variability of nickel to adsorb to sediments (Mouvet and Bourg 1983).

Nickel removed by coprecipitation can be remobilized by microbial action under anaerobic conditions (Francis and Dodge 1990). Remobilization results from enzymatic reductive dissolution of iron with subsequent release of coprecipitated metals. A lowering of pH as a result of enzymatic reactions may indirectly enhance the dissolution of nickel. Experiments using mixed precipitates with goethite (α-FeOOH) indicated that a *Clostridium* species released 55% of the coprecipitated nickel after 40 hours. Similarly, precipitated nickel sulfides in sediment can be mobilized through sulfur oxidation by *Thiobacilli* (Wood 1987). In this case, the oxidized sulfur may produce H_2SO_4 and decrease the pH.

6.3.2.3 Sediment and Soil

An analysis of the thermodynamic stability models of various nickel minerals and solution species indicates that nickel ferrite is the solid species that will most likely precipitate in soils (Sadiq and Enfield 1984a). Experiments on 21 mineral soils supported its formation in soil suspensions following nickel adsorption (Sadiq and Enfield 1984b). The formation of nickel aluminate, phosphate, or silicate was not

significant. Ni^{2+} and $Ni(OH)^{+}$ are major components of the soil solution in alkaline soils. In acid soils, the predominant solution species will probably be Ni^{2+}, $NiSO_4$, and $NiHPO_4$ (Sadiq and Enfield 1984a).

A large percentage of nickel in sewage sludges exists in a form that is easily released from the solid matrix (Rudd et al. 1988). Although the availability of nickel to plants grown in sludge-amended soil is correlated with soil-solution nickel, it is only significantly correlated with DTPA-extractable nickel (Adams and Kissel 1989).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Mean ambient air concentrations of nickel typically range between 6 and 20 ng/m^3 and can be high as 150 ng/m^3 near anthropogenic sources of airborne nickel (Barceloux 1999). Schroeder et al. (1987) reported nickel concentrations in particulate matter in the U.S. atmosphere of 0.01–60, 0.6–78, and 1–328 ng/m^3 in remote, rural, and urban areas, respectively. Nickel concentrations in particulate matter ($PM_{2.5-8}$), collected in Spokane, Washington, from January 1995 to March 1999, averaged 1.2±0.9 (1 SD) ng/m^3 (Claiborn et al. 2002). Based on emission data contained in the EPA 1996 NTI database, an average concentration of nickel in ambient air in the contiguous United States was estimated to be 2.22 ng/m^3 (median concentration = 0.948 ng/m^3) (EPA 2003u). The five states with the highest average concentrations of nickel in ambient air were (ng/m^3): West Virginia (6.60), Utah (4.42), Delaware (4.10), New York (3.80), and Pennsylvania (3.69); the five states with the lowest concentrations were: Wyoming (0.127), South Dakota (0.157), North Dakota (0.211), Montana (0.311), and Vermont (0.311). Annual mean nickel concentrations in 11 Canadian cities measured during 1987–1990 ranged from 1 to 20 ng/m^3, while at a rural location the mean nickel concentration was 1 ng/m^3 (CEPA 1994). In another Canadian study, mean exposure concentrations for nickel in air for residents living near copper smelters and refineries and zinc plants ranged between 0.005 and 0.151 μg/m^3 (5–151 ng/m^3) in comparison to background levels of 0.00069 μg/m^3 (0.69 ng/m^3) (Newhook et al. 2003). Annual average nickel concentrations at three remote sites in the arctic region of Canada ranged from 0.14 to 0.45 ng/m^3 (Barrie and Hoff 1985). Levels of nickel and other anthropogenic species peaked during January and February, possibly indicating the significance of combustion sources. Nickel levels in the air at three native villages in northern Alberta, Canada, were 0.779±0.774, 1.1±0.57, and 4.97±9.2 ng/m^3, indicating that air concentrations of nickel can be highly variable (Moon et al. 1988).

According to the EPA's National Air Surveillance Network (NASN) report for 1977, 1978, and 1979, median nickel concentrations were below the detection limit for urban and nonurban samples except for 1978; during 1978, the urban median was 6 ng/m^3 (Evans et al. 1984). The detection limit for inductively-coupled-plasma atomic emission spectroscopy (ICP-AES), the method used in the EPA study, was 1 ng/m^3 (EPA 1986a; Evans et al. 1984). In the EPA study, 10,769 urban samples and 1,402 nonurban 24-hour air samples were analyzed. Five percent of the urban samples were >33, 32, and 30 ng nickel/m^3 for 1977, 1978, and 1979, respectively; 5% of the nonurban samples were >10, 10, and 6 ng/m^3, respectively, for these 3 years. Ninety-nine percent of the urban and nonurban samples for these 3 years did not exceed 68 and 52 ng/m^3, respectively (Evans et al. 1984). Combined urban and nonurban measurements for the 99th percentile from the NASN (1977–1979) and its successor, the National Air Monitoring Filter Sites (NAMFS) (1980–1982), showed a sharp decline from 62 and 67 ng/m^3 in 1977 and 1978 to 23 and 30 ng/m^3 in 1981 and 1982. Mean levels for the combined urban and nonurban sites over the 6-year period ranged from 7 to 12 ng/m^3 (EPA 1986a). According to the NASN data for 1965–1968, the average atmospheric nickel concentration in the air of 28 cities ranged from 3 to 90 ng/m^3, with an overall average of 26 ng/m^3 (NAS 1975). These data suggest that atmospheric nickel concentrations in the United States have been declining. No reason for this downward trend was suggested (EPA 1986a).

The most intensive study of the nickel concentration in the United States was the result of analyzing air samples collected during 1968–1971 for use in a lead survey (Saltzman et al. 1985). This study is significant because numerous sites in four cities were analyzed continuously over 1 year and analyzed by a single, highly experienced laboratory. Samples from 33 sites in Chicago, Houston, New York, and Washington, DC, were analyzed for nickel resulting in respective geometric mean nickel concentrations of 15, 18, 23, and 42 ng/m^3. The results for Washington, DC, are in basic agreement with the results obtained from Kowalczyk et al. (1982). In this study, 24-hour samples collected at 10 locations yielded average nickel concentrations ranging from 5.7 to 35 ng/m^3, with a mean concentration of 17 ng/m^3. The two major contributing sources are believed to be oil and coal combustion. The enrichment factor for nickel over crustal levels in 29 cities is 11 (Gladney et al. 1984). An enrichment factor considerably >1 indicates that the source of an element is anthropogenic. In Houston, the average concentration of nickel in both the fine (0.1–2.5 μm) aerosols and those >2.5 μm was 4±1 ng/m^3 (Johnson et al. 1984).

As part of the Airborne Toxic Element and Organic Substances project for determining patterns of toxic elements in different settings, three urban areas (Camden, Elizabeth, and Newark) and one rural site

(Ringwood) in New Jersey were studied during two summers and winters between 1981 and 1983 (Lioy et al. 1987). Each site was sampled every 24 hours for 39 consecutive days. The geometric mean nickel concentrations were 8.0–34.0, 5.0–28.0, 10.0–27.0, and 5.0–13.0 ng/m^3 for Camden, Elizabeth, Newark, and Ringwood, respectively. The nickel levels measured in the industrial urban areas may be compared to the arithmetic mean values reported in the National Air Surveillance survey (9.6–11.0 ng/m^3) for 1977–1979 (Evans et al. 1984). Summer and winter maxima in the three urban areas ranged from 24.0 to 39.0 and from 81.0 to 112.0 ng/m^3, respectively, and 22.0 and 32.0 ng/m^3, respectively, for Ringwood.

The first and second highest annual average nickel concentrations in the air in Texas between 1978 and 1982, according to the Texas Air Control Board, were 49 and 34 ng/m^3 at Port Arthur and Beaumont, respectively (Wiersema et al. 1984). The statewide 1978–1982 average was 1 ng/m^3. Mean nickel levels showed relatively little geographic variation in Ontario where concentrations in southern, central, and northern Ontario were 0.81, 0.91, and 0.58 ng/m^3, respectively (Chan et al. 1986).

Voutsa and Samara (2002) report elevated concentrations of nickel in particulate matter ($PM_{7.2}$) collected near industrial sites within the greater Thessaloniki (Greece) area during the time period summer 1997 through summer 1998. The mean (±1 SD) concentration of nickel in particulate matter collected at three industrial sites (e.g., Pb and Zn smelters, non-ferrous metal industries, iron and steel manufacturing, etc.) of 12.8 (±8.2) ng/m^3 was statistically greater than the mean concentration of 6.8 (±5.3) ng/m^3 for nickel measured in $PM_{7.2}$ collected at three urban sites.

Nickel concentrations in particulate matter PM_{10} was measured at three Midwestern sites, two urban sites with a large industrial component and one rural site, in samples collected from September 1985 to June 1988 (Sweet et al. 1993). Nickel concentrations in the fine PM_{10} particles (<1–2.5 μm) taken from collection sites in East St. Louis and Southeast Chicago averaged 2.1±1.4 (1 SD) and 2.7±2.6 ng/m^3, respectively, and were similar to those measured in the coarser PM_{10} particles (2.5–10 μm) of 1.8±1.5 and 2.1±1.0 ng/m^3, respectively. The concentrations of nickel measured in both the fine and coarse particles collected at the East St. Louis and Southeast Chicago sites were higher than the average concentration of nickel of 0.5±0.3 and 0.7±0.5 ng/m^3 measured in fine and coarse particles, respectively, collected from a rural site (Bondville, Illinois). The higher concentrations of nickel in the East St. Louis and Southeast Chicago sites are attributed to emissions from zinc smelters and steel mills/oil combustion, respectively.

Nickel concentrations in indoor air are generally <10 ng/m^3. In a study of 10 homes in the southeast Chicago area, indoor and outdoor air samples were regularly sampled between June 1994 and April

1995 (van Winkle and Scheff 2001). Of the 48 samples taken, 35 had nickel concentrations above the detection limit of the assay with a mean (±1 SD) concentration of 0.002±0.002 μg/m^3 and a maximum value of 0.008 μg/m^3. The median indoor nickel concentration of 0.003 μg/m^3 was similar to the median outdoor nickel concentration of 0.0034 μg/m^3. Indoor air samples taken from 394 homes in Suffolk and Onondaga Counties of New York state contained nickel concentrations that were similar to those found in the Chicago study (Koutrakis et al. 1992). A mean indoor nickel concentration of 2 ng/m^3 (0.002 μg/m^3) was derived from a sampling 28 homes. The New York study also examined nickel concentrations in indoor air as a function of combustion sources within the home (e.g., resident smoker, wood-burning stove, kerosene heater) and found no difference in the mean nickel concentrations between homes containing these combustion sources and homes without. In a study of 46 high school students in New York City conducted in the winter and summer of 1999, the concentrations of nickel in collected particulates ($PM_{2.5}$) to which these students were exposed was assessed using personal monitoring devices and stationary measurements of airborne nickel both within and outside the home (Kinney et al. 2002). The mean (±1 SD) air concentrations of nickel obtained from the outdoor, indoor and personal monitors measured during the winter survey period were similar (32.3±22.4, 31.6±54.5, and 49.6±114 ng/m, respectively). Likewise, the mean nickel concentrations obtained from all three monitors during the summer survey period were also found to be similar (11.7±6.3, 12.6±8.4, and 17.3±24.7 ng/m, respectively), although somewhat lower than the winter concentrations. These results suggest that ambient concentrations of nickel are the dominating force in determining both indoor and personal exposures to nickel.

6.4.2 Water

Surface water contains low nickel levels. Uncontaminated freshwater and seawater typically contain about 300 ng/L of nickel (Barceloux 1999). The concentration in seawater ranges from 100 to 3,000 ng nickel/L. Higher levels are found in deeper waters than in surface water (Mart et al. 1984; Sunderman 1986; van Geen et al. 1988; Yeats 1988). Water from the surface of the Atlantic Ocean, deep within the Atlantic Ocean (400 m), and the Atlantic shelf contained 1.8 nM (106 ng/L), 2.7 nM (158 ng/L), and 3.5 nM (205 ng/L) nickel, respectively (van Geen et al. 1988). Helmers and Schrems (1995) reported a concentration of 50 ng/L for nickel in surface waters in the equatorial Atlantic Ocean. The mean value of nickel in surface water of the eastern Arctic Ocean is 126±54 ng/L (Mart et al. 1984). Deep water samples taken at 1,500 and 2,000 m contained higher levels of nickel (220 and 230 ng/L, respectively). Nickel concentrations in surface water transected on a cruise from Nova Scotia to the Sargasso Sea ranged from 117 to 329 ng/L, with a median concentration of 200 ng/L (Yeats 1988). Concentrations

were ≈2 times higher in deep water. The nickel levels reported in the North Pacific and Pacific Antarctic were somewhat higher. Nickel concentration in surface water decreased by a factor of approximately 2 with increases in percent salinity from approximately 30 to 36% and increased with increasing phosphorus concentration. Nickel concentrations in South San Francisco Bay were about 3,000 ng/L, with one-third to one-half of the nickel complexed to a class of strong organic ligands (Donat et al. 1994).

The nickel content of fresh surface water has been reported to average between 15 and 20 μg nickel/L (Grandjean 1984; NAS 1975). The concentration of dissolved nickel in the lower Mississippi River ranged from 1.2 to 1.5 μg/L in seven samples taken at different flow conditions (Shiller and Boyle 1987). In a 1977–1979 study of representative groundwaters and surface waters throughout New Jersey, in which >1,000 wells and 600 surface waters were sampled, the median nickel levels in groundwater and surface water were both 3.0 μg/L (Page 1981). The respective 90 percentile and maximum levels were 11 and 600 μg/L for groundwater and 10 and 45 μg/L for surface water. The nature of the sites with elevated nickel levels was not indicated. However, groundwater polluted with nickel compounds from a nickel-plating facility contained as high as 2,500 μg/L (IARC 1990). Nickel concentrations were measured in 30 groundwater samples taken from the South Platte River alluvial aquifer underlying Denver, Colorado (Bruce and McMahon 1996). The samples represented a variety of land-use activities, including commercial, industrial, residential, and agricultural. A median nickel concentration of 3 μg/L was determined, with maximum and minimum concentrations values of 20 and 1 μg/L, respectively.

Nickel concentrations from five stations in Lake Huron in 1980 had median and maximum nickel concentrations of 0.54 and 3.8 μg/L, respectively (Dolan et al. 1986). In a 1982 survey, nickel concentrations in Hamilton Harbor, Lake Ontario, ranged from <1 to 17 μg/L, with a median of 6 μg/L (Poulton 1987). The median nickel concentration from an analogous 1980 survey was 4 μg/L. Suspended sediment in surface samples (0.2 m) at Hamilton Harbor, Lake Ontario, contained 17–23 ppm nickel; samples from a depth of 20 m contained 67–87 ppm, similar to the 66 ppm of nickel found in bottom sediment samples (Poulton 1987). These findings suggest that resuspension of bottom sediment is a major contributor to the suspended sediment at 20 m depth. In a 1993 survey of heavy metal concentrations in the Great Lakes, average nickel concentrations of 872 and 752 ng/L were measured in Lakes Erie and Ontario, respectively (Nriagu et al. 1996). Concentrations were highest in near-shore waters due to their proximity to urban centers and polluted river mouths. A decrease in the average concentration of nickel measured in Lake Ontario, from 838 ng/L measured in May/June to a value of 751 ng/L obtained in October, indicates that sedimentation of suspended particles results in a fast depletion of nickel during the summer stratification (Nriagu et al. 1996).

Tap water that is used for drinking purposes generally contains nickel at concentrations ranging from 0.55 to 25 μg/L,in the United States (FDA 2000; O'Rourke et al. 1999; Thomas et al. 1999). Nickel concentrations in tap water measured in the Total Diet Study 1991–1999 ranged from 0 to 0.025 mg/kg (≈0–25 μg/L) with a mean value of 0.002 mg/kg (≈2 μg/L) (FDA 2000). Analysis of data obtained during 1995–1997 from the National Human Exposure Assessment Study (NHEXAS) yielded median concentrations of nickel in tap water (used as drinking water) of 4.3 μg/L (10.6 μg/L, 90% percentile) in the Arizona study and 4.0 μg/L (11 μg/L, 90% percentile) in the EPA Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) study (O'Rourke et al. 1999; Thomas et al. 1999). Mean levels for nickel in European drinking water range from 1 to 11 μg/L (Andersen et al. 1983; Barceloux 1999; Dabeka 1989; IARC 1990). In a 1969–1970 survey of 969 water supplies in the United States representing all water supplies in eight metropolitan areas and one state (2,503 samples), 21.7% of samples had concentrations <1 μg/L, 43.2% of the samples contained between 1 and 5 μg nickel/L, 25.6% of the samples contained between 6 and 10 μg nickel/L, 8.5% of the samples contained between 11 and 20 μg nickel/L, and 1% had levels >20 μg nickel/L (NAS 1975). In a national survey of raw, treated, and distributed water from 71 municipalities across Canada, the median nickel concentration in both treated and distributed provincial drinking water were ≤0.6–1.3 μg/L for treated water and 1.8 μg/L for distributed water (Meranger et al. 1981). The maximum value was 72.4 μg/L from Sudbury, Ontario. The similarity between median and maximum values for treated and distributed water suggests that nickel is not generally picked up in the distribution system. An exception is in Quebec where the maximum nickel concentration increased from 8.3 to 22.0 μg/L between the treated and distributed water. The median nickel levels in the provincial raw water ranged from ≤0.6 to 2.3 μg/L. The maximum levels in tap waters from British Columbia, Prince Edward Island, the Yukon, and Northwest Territories were below the detection limit. The similarity in values between raw and treated water indicates that treatment methods (mainly treatment with lime, alum, or soda ash) did not remove nickel effectively.

Elevated nickel levels may exist in drinking water as a result of the corrosion of nickel-containing alloys used as valves and other components in the water distribution system as well as from nickel-plated or chromium-nickel-plated faucets. In a Seattle study, mean and maximum nickel levels in standing water were 7.0 and 43 μg/L, respectively, compared with 2.0 and 28 μg/L in running water (Ohanian 1986). A similar result was observed in a comparison of the mean (±1 standard deviation) and 90th percentile concentrations of nickel measured during the NHEXAS EPA Region 5 study in standing tap water of (9.2 [±21] and 16 μg/L) and in tap water sampled after the water line had been flushed for 3 minutes (5.3 [±4.4] and 11 μg/L) (Thomas et al. 1999). Even if an individual was to consume only first draw

water (containing nickel at the maximum concentration [48 μg/L] obtained from the Seattle study) as their sole source of drinking water, their daily intake of 86 μg/day is still less than the lifetime daily limit of 100 μg/day (Table 8-1) set by EPA, assuming the consumption of 2 L/day (EPA 2000). Although leaching of metals from pipes generally increases with decreasing pH, none of the nickel studies reported the pH of the tap water. First water drawn from hot water taps plated with nickel may contain concentrations as high as 1–1.3 mg/L (Barceloux 1999). Andersen et al. (1983) reported nickel concentrations in standing water sampled from hot or cold water taps in 35 flats located in Denmark, and 46 locations in Sweden and 10 other European cities. Nickel concentrations in standing water drawn from hot water taps ranged between 5 and 490 μg/L; nickel concentrations in standing water drawn from cold water taps ranged between 5 and 75 μg/L.

Nickel concentrations were measured as part of a study of heavy metal content in streams and creeks, located in the Black Hills of South Dakota that are impacted by abandoned or active mining operations (May et al. 2001). The concentrations of nickel in these surface waters generally ranged between 1.3 and 7.6 μg/L and were typically highest near where they received drainage water from abandoned or active mining operations. At one location, nickel concentrations as high as 20 μg/L were determined and were attributed to effluent and entrained streambed tailings from previous mining activities. The concentrations of nickel in water did not correlate with the concentrations of nickel in the underlying sediments.

Several investigators reported the presence of nickel concentrations in rain. The annual mean nickel concentration in precipitation at Lewes, Delaware, was 0.79 μg/L (Barrie et al. 1987). The mean concentration (± standard deviation) of nickel collected from rain showers in southern Ontario, Canada, in 1982 was 0.56±0.07 μg/L (Chan et al. 1986). The mean concentrations in northern and central Ontario were both 0.61 μg/L, indicating a lack of spatial variability. Sudbury, the site of a large nickel smelter, is located in central Ontario. Rainwater samples collected near two nickel smelters and one ore roaster in northwestern Russia, located near the Finnish and Norwegian borders, had median nickel concentrations ranging between 1.31 and 57 μg/L with values as high as 132 μg/L (Reimann et al. 1997). The differences observed in the concentration of nickel in rainwater between the three sites roughly correlated with the reported emission rates for nickel into air from these sites. Background measurements of nickel in rainwater sampled several hundred kilometers from these industrial sites had median values ranging between 0.09 and 0.21 μg/L. Nickel concentrations from rain samples collected at four sites in Sweden had a mean range of 0.017–0.51 μg/L (Hansson et al. 1988). The nickel concentration in rainwater collected near a large municipal incinerator in Claremont, New Hampshire, was measured at a mean value

of 0.69 μg/L (Feng et al. 2000). Nickel concentrations in rain collected between 1985 and 1990 from remote regions of the Atlantic Ocean ranged from 0.63 to 1.42 μg/L (Helmers and Schrems 1995). The concentration of nickel in cloud water sampled on the Olympic Peninsula of Washington state in May 1993 was measured at 0.5±0.4 μg/L; the air-equivalent concentration is 0.2 ng/m^3 (Vong et al. 1997).

Nickel in snow from Montreal, Canada, was highly enriched compared with ambient air, ranging from 2 to 300 ppb (Landsberger et al. 1983). The nickel content of snow particulate matter was 100–500 ppb. Nickel concentrations were highly correlated with those of vanadium, suggesting that oil combustion was a source. The nickel concentration in snow collected near a large municipal incinerator in Claremont, New Hampshire, was measured at a mean value of 0.62 μg/L (Feng et al. 2000). Snow samples were collected several hundred kilometers from the nearest known nickel emission sources (e.g., smelters and ore processing facilities) in northwestern Russia, near the Finish and Norwegian borders. Mean nickel concentrations of 0.0019 mg/L (1.9 μg/L) were measured in the snow melt or, based on the volume of accumulated snow, 0.26 mg/m^3 (Kashulin et al. 1997).

6.4.3 Sediment and Soil

Sediment is an important sink for nickel in water. Mean nickel levels in pristine sediment from five sites off the northern coast of Alaska ranged from 25 to 31 ppm (Sweeney and Naidu 1989). Of this amount, ≈10% was extractable. Nickel was most highly associated with silt and clay. Background nickel concentrations in sediment cores from open water of Lake St. Clair ranged from 8.5 to 21.1 ppm, with mean concentrations of 13.6 and 17.6 ppm in sand and silty clay sediment, respectively (Rossmann 1988). The average nickel concentrations in surface sediment of four Rocky Mountain lakes ranged from 9.6 to 18 ppm (dry weight). The nickel concentrations of the five other lakes reported in the literature ranged from 6.4 to 38 ppm (Heit et al. 1984). Nickel concentrations measured in the sediments taken in 1998 from the Clark, Fork-Pend, and Spokane river basins in the region adjoined by the states of Washington, Idaho, and Montana ranged from 12 to 27 μg/g, dry weight (USGS 2000).

The range and mean nickel levels in surface sediment of Penobscot Bay, Maine, were 8.22–35.0 and 26.6 ppm (dry weight), respectively (Larsen et al. 1983). This is higher than the levels found at cleaner sites in Casco Bay in the Gulf of Maine (17.6 ppm) and Eastern Long Island (7.6 ppm) (Larsen et al. 1983). As part of the Long Island-New Jersey National Water-Quality Assessment (LINJ-NAWQA) Program, nickel concentrations were measured in bed-sediments taken from streams and rivers in New Jersey in the fall of 1997 (USGS 2000b). A median nickel concentration of 30 μg/g (wet weight) was

determined in bed-sediments, with values ranging from 18 to 43 μg/g. In a similar NAWQA study of the Northern Rockies Intermontane Basins study area, a median nickel concentration in bed-sediments of 18 μg/g (wet weight) was determined, with a range of values of 12–24 μg/g (USGS 2000a). Rice (1999) gives a summary of trace metal concentrations in 541 bed-sediment samples taken from throughout the conterminous United States as part of the NAWQA study, reporting a median nickel concentration of 27 μg/g, with a larger range of values 6–530 μg/g than found from the results of the separate NAWQA studies noted above. Nickel is more highly associated with fine-grained sediment with a higher organic carbon content. Levels reflect anthropogenic input as well as mineralization of the regional bedrock.

Nickel content in sediments is expected to be high near sources of nickel emissions. For example, Lake Kuetsjärvi is located approximately 1 km from the large Pechenganickel nickel smelter in northwestern Russia and receives both airborne and waste water emissions from the plant (Lukin et al. 2003). Sediment core samples taken from the lake, with nickel measurements, were acquired from the top 1 cm surface of the core (current status) and at a core depth of 20–30 cm (background). The average nickel concentrations determined for surface layer and background levels of the sediment core were 2,218 and 85 μg/g, dry weight, respectively. Surface and deep (4.5 meter) sediment samples taken from Lake Kochejavr, which is located 120 kilometers from the Pechenganickel smelter, showed little difference in nickel concentrations (21 and 16 μg/g, dry weight, respectively), even though this lake does receive airborne emissions from the Pechenganickel plant (Kashulin et al. 2001). Nickel carried into creeks and streams from drainage and runoff originating from active or abandoned mining operations in the Black Hills of South Dakota can lead to increased concentrations of this metal in sediments (May et al. 2001). Nickel concentrations varied between 10 and 64 μg/g, dry weight, depending on proximity to nearby mines.

Nickel occurs naturally in the earth's crust with an average concentration of 0.0086% (86 ppm) (Duke 1980a). The nickel content of soil may vary depending on local geology. A nickel content of 0.5% (5,000 ppm) is common in podzol soil in southeastern United States, and nickel concentrations of >1,000 ppm are not unusual in glacial till in southern Quebec. Both areas are underlaid with ultramafic rock, which is rich in nickel. Typical nickel levels reported in soil range from 4 to 80 ppm. In a region north of Sydney, Australia, nickel concentrations as high as 2,030 ppm have been reported in ferrosol topsoils, which are naturally-enriched in nickel throughout the weathering of underlying haematite, magnetite, quartz, and kaolinite minerals (Lottermoser 2002). A soil survey by the U.S. Geological Survey throughout the United States reported that nickel concentrations ranged from <5 to 700 ppm, with a geometric mean of 13±2.31 ppm, ranking 15th among the 50 elements surveyed (Shacklette and

Boerngen 1984). In this survey, samples were taken at 20 cm from 1,318 sampling sites. Cultivated soils contained 5–500 ppm of nickel, with a typical concentration of 50 ppm (Bennett 1984). Nickel concentrations in Canadian soils were generally 5–50 ppm (Webber and Shamess 1987). An extensive survey in England and Wales reported that nickel concentrations typically ranged from 4 to 80 ppm, with a median value of 26 ppm (Bennett 1984). The average farm soil in the United States contained >30 ppm nickel (NAS 1975). Mean nickel concentrations in the forest floor from samples collected from 78 sites in nine northeastern states averaged 11±0.8 ppm (Friedland et al. 1986).

Nickel concentrations in contaminated soils within ≈8 km of the large nickel smelter at Sudbury, Ontario, ranged from 80 to 5,100 ppm (Duke 1980b). A study of wetland soil-sediment in Sudbury found 9,372 and 5,518 ppm of nickel at sites located 2.0 and 3.1 km from the smelter, respectively (Taylor and Crowder 1983). Nickel concentrations declined logarithmically with increasing distance from the smelter. This indicates that nickel accumulations result from atmospheric deposition and soil runoff (Taylor and Crowder 1983). In a more recent survey of nickel content in soils in the Sudbury region, soil samples were taken within 5 km of each of the three smelters located in the area, Copper Cliff, Coniston, and Falconbridge (Adamo et al. 1996). Mean total concentrations of nickel in soil (based on dry weight) of 580, 286, and 210 mg/kg were obtained for the three sites, respectively. Concentration ranges were 80–2149, 156–628, and 23–475 mg/kg for the Copper Cliff, Coniston and Falconbridge sites, respectively.

Soils from the Idaho National Engineering Laboratory (INEL) and two background sites in southern Idaho had geometric mean nickel concentrations of 11.8–23.4 ppm dry weight; concentrations are significantly higher near INEL (Rope et al. 1988). The coal-fired steam plant that was constructed at the laboratory in 1982–1983 may be responsible for the higher nickel concentrations.

Nickel concentrations in 57 sludge-treated soils in an agricultural area of Ontario, Canada, ranged from 6.2 to 34 ppm (dry weight), with a mean of 20 ppm (Webber and Shamess 1987). For 252 untreated soils, the range and mean values were 4.0–48 and 16.2 ppm, respectively. The mean for sludge-treated soil was significantly elevated.

6.4.4 Other Environmental Media

There have been several studies regarding nickel content in an average diet. Current information on the dietary intake of nickel in the United States is based on data gathered from the NHEXAS study. Nickel

concentrations were measured in duplicate diet samples which, in combination with study participant's estimates of food and water intake, were used to determine both the overall concentration of nickel in combined solids and liquids in the total diet and the average nickel intake of study participants. In the EPA Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) study, the mean and median concentrations of nickel in combined dietary solids and liquids were 47 and 43 μg/kg, respectively (Thomas et al. 1999).

In other studies of nickel in the diet, Myron et al. (1978) analyzed nine institutional diets consisting of three meals each. Four of these meals were sampled from the student center at the University of North Dakota. The remaining five diets were special diets from a rehabilitation hospital. The average nickel concentration and nickel content of the student meals ranged from 0.19 to 0.29 ppm and from 140 to 221 μg, respectively. For the hospital meals, the nickel concentration ranged from 0.21 ppm (107 μg) in the puree meals to 0.41 ppm (176 μg) in the low-calorie meal. Breakfast had the lowest nickel content. The average daily dietary nickel intake for the nine diets was 168±11 μg. The average nickel concentration in the food was 0.27 ppm (dry weight). These results are comparable with estimated daily intakes of nickel of 150 μg in Denmark, 73–142 μg in Switzerland, and 140–150 μg in the United Kingdom (IARC 1990; Nielsen and Flyvholm 1984). A 1962 study that used the nickel content of individual foods to estimate average dietary nickel intake reported intakes of 300–600 μg, which are much higher than those reported above (Grandjean 1984).

A study of dietary intake of heavy metals for 44 individuals (21 men, 43 women) living in central Italy was conducted using dietary history, weighted record methods, and concurrent chemical analysis of duplicate portions (Alberti-Fidanza et al. 2003). Based on chemical analysis, the mean (±1 SD) daily intakes of nickel were measured to be 222.3±87.7 μg in men and 165.7±53.8 μg in women. Calculation of daily nickel intake based on dietary history or food basket data resulted in lower intake values for both men and women. Based on dietary histories, daily nickel intakes for men and women were determined to be 105.3±32.6 and 84.8±24.9 μg, respectively; calculations based on food basket data gave daily nickel intakes of 123.8±37.8 and 98.3±25.6 μg for men and women, respectively. In another study of trace metal intake from components in the Italian diet, it was determined that the average Italian adult obtained 280 μg of nickel per week through the consumption of beverages such as wine, beer, coffee, tea, and mineral water (Minoia et al. 1994). Wine and tea were identified as the largest sources of nickel intake at 25.2 and 15.6 μg/week, respectively.

The nickel content of specific food items has also been determined. In the average Danish diet, the ranges of mean nickel levels in various food categories (in ppm) have been reported as follows: milk products, 0.01–0.1; meat, fish, and eggs, 0.02–0.11; vegetables, 0.04–0.52; fruits, 0.01–0.31; and grains, 0.1–1.76 (IARC 1990; Nielsen and Flyvholm 1984). The mean nickel level in meats, fruits, and vegetables is ≤0.2 ppm. The foods with the highest mean nickel content were oatmeal, spinach, asparagus, and peas. Nuts and cocoa may have nickel levels as high as 3 and 10 ppm, respectively (IARC 1990). In a market basket survey completed in the United States (Pennington and Jones 1987), the highest average levels of nickel in μg/100 g were found in nuts (128.2), legumes (55), sweeteners (31.6), grains and grain products (26.2), and mixed dishes and soups (25.3). From data gathered in the FDA Total Diet Study 1991–1996, the mean and median nickel concentrations in the food items that were surveyed were 0.136 and 0.057 mg/kg, respectively (Capar and Cunningham 2000). The highest concentrations of nickel were found in mixed nuts (3.04 mg/kg), oat ring cereal (2.32 mg/kg), chocolate syrup (1.04 mg/kg), granola cereal (1.01 mg/kg), and peanuts (0.956 mg/kg). Other products with notable nickel concentrations are legumes and nuts (0.368–3.04 mg/kg), cereals containing largely whole wheat, corn, oats, or rice (0.216–2.32 mg/kg), chocolate products (0.19–1.04 mg/kg), and canned peaches and pineapple juice (0.408–0.668 mg/kg). In an analysis of trace metals in tissue samples taken from livestock and poultry, mean nickel concentrations were 0.23–0.82 ppm in muscle, 0.23–0.29 ppm in liver, and 0.28–0.57 ppm in kidney (Coleman et al. 1992).

A Canadian survey of nickel in infant formulas gave a median value of 3.53 μg/L for evaporated milk (Dabeka 1989). Different types of milk-based formulas contained from 5.8 to 28.9 μg nickel/L (Dabeka 1989). All concentrations are on a ready-to-use basis. Formulas fortified with iron had a higher nickel content. The median nickel content of soy-based formula ranged from 31.2 to 187 μg nickel/L. The average daily dietary intake of nickel by infants between the ages of 0 and 12 months could vary from 35.7 μg (4.5 μg/kg) (if evaporated milk was fed) to 74.7 μg (10.2 μg/kg) (if concentrated liquid soy-based formula was used). Infant formula (base not stated) in the United States contained an average of 0.2 μg nickel/100 g (Pennington and Jones 1987).

There is limited evidence that stainless steel pots and utensils may release nickel into acid solution (IARC 1990). Six stainless steel pots of different origins were tested to see whether they would release nickel by boiling 350 mL of 5% acetic acid in them for 5 minutes (Kuligowski and Halperin 1992). The resulting concentrations of nickel ranged from 0.01 to 0.21 ppm. Cooking acidic fruits in new stainless steel pans resulted in an increase of nickel that was about one-fifth the average daily nickel intake (Flint and Packirisamy 1995). Further use of the pans did not result in any release of nickel into the food. The use

of nickel-containing catalysts in the hydrogenation of food fats may contribute to elevated nickel levels in food (Mastromatteo 1986). Grain milling may also lead to higher nickel levels (IARC 1990). The results from a recent study that attempted to identify the influence of the container on the trace metal content of preserved pork products showed no clear evidence that the metal container contributed to the metal content of the food (Brito et al. 1990). The nickel concentration was highest in products in china and glass containers, rather than those in metal and plastic containers.

The nickel content of cigarettes is 1–3 μg; ≈10–20% of this nickel is released in mainstream smoke (Sunderman 1986). This indicates that 2–12 μg of nickel are inhaled for each pack of cigarettes smoked. Most of the nickel is in the gaseous phase, but the chemical form of the nickel is unknown (IARC 1990).

In a comprehensive survey of heavy metals in sewage sludge, 31 sludges from 23 American cities were analyzed by electrothermal atomic absorption spectroscopy (AAS) (Mumma et al. 1984). The nickel concentration in the sludges ranged from 29.0 to 800 ppm (dry weight) and had a median value of 195 ppm. The highest concentration of nickel in sludge was in Detroit, Michigan. For comparison, the concentration of nickel in cow manure was 28.0 ppm. In another study of heavy metal in sludges generated at waste water treatment plants in 16 large U.S. cities, nickel concentrations (dry weight) were found to range from 18 to 186 ppm, with a median value of 66.8 ppm (Gutemann et al. 1994).

Nickel was detected in a large number of the 283 point samples taken from leachate collected from 48 codisposal, hazardous, or municipal solid waste (MSW) sites (Gibbons et al. 1999). Codisposal sites were defined as those facilities accepting municipal wastes and relatively large volumes of industrial sludges, liquids, and solids. Dissolved nickel was detected in 43 of 45 codisposal sites, all 48 old (accepting waste before 1986) hazardous waste sites, all 29 old (accepting waste before 1984) MSW sites, and 1 of 1 new (accepting waste after 1984) MSW site. Solid nickel was detected in 105 of 111 codisposal sites, 108 of 126 old (accepting waste before 1986) hazardous waste sites, 108 of 116 old (accepting waste before 1984) MSW sites, and 36 of 43 new (accepting waste after 1984) MSW sites.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Nickel occurs naturally in the earth's crust, and the general population will be exposed to low levels of nickel in ambient air, water, and food. The average daily dietary intake of nickel in food ranges between 69 and 162 μg/day (O'Rourke et al. 1999; Pennington and Jones 1987; Thomas et al. 1999). The daily intake from drinking water is ≈8 μg, assuming a median nickel concentration of ≈4 μg/L and a

consumption rate of 2 L water/day. For the highest municipal level in drinking water, which is 68 μg/L in Sudbury, Ontario, the average daily intake of nickel would be 140 μg. Assuming that a person inhales 20 m^3 air/day and the range of average nickel concentrations in ambient air in the United States is 2.22 ng/m^3, the average nickel intake by inhalation would be 0.0444 μg/day. Based on the highest ambient nickel levels reported for the Copper Cliff (6,100 ng/m^3) and Sudbury basin region (732 ng/m^3) in Ontario (CEPA 1994), the daily inhalation intake for individual living in these areas could have been as high as 122 and 15 μg/day, respectively. However, based on the mean ambient nickel concentrations measured in Sudbury area of 21 ng/m^3 (CEPA 1994) the daily nickel the average daily nickel intake is estimated to be 0.42 μg/day. The nickel intake via inhalation is, therefore, a minor source of nickel to the general, nonsmoking population.

A market basket survey in England completed in 1984 estimated a dietary intake of 154–166 μg/day or 2.2–2.4 μg/kg/day for a 70-kg person (Smart and Sherlock 1987). Dietary intake of nickel in the United States has been estimated to range from 69 μg/day for 6–11-month-old infants to 162 μg/day for teenage boys, with a level of 146.2 μg/day or 2 μg/kg/day for a 25–30-year-old male weighing 70 kg (Pennington and Jones 1987). More recent data on nickel intakes from the U.S. diet come from the results of the NHEXAS studies. Mean and median dietary intakes of nickel for study participants in the EPA Region 5 study were calculated to be 2.2 and 1.4 μg/kg body weight/day, respectively, or 154 and 98 μg/day for a 70-kg adult, respectively (Thomas et al. 1999). O'Rourke et al. (1999) have taken the dietary nickel data obtained from the Arizona study and determined the dietary nickel intake for various subpopulations (Table 6-4). The mean daily nickel intake for all subjects was 153 μg/day, with the highest mean intake for an adult male (163 μg/day) and lowest intake for children (125 μg/day). Hispanic study participants were found to have a lower mean dietary intake (141 μg/day) than non-Hispanic participants (155 μg/day). Total nickel intake for Canadians in the general population has been estimated to range from 4.4 to 22.1 μg/kg/day, with greater intake estimated for infants than for adults (CEPA 1994). Food, from which nickel is poorly absorbed, accounted for most of the intake (4.4–22 μg/kg/day). It was estimated that cigarette smoking may increase total daily intake by 0.12–0.15 μg/kg/day. Living in the vicinity of Sudbury, Ontario, where large nickel deposits are found, water intake of nickel for individuals aged 12 years old or older ranged from 0.6–2.5 μg/kg/day. However, the estimated water intake of nickel increased with decreasing age of the study group, for example 0.87–3.6 μg/kg/day for children ages 5–11 years old to 2.8–12 μg/kg/day for newborns and infants under the age of 0.5 years.

In another approach to determining daily nickel intake within subpopulations in the United States, Moschandreas et al. (2002) used the Dietary Exposure Potential Model (DEPM) and data obtained from

Table 6-4. Total Dietary Exposure Estimates of Study Participants to Nickel Based on the Dietary Information Obtained from the NHEXAS Arizona Study[a]

Exposure population	Number of participants evaluated	Daily nickel intake (μg)		
		Mean intake	Median intake	Range
All subjects	176	153	135	27–562
Adult male (>18 years of age)	55	163	145	38–372
Adult female (>18 years of age)	86	157	135	23–563
Children (<18 years of age)[b]	35	125	107	31–343
Hispanic	54	141	134	27–401
Non-Hispanic	119	155	132	42–563

[a] O'Rourke et al. 1999
[b] Either gender

Combined National Residue Database (CNRD) to estimate dietary nickel intake based on food consumption patterns in subpopulations and nickel content in specific food items. The food items used in the model are based on 11 food groups consisting of approximately 800 exposure core foods that represent 6,500 common food items. The results of their model (Table 6-5) yielded an average dietary nickel intake in the U.S. population of 0.374 μg/kg body weight/day, or 26.2 μg/day for a 70-kg adult. Their results also indicate that children under the age of 7 have a nickel intake that is at least 1.8 times higher than the average for the overall population. However, the estimates obtained for dietary nickel intake from the DEPM model are lower than the daily nickel intakes determined from the NHEXAS study (Table 6-4). Moschandreas et al. attribute these differences in intake values for nickel to differences in study populations, methods for assigning values to measurements that are below the level of detection, and potential errors in recording portion sizes in the NHEXAS study.

The general population is also exposed to nickel in nickel alloys and nickel-plated materials including steel, coins, and jewelry (Barceloux 1999). Jewelry and other items made of silver may either contain, or be coated with, nickel to reduce oxidation. White gold contains 10–15% nickel and some gold-plated items may have a nickel undercoating. Residual nickel may be present in soaps, fats, and oils hydrogenated with nickel catalysts (Sunderman 1986).

A NOES survey conducted by NIOSH from 1981 to 1983 estimated that 727,240 workers are potentially exposed to nickel metal, alloys, dust, fumes, salts, or inorganic nickel compounds in the United States (NIOSH 1990). Seventy percent of these estimated exposures are to nickel of an unknown molecular formula. The numbers of workers estimated to be exposed to nickel chloride, nickel oxide, and nickel sulfate are 48,717, 18,166, and 56,844, respectively. The estimate is provisional because all of the data for trade name products that may contain nickel have not been analyzed. The NOES was based on field surveys of 4,490 businesses employing nearly 1.8 million workers and was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where eight or more persons are employed in all standard industrial codes except mining or agriculture. Industries with especially large numbers of potentially exposed workers include the following: plumbing, heating, air conditioning, pressed and blown glass, steel, plating and polishing, aircraft, shipbuilding, railroad, control and measuring instruments, and repair services (NIOSH 1990).

Occupational exposure to nickel will be highest for those involved in production, processing, and use of nickel. There are currently no people in the United States employed in nickel mines, smelters, and refineries at the end of 2001. Primary nickel production in the United States ceased for several years in

Table 6-5. Dietary Exposure Estimates of U.S. Populations to Nickel Based on the Dietary Exposure Potential Model (DEPM)[a]

Subpopulation	Nickel intake (μg/kg BW[b]/day)
U.S. population	0.374
Age/gender	
Nonnursing infants	0.870[c]
Children 1–6	0.669
Children 7–12	0.425
Females 13–19	0.281
Females 20+	0.350
Females 55+	0.368
Males 13–19	0.324
Males 20+	0.342
Males 55+	0.369
Ethnicity	
Hispanic	0.407
Non-Hispanic white	0.424[c]
Non-Hispanic black	0.295
Non-Hispanic other	0.258
Geographic region[d]	
North central	0.238
Northeast	0.379
Southern	0.359
Western	0.423[c]
Family income[e]	
Poverty 0–130%	0.420[c]
Poverty 131%+	0.362

[a] Moschandreas et al. 2002
[b] BW = body weight
[c] Values indicate the maximum exposure to nickel for each subpopulation group.
[d] The regional classification is as defined by the U.S. Department of Agriculture, and is based upon U.S. Census Bureau regions.
[e] Annual household income as a percentage of the Poverty Index.

the late 1980s (Kirk 1988a). The mining and smelting operation in Riddle, Oregon, was reactivated in 1989–1990, and was decommissioned in 2001 (Kuck 2001). The concentration range of airborne nickel that workers were exposed to in laterite mining and smelting in Riddle, Oregon, was 4–420 μg nickel/m^3 (Warner 1984). The ranges of airborne nickel concentrations reported for other industries are as follows: stainless steel production, <1–189 μg/m^3; high nickel alloy production, 1–4.4 μg/m^3; foundry operations, from not detectable to 900 μg/m^3; electroplating, from <2 to <16 μg/m^3; nickel-cadmium battery manufacture, 20–1,910 μg/m^3; nickel catalyst production from nickel sulfate, 1–1,240 μg/m^3; production of nickel salts from nickel or nickel oxide, 9–590 μg/m^3; and production of wrought nickel and alloys from metal powder, 1–60,000 μg/m^3 (Anttila et al. 1998; Haber et al. 2000; Magari et al. 2002; Warner 1984). Average nickel concentrations for selected work areas or operations in these industries, other than producing wrought nickel and alloys from metal powder, range from <3 to 378 μg/m^3; for wrought nickel and alloy production from metal powder, the average concentration is 1,500 μg/m^3. Operations that produce the highest levels of airborne nickel are those that involve grinding, welding, and handling powders. Not only do occupational exposures vary widely among these operations and industries, but also the form of nickel that workers are exposed to varies (Table 6-6). Because sulfur has a deleterious effect on many metals and alloys, nickel sulfate and sulfidic nickel compounds are generally not found in metallurgical workplaces (Warner 1984). Nickel subsulfide is known to exist in only one application in nickel-using industries, namely in certain spent catalysts. Nickel oxide is used as a raw material in steel production, and oxide fumes and dust may occur in melting, casting, and welding operations. There are probably more exposures to metallic nickel in nickel-using industries than in nickel-producing industries. These occur during powder handling, grinding, and polishing operations and in casting operations.

Nickel is an essential trace element for animals (Sunderman 1986), and a 70-kg reference man contains 10 mg of nickel, giving an average body concentration of 0.1 ppm (Iyengar 1986). The highest tissue concentrations of nickel are found in the lungs of nickel smelting and refinery workers. The highest nickel concentration reported in lung tissue of 39 nickel refinery workers autopsied in 1978–1984 was 1,344 ppm (dry weight), compared to 1.7 ppm in unexposed persons (Andersen and Svenes 1989). In another study of nickel content in the lungs of 15 former nickel refinery workers, the arithmetic mean (±1 SD) for nickel concentrations in workers was 50±150 μg/g, dry weight, in comparison to a value of 0.74±0.44 μg/g in 10 individuals not connected to the refinery industry (Svenes and Anderson 1998).

Ten studies of nickel in human milk gave disparate results. Six median values ranged from 5 to 16 μg/L, and 10 mean values ranged from 1.5 to 39 μg/L (Iyengar 1989). Five of the six medians ranged from

Table 6-6. Nickel Levels in Air and Distribution of Different Forms of Nickel as a Proportion (by Weight) of Total Nickel in Selected Departments and Time Periods at a Nickel Refinery in Norway[a]

Department and period	Total nickel in air (mg/m^3)	Proportion of total nickel			
		Soluble nickel	Sulfidic nickel	Metallic nickel	Oxidic nickel
Crushing and grinding					
1990–1994	0.7–1.4	0.12	0.72	0.11	0.04
Smelter					
1910–1929	4.0	0.10	0.05	0.01	0.84
1930–1950	4.0	0.10	0.05	0.08	0.77
1951–1977	2.6–4.4	0.10	0.04	0.18	0.68
Calcining, smelting					
1951–1977	1.5–3.4	0.10	0.05	0.01	0.84
1978–1994	0.5	0.12	0.13	0.01	0.74
Roasting					
1910–1977	1.9–5.3	0.10	0.15	0.03	0.72
1978–1994	0.4	0.15	0.05	0.00	0.80
Copper leaching					
1910–1994	0.1–1.5	0.49	0.01	0.01	0.49
Copper electrolysis					
1910–1994	0.03–0.2	0.80	0.04	0.04	0.13
Copper cementation					
1927–1977	0.6–1.2	0.45	0.05	0.45	0.05
Electrolytic purification					
1927–1977	0.2–0.5	0.80	0.03	0.15	0.02
1978–1994	0.03–0.2	0.98	0.01	0.00	0.01
Nickel electrolysis					
1910–1977	0.1–0.2	0.87	0.05	0.01	0.08
1978–1994	0.03–0.1	0.83	0.04	0.02	0.11

[a]Grimsrud et al. 2002

11 to 16 μg/L. The lowest and highest mean values were from Finland and Germany GDR, respectively. None of the studies were from the United States. Individual values ranged from not detectable to 130 μg nickel/L.

Nickel concentrations in human serum taken from 30 individuals not occupationally exposed to nickel ranged from <0.05 to 1.05 μg/L with a mean value of 0.34 μg/L (Barceloux 1999). In another example, nickel concentrations in serum obtained from individuals without occupational exposures to nickel ranged from 0.18 to 0.54 μg/L with an average of 0.36 μg/L (Christensen 1995). Serum nickel levels in hospital workers averaged 0.6±0.3 μg/L in Sudbury, Ontario, versus 0.2±0.2 μg/L in Hartford, Connecticut (Hopfer et al. 1989). Measurements of nickel content of tap water in these communities were reported as 109±46 and 0.4±0.2 μg/L, respectively (Hopfer et al. 1989). A mean nickel concentration of 4.80±2.69 μg/L was measured in urine samples collected for the NHEXAS Arizona study (EPA 2003t). Concentrations of nickel in the blood and urine of workers at a rolling mill in Poland were 18.5±4.0 and 25.7±5.1 μg/L, respectively (Baranowska-Dutkiewicz et al. 1992). Mean concentrations of nickel in urine of individuals not occupationally exposed to nickel are generally <2 μg/L and can range as high as 9–10 μg/L (95% upper confidence limit) in healthy adults (Barceloux 1999). Workers at a galvanizing plant in Brazil exposed to airborne nickel sulfate at concentrations of 2.8–116.7 $\mu g/m^3$ had nickel concentrations in their urine ranging between 2.1 and 58.7 μg/g creatinine (2.3–54.9 μg Ni/L) with mean values of 8.7±7.8 and 14.7±13.5 μg/g creatinine (10.5±7.5 and 20.6±18.1 μg Ni/L) in preshift and postshift samples, respectively (Oliveira et al. 2000). Mean concentrations of nickel in the urine of the control group (workers in a zinc plating plant) were 3.7±2.5 μg/g creatinine or 4.9±2.2 μg/L. Nickel concentrations in the urine of preschool children in Poland were 10.6±4.1 and 9.4±4.7 μg/L for children from an industrial region and a health resort, respectively (Baranowska-Dutkiewicz et al. 1992). After reviewing studies of nickel concentrations in humans, Templeton et al. (1994) indicated that the most reliable reference values were 0.2 μg/L for nickel in serum of healthy adults and 1–3 μg/L for nickel in urine. These values are dependent on food and fluid intake and environmental factors. Fewer studies of nickel in whole blood were identified, and a reference value was not suggested.

Fingernail samples from 71 Americans contained 0.57 ppm of nickel; samples from residents of Japan, India, Canada, and Poland had nickel concentrations that ranged from 1.1 to 3.9 ppm (Takagi et al. 1988). Nickel levels are higher in males than in females. Higher levels occur in younger people and decrease with age. The mean concentration of nickel in hair samples from 55 men and women from Scranton, Pennsylvania, was 1.01 ppm; populations from cities in Japan, India, Canada, and Poland had mean nickel levels between 0.26 and 2.70 ppm (Takagi et al. 1986). A more recent National Health and

Nutritional Examination Survey II of hair from a random sample of 271 adults, ages 20–71, from three communities had geometric mean and median nickel levels of 0.39 and 0.45 ppm, respectively. Ten percent of the group had nickel levels >1.50 ppm (DiPietro et al. 1989).

The nickel content of most natural vegetation is 0.05–5 ppm on a dry weight basis (NAS 1975). Near source areas, nickel on plants may be elevated because of direct foliar deposition. Some species of plants have the ability to hyperaccumulate nickel (Brooks 1980). The concentration in the leaves of *Alyssum bertolonii* contained 120 ppm nickel. These plants are thought to produce organic ligands that complex with nickel.

The modal concentration of nickel in 159 species of edible fin fish from the U.S. National Marine Fisheries Survey was 0.2–0.3 ppm (wet weight) (Heit et al. 1989). Jenkins (1980) has compiled literature concentrations of nickel levels in aquatic species. The ranges of nickel concentrations in freshwater fish, marine fish, and mollusks from areas thought to be uncontaminated are from <0.2 to 2.0, from not detectable to 4.0, and from 0.4 to 2.0 ppm (wet weight), respectively. The highest levels found near sources of pollution, especially near nickel smelters, were 51.6 ppm for freshwater fish and 191.0 ppm for mollusks. The nickel content of muscle tissue of several fish species collected from metal-contaminated lakes near Sudbury, Ontario, was below the detection limit (2.0 ppm dry weight), except for two of four yellow perch, which had levels of 2.8 and 3.4 ppm (Bradley and Morris 1986). A more recent survey of metals in stocked lake trout in five lakes near Sudbury, Ontario, reported that concentrations of metal in trout muscle were not significantly different from those in the hatchery (0.34–0.83 ppm wet weight versus 0.49 ppm) (Bowlby et al. 1988). Nickel concentrations in the lower Savannah River and Savannah National Wildlife Refuge in Georgia were higher than those reported above for uncontaminated areas. These levels were consistently higher in gar (2.35–6.67 ppm wet weight) than in catfish (0.37–1.41 ppm) (Winger et al. 1990). Nickel could not be measured above the detection limit (0.5 μg/g, dry weight) in livers taken from lesser scaup collected along the Mississippi Flyway between Manitoba and Louisiana (Custer et al. 2003). As part of the National Status and Trends Program for Marine Environmental Quality, the concentration of nickel in oysters and mussels was investigated (NOAA 1987). The nickel concentration in bivalve tissue collected in 1986 ranged from 0.55 to 12.57 ppm (dry weight). The highest tissue concentration was found in Matagorda Bay, Texas, and the second highest concentration, 6.57 ppm, was found in both Tomales Bay, California, and Chesapeake Bay, Maryland. Oysters around three coastal marinas in South Carolina with sediment nickel levels of 25.8–40.8 ppm (dry weight) had levels of 0.3–5.2 ppm (Marcus and Thompson 1986). Mean nickel levels in oysters at four sites in the Mississippi Sound varied from <0.5 to 4.7 ppm (wet weight) (Lytle and Lytle 1990).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Exposures of children to airborne nickel are expected to be similar to those found for adults. However, differences in the exposure to nickel contained in deposited particulates (e.g., household dust) are expected to be higher in children, due to greater contact of children with floors and other surfaces, in addition to greater oral and dermal contact with these deposited particulates through the mouthing of toys, hands, feet, etc. Concentrations of nickel in dust collected from homes in Ottawa, Ontario, averaged 62.9 mg/kg with values as high as 116.4 mg/kg (Butte and Heinzow 2002). However, it is not known how much nickel a child absorbs through oral or dermal contact with household dust.

Nickel that is dissolved in water is expected to be a minor exposure route for children, due to the generally low concentrations of nickel in drinking water and groundwater (Sections 6.4.2 and 6.5). However, in areas near nickel smelters and refineries where source water used to produce drinking water is contaminated with nickel, intake of nickel through drinking water for individuals in the affected area will be elevated above that for individuals in the surrounding region whose drinking water is unaffected by these sources of nickel contamination, but is expected to be less than nickel intake through food. Exposure to nickel through consumption of human breast milk is expected to be comparable to milk-based and soy-based formulas, based on the similar concentration ranges of nickel in these fluids (Dabeka 1989; FDA 2000; Iyengar 1989).

Another source of nickel exposure in children is through soil. Children generally receive higher exposure to soil contaminants per unit body weight than adults (Lottermoser 2002). Small children have large surface-to-mass ratios, which provide a greater potential to transdermally absorbed compounds, especially for children crawling in dirt. Also, the skin of newborns and children is more permeable than adult skin. Nickel in an ionized form, such has nickel salts, does not penetrate intact skin but can be absorbed at sites of injury to skin or in conjunction with nickel-induced contact dermatitis (Barceloux 1999). However, nickel exposure through dermal exposure is minimal compared to exposures to nickel through ingestion of soil. The largest target population at greatest risk are children between the ages of 2 and 3 years old as a result of hand-to-mouth activities and those with soil-eating disorders (Lottermoser 2002). A child's intake of nickel through ingestion of soil could be especially important in areas where soils that are naturally enriched with nickel (for example, some soils in the southeastern United States, southern Ontario, or eastern Australia) or have been contaminated with nickel (for example in the Sudbury, Ontario, region) (Section 6.4.3). However, due to the limited bioavailability of nickel in some soils, the amount of nickel that a child actually absorbs from ingested soils could be rather limited. For example, ingestion of 100 mg of ferrosol soil containing 149 mg nickel per kg of soil is calculated to contribute an intake of 0.000149 mg nickel/day, assuming a relative bioavailability for nickel of 1% (Lottermoser 2002).

The primary route of nickel exposure in children is expected to be through the diet. Measurements of nickel in duplicate diet samples obtained from the EPA Region 5 studies indicates that average nickel concentration in combined solids and liquids of 47 μg/kg, which is higher than the average nickel concentration in drinking water of approximately 5 μg/kg (5.3 μg/L) (Thomas et al. 1999). Using the portion size information recorded by study participants in the NHEXAS Arizona study, daily dietary intakes of nickel for children (<18 years of age) have been calculated to range from 31 to 343 μg, with a mean value of 125 μg (O'Rourke et al. 1999). These intake levels were lower than the average dietary nickel intake of 153 μg/day calculated for the overall study population (Table 6-4). Information on dietary nickel intake for non-nursing children and children ages 1–6 (Table 6-5) obtained from DEPM model (Moschandreas et al. 2002) indicates that these children have a higher intake of nickel than the average intake for the U.S. population. Even so, the daily intake of nickel in these children is estimated (4–13 μg/day based on 6–20 kg total body weight) to be much lower than the average dietary nickel intake (125 μg/day) obtained from the NHEXAS study. Also, results from a study of dietary nickel in 2-year-old children in the United Kingdom, where an average daily intake of 81 μg/day (range of

14–260 μg/day) was estimated from the weekly nickel intake of 0.57 mg of nickel (range of 0.1–1.8 mg) given in the reference (Smart et al. 1987), would suggest a higher daily nickel intake in young children than is indicated based on the results of the DEPM model.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In discussing nickel exposure, it is important to consider what form of nickel a person is exposed to and its bioavailability. Such information is not often available. Although high concentrations of nickel may be found in contaminated soil and sediment, it may be embedded in a crystalline matrix or bound to hydrated iron, aluminum, and manganese oxides and, therefore, not bioavailable.

Nickel-containing alloys are used in patients in joint prostheses, sutures, clips, and screws for fractured bones. Corrosion of these implants may lead to elevated nickel levels in the surrounding tissue and to the release of nickel into extracellular fluid (IARC 1990; Ries et al. 2003; Sunderman 1989a; Sunderman et al. 1986, 1989c). Serum albumin solutions used for intravenous infusion fluids have been reported to contain as much as 222 μg nickel/L. Dialysis fluid has been reported to contain as much as 0.82 μg nickel/L. Patients receiving transfusions may be exposed to high levels of nickel.

People who live near or work at facilities that produce stainless steel and other nickel-containing alloys, oil-fired power plants, coal-fired power plants, and refuse incinerators may be exposed to high levels of nickel in airborne dust, soil, and vegetation. People who live near or work at waste sites that receive waste from nickel-producing or using industries or that handle bottom ash or fly ash from power plants or refuse incinerators may also be exposed to higher levels of nickel (Newhook et al. 2003). Exposure would result from inhalation, dermal contact, or ingestion of contaminated soil or vegetation. It is possible that nickel from waste sites will contaminate groundwater. This situation is most probable with electroplating waste. People using this groundwater may be exposed to high nickel concentrations.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of nickel is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the

initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of nickel.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Except for differences between black and green nickel oxide, the physical and chemical properties of nickel and its compounds reported in Table 4-2 (HSDB 2003) have been adequately characterized.

Production, Import/Export, Use, and Release and Disposal. Information on the production, import, export, and use of nickel metal, nickel alloys, and nickel compounds is readily available (Chamberlain 1985; Kirk 1988a, 1988b; Kuck 2001; NTD 1996; Tien and Howson 1981). Except for recycling of metal scrap, little information is available regarding the disposal of nickel and its compounds.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 2000 is available on a yearly basis and provides a list of industrial production facilities and emissions.

Releases according to the TRI database are reported in Tables 6-1 and 6-2 (TRI01 2003). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Much of the nickel released to the environment is transferred off-site for disposal and probably landfilled. Nickel wastes from former mining and smelting operations may have been discarded in large tailing piles. Acid conditions are often created in tailing piles from sulfidic ores that increase the potential for leaching (Wood 1987). This is not the case with lateritic deposits such as those found in Riddle, Oregon. Information regarding nickel leaching from slag heaps is important in assessing releases

to the environment. More detailed information regarding disposal methods and the form of nickel disposed of is necessary to assess potential nickel exposure.

Environmental Fate. Nickel is an element and therefore, is not destroyed in the environment. In assessing human exposure, one must consider the form of nickel and its bioavailability. This information is site specific. Data regarding the forms of nickel in air, soil, and sediment are fragmentary and inadequate (Sadiq and Enfield 1984a; Schroeder et al. 1987). Also lacking is adequate information on the transformations that may occur, the transformation rates, and the conditions that facilitate these transformations. Information relating to the adsorption of nickel by soil and sediment is not adequate. In some situations, adsorption appears to be irreversible. In other situations, however, adsorption is reversible. More data would be helpful in detailing those situations where adsorbed nickel may be released and those where release is unlikely.

Bioavailability from Environmental Media. The absorption and distribution of nickel as a result of inhalation, ingestion, and dermal exposure are discussed in Sections 3.4.1 and 3.4.2. Quantitative data relating the physical/chemical properties of nickel (e.g., particle size, chemical forms of nickel) with its bioavailability are available for inhaled nickel. In aqueous media, nickel is in the form of the hexahydrate ion, which is poorly absorbed by most living organisms (Sunderman and Oskarsson 1991). Additional studies that examine the absorption of nickel from soil would be useful.

Food Chain Bioaccumulation. Data are available on the bioconcentration of nickel in fish and aquatic organisms (Birge and Black 1980; Callahan et al. 1978; McGeer et al. 2003; Suedel et al. 1994; Zaroogian and Johnson 1984). Higher levels of nickel have been found in gar compared with catfish from the same environment (Winger et al. 1990). More data on different species of fish at different sites would be useful in explaining these results. Data are limited on the nickel levels in wild birds and mammals (Alberici et al. 1989; Dressler et al. 1986; Jenkins 1980). A larger database including information on both herbivorous and carnivorous species living in both polluted and unpolluted environments is desirable in establishing whether nickel biomagnification in the food chain occurs under some circumstances.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of nickel in contaminated media at hazardous waste sites are needed so that the information obtained on levels of nickel in the environment can be used in combination with the known body burden of nickel to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Representative and recent monitoring data for nickel in air, water, and foods are essential for estimating

the extent of exposure from each of these sources. Nickel levels in environmental media are often below the detection limit of the analytical method employed. When a substantial fraction of determinations of nickel levels in environmental samples are below the detection limit, an arithmetic mean may not adequately represent the data. Data on the levels of nickel in ambient air are available (Claiborne et al. 2002; EPA 1986a; Evans et al. 1984; Kinney et al. 2002; Koutrakis et al. 1992; Kowalczyk et al. 1982; Lioy et al. 1987; Salztman et al. 1985; Sweet et al. 1993; van Winkle and Scheff 2001; Vousta and Samara 2002; Wiersema et al. 1984). Data provided by EPA's National Human Exposure Assessment Study (NHEXAS) have contributed to the assessment of current levels of exposure to nickel by the U.S. population via inhalation, drinking water and food. Analyses of data obtained from the Arizona and EPA Region 5 NHEXAS studies (O'Rourke et al. 1999; Thomas et al. 1999) have provided information on daily dietary nickel intake for these study populations. These data have provided the first update of nickel content within the U.S. diet since the last comprehensive survey of nickel in U.S. drinking water in 1969–1970 (NAS 1975) and the information on dietary nickel that had been limited to one study from North Dakota (Myron et al. 1978). While these recent results are in agreement with ones from Europe (Alberti-Fidanza et al. 2003; IARC 1990), they do differ from the estimated dietary nickel intakes obtained by Moschandreas et al. (2002). Therefore, additional data on nickel content within the U.S. diet, especially information covering a larger geographic area in the United States is desirable. Also, few data are available regarding nickel levels at contaminated or hazardous waste sites (Bradley and Morris 1986; Duke 1980b; Taylor and Crowder 1983). This information is necessary for exposure assessment analysis at these sites. Since nickel is found in all soil, studies should focus on waste sites where nickel levels are substantially above those found in ordinary soil.

Exposure Levels in Humans. The nickel levels in body fluids, tissue, hair, nails, and breast milk are available (DiPietro et al. 1989; Hopfer et al. 1989; IARC 1990; Iyengar 1989; Takagi et al. 1986, 1988). Serum and urine levels in some exposed workers have also been published (Angerer and Lehnert 1990; Barceloux 1999; Bencko et al. 1986; Bernacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Morgan and Rouge 1984; Oliveira et al. 2000; Torjussen and Andersen 1979). These data do not refer to populations living around the hazardous waste sites that contain elevated levels of nickel. Additional studies that examine nickel levels or make use of biomarker end points, such as changes in gene expression as measured with gene arrays, in body fluids and tissues from persons living near hazardous waste sites that contain elevated levels of nickel or have occupational exposures to nickel, would be useful.

Exposure of Children. This information is necessary for assessing the need to conduct health studies on children. The nickel levels in urine are available (Baranowska-Dutkiewicz et al. 1992), but information on levels in other body fluids, tissue, hair, and nails is not available. These data do not refer to populations living around the hazardous waste sites that contain elevated levels of nickel. Additional studies that examine nickel levels in body fluids and tissues from children living near hazardous waste sites that contain elevated levels of nickel would be useful. Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

Exposure Registries. Although there is no U.S. exposure registry for nickel, a Finnish exposure registry for occupational carcinogens exists, and this registry contains information on nickel and inorganic nickel compounds (Grandjean 1984). This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

A number of ongoing studies concerning the fate/transport of nickel and human exposures to nickel were identified in the FEDRIP (2003) database. These studies are summarized in Table 6-7.

Table 6-7. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Nickel[a]

Investigator	Affiliation	Research description	Sponsor
Salt, DE	Purdue Universty	Identification of genes involved in nickel and zinc hyperaccumulation in plants	Hatch
Kpomblekou-Ademawou, K; Ankumah, RO	Tuskegee University	Determine total arsenic, chromium, copper, manganese, nickel, selenium, and zinc concentrations and the distribution of the chemical forms in soils under long-term broiler litter treatments	USDA
Chaney, RL	Beltsville ARC, Beltsville, Maryland	Characterize trace element adsorbents in municipal, industrial, and agricultural byproduct amended soils, which limit plant uptake and bioavailability of trace elements	USDA
Vincent, JH	University of Michigan	Develop a smaller and lighter sampling instrument to assess the occupational exposure of people to aerosol fractions most relevant to ill-health	NIH
Sparks, DL; Scheidegger, AM; Lamble, GM	University of Delaware	Determine the effects of residence time on the mechanisms of nickel sorption/release on soils and soil components and suing this information to develop predictions about long-term fate of nickel in soils	NRI
Fiedler, NL	University of Medicine/Dentistry New Jersey	Develop a smaller and lighter sampling instrument to assess the occupational exposure of people to aerosol fractions most relevant to ill-health	NIH
Sweeney, JR	Clemson University	Determine normal concentrations in key tissues and normal whole-body burdens of selected heavy metals in wildlife inhabiting forested landscapes in the lower Atlantic Coastal Plain and effect of barker boiler ash land applications on the wildlife inhabitants	DOI, Bureau of Mines
Sparks, DL; Ford, RG	University of Delaware	Examine nickel and zinc sorption-desorption kinetic behavior on model and natural soil components, characterize structure of the sorption complex and investigate effect of competition of soil components with metal-Al precipitates	USDA
Tu, S	ERRC, Wyndmoor, Pennsylvania	Determine the kinetics and mechanism of heavy metal retention/release by soil mineral colloids as affected by inorganic anions and use information to predict long-term fate of metal in soil	USDA
Odom, JW	Auburn University	Develop analytical techniques for determining total and extractable heavy metals in Alabama soils and plant materials and assess the normal occurrence of metals in select soil profiles	Hatch

Table 6-7. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Nickel[a]

Investigator	Affiliation	Research description	Sponsor
McBride, MB	Cornell University	Develop methods to measure chemical lability of heavy metals in soils and soil materials, comparing labilities to solubility and plant availability and determine the forms that metals take in mineral soils over long terms	USDA
Helmke, PA; Bleam, WF	University of Wisconsin	Investigate the solubility behavior of major and trace element cations in an international suite of soils to determine whether adsorption-desorption or solubility phenomena controls the speciation and concentration of the dissolved trace elements	USDA
Fendorf, SE	University of Idaho	Ascertain the stability and redoxreactivity of heavy retained on soil minerals	USDA
Ramachandran, G	University of Minnesota, Twin Cities	Develop an improved exposure and dose assessment method for epidemiologic research on occupational cancer that accounts for the uncertainties in exposure reconstruction due to sparse data, relevant dose, and exposures to multiple chemicals	NIH
Ross, DS	University of Vermont	Characterize the reactive sites on soil manganese oxides, determine differences between soil oxides and synthetic oxides, and elucidate mechanisms of surface oxidation reactions.	USDA
Kinraide, TB	ARS, Beaver, West Virgina	Elucidate physiological features of plants that determine heavy metal accumulation, binding characteristics of root plasma membranes, and correlate with genotypic differences in heavy metal accumulation	USDA
Hamilton, JW	Dartmouth College	Determine the impact of toxic metals found at Superfund sites, at other waste sites, and in the environment on adverse effects on human health and on the environment	NIH
Baligar, VC; Clark, RB; Zelazny, LC; Persaud, N; Ritchey, KD; Martens, DC	Virginia Polytechnic Institute	Evaluate mineralogy and chemistry of trace elements and sulfate in soil treated with coal-fired power plant by-products (CCB) and determine the co-utilization of CCB with organic amendments on changes in physical and chemical properties of soils	USDA
Volk, VV; Roseberg, RJ; Baham, J	Oregon State University	Assess potential of plants to remove trace metals from soils, identify plant nutrient requirements and determine impact of trace metals on plant health	Hatch
Bleam, WF; Helmke, PA	University of Wisconsin at Madison	Improve understanding of how humic substances in soil bind trace metals by elucidating specific binding sites and their affinities for trace metals	USDA

Table 6-7. Ongoing Studies on Environmental Fate and the Potential for Human Exposure to Nickel[a]

Investigator	Affiliation	Research description	Sponsor
Thompson, ML; Horton, R; Tabatabai, MA	Iowa State University	Identify and quantify the fundamental processes that determine the fate and transport of metals and pesticides once they are applied to the soil or where they occur in contaminated soils	USDA

[a] FEDRIP 2003

ARC = Agricultural Research Center; ARS = Agricultural Research Service; DOI = Department of the Interior; ERRC = Eastern Regional Research Center; NIEHS = National Institutes of Environmental Health and Sciences; NIH = National Institutes of Health; NRI = National Research Institute; USDA = U.S. Department of Agriculture

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring nickel, its metabolites, and other biomarkers of exposure and effect to nickel. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Analytical methods that determine nickel in biological materials are the same as those used for environmental samples. The most common methods determine the total nickel content of the sample instead of the particular nickel compound that may be present. Methodological differences are a function of the nickel level in the sample, digestion procedure required to solubilize the sample, and the level of potentially interfering substances that may be present. Either wet ashing with sulfuric acid or dry ashing through dissolution of the ash with dilute sulfuric or hydrochloric acid is generally a satisfactory method to detect nickel in tissue or food (Boyer and Horowitz 1986; Coleman et al. 1992). Another methodological approach utilizes digestion of biological samples with nitric acid (Custer et al. 2003; Odland et al. 2003) that can also be followed by treatment with hydrogen peroxide to remove residual biological material (USGS 2000). Digestion procedures for biological and environmental samples with particular reference to nickel determinations have been reviewed (Stoeppler 1980; Sunderman 1993; Versieck 1985). As the digestion procedures require the use of strong acids and substances with explosion hazards (e.g., perchloric acid), all safety procedures should be carefully reviewed before the analyses are completed.

Nickel is normally present at very low levels in biological samples. To determine trace nickel levels in these samples accurately, sensitive and selective methods are required. Atomic absorption spectrometry (AAS) and inductively coupled plasma-atomic emission spectroscopy (ICP-AES), with or without

preconcentration or separation steps, are the most common methods. These methods have been adopted in standard procedures by EPA, NIOSH, IARC, and the International Union of Pure and Applied Chemistry (Brown et al. 1981). Direct aspiration into a flame and atomization in an electrically heated graphite furnace or carbon rod are the two variants of atomic absorption. The latter is sometimes referred to as electrothermal AAS. Typical detection limits for electrothermal AAS are <0.4 μg/L, while the limit for flame AAS and ICP-AES is 3.0 μg/L (Stoeppler 1984; Sunderman 1993). The precision of analytical techniques for elemental determinations in blood, muscles, and various biological materials has been investigated (Iyengar 1989). Good precision was obtained with flame AAS after preconcentration and separation, electrothermal AAS, and ICP-AES. Inductively coupled plasma-mass spectrometry (ICP-MS) techniques have been used to quantify nickel in urine with detection sensitivities down to approximately 1 μg/L (Sunderman 1993). The quantification of nickel in biological materials is hampered by the presence of calcium, sodium, and potassium and requires the use of isotope dilution techniques to validate the measurements of nickel in samples.

Voltammetric techniques are becoming increasingly important for nickel determinations since such techniques have extraordinary sensitivity as well as good precision and accuracy. The addition of dimethylglyoxime, a chelating agent, to the electrolyte significantly enhances the method's sensitivity (IARC 1990; Stoeppler 1984). Detection limits of <0.001 μg/L have been achieved with differential pulse anodic stripping voltammetry (DPASV) using dimethylglyoxime chelation (Sunderman 1993).

Analytical methods and detection limits for nickel in biological materials are reported in Table 7-1. The presence of nickel in other biological materials such as hair and nails can be determined by the same analytical techniques used for blood and tissue after suitable procedures for dissolving the sample have been utilized (Stoeppler 1980; Takagi et al. 1986, 1988).

Detailed reviews regarding the methodology used to determine nickel in environmental and biological samples are available (Stoeppler 1980, 1984; Sunderman 1993).

7.2 ENVIRONMENTAL SAMPLES

Analytical methods that detect nickel in environmental samples generally determine the total nickel content of the sample; determining specific nickel compounds is difficult. Filtering a water sample through a 0.45-μm membrane filter can distinguish between total and dissolved nickel (Martin et al. 1992). The most common methods used to detect nickel in environmental samples are AAS, either flame

Table 7-1. Analytical Methods for Determining Nickel in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood fluid, tissue, and excreta[a]	Acid digestion in mixture of nitric, sulfuric, and perchloric acid	Electrothermal AAS	0.2 μg Ni/L fluid; 0.49 μg Ni/kg of tissue	98% at 5 μg Ni/L; 97% at 8 μg Ni/L	IARC 1986 (Method 11)
Urine	Polydithiocarbamate resin extraction; ash filter and resins in a low temperature oxygen plasma asher or digest with HNO_3:$HClO_4$	ICP-AES; NIOSH 8310	0.1 μg/sample	80%	NIOSH 1994b
Urine	Diluted 1:1 in water	STPGFAA	0.56 μg/L	100.7%	Oliveira et al. 2000
Blood or tissue	Acid digestion in 3:1:1 (v/v/v) HNO_3:$HClO_4$:H_2SO_4	ICP-AES; NIOSH 8005	1 μg/100 g blood; 0.2 μg/g tissue	86% in blood	NIOSH 1994b
Lung tissue	Acid digestion in 4:2:1 (v/v/v) HNO_3:$HClO_4$:H_2SO_4	Electrothermal AAS	5 ng/g	No data	Svenes and Andersen 1998

[a]If substantial quantities of iron are present (e.g., whole blood, tissues), hydrochloric acid is added, and the resulting ferric chloride is extracted with methyl isobutyl ketone.

AAS = atomic absorption spectrometry; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; H_2SO_4 = sulfuric acid; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; Ni = nickel; NIOSH = National Institute for Occupational Safety and Health; STPGFAA = stabilized temperature graphite furnace atomic absorption; v = volume

or graphite furnace, ICP-AES, or ICP-MS. Nickel in water and waste water samples can be analyzed using ASTM Test Methods D1976 (ICP-AES) (ASTM 2000) and D5673 (ICP-MS) (ASTM 2000) or EPA Test Methods 249.1 (atomic absorption, direct aspiration) (EPA 1983), 249.2 (atomic absorption, furnace technique) (EPA 1983), 200.7 (ICP-AES) (EPA 1983), 200.8 (ICP-MS) (EPA 1994), 1638 (ICP-MS) (EPA 1996e), and 200.12 (atomic absorption, graphite furnace technique) (EPA 1997b), or a direct current plasma atomic emission spectrophotometric method (EPA 1990b). Nickel can also be analyzed in ambient and marine water using stabilized temperature graphite furnace atomic absorption (STGFAA) detection techniques as described in EPA methods 1639 (EPA 1996d) and 200.12 (EPA 1997b), respectively, which give limits of detection for nickel concentrations ranging between 0.65 and 1.8 μg/L and recoveries of >92%.

Although these methods are suitable for groundwater and surface water samples and domestic and industrial effluents, the nickel concentration in some groundwater, surface water, marine water, and drinking water is often below the method detection limits. Therefore, the sample must be preconcentrated or other test methods must be used. One EPA standardized test method, 1640, uses a chelation preconcentration step to increase the detection sensitivity of the ICP-MS based assay (EPA 1996c). Two other EPA standard test methods, 200.10 and 200.13, also use preconcentration techniques in conjunction with ICP-MS (EPA 1997c) or graphite furnace AAS (EPA 1997d) detection techniques, respectively, for analysis of nickel in marine water. Measurement of trace metals, including nickel, in waste water, surface runoff, and seawater can be completed using an in-line system with stripping voltammetry or chronopotentiometry (Sedlak et al. 1997; van den Berg and Achterberg 1994). These methods provide rapid analysis (1–15 minutes) with little sample preparation. The detection limit of these methods for nickel was not stated. Recommended EPA methods for soil sediment, sludge, and solid waste are Methods 7520 (AAS) and 6010B (ICP-AES). Before the widespread use of AAS, colorimetric methods were employed, and a number of colorimetric reagents have been used (Stoeppler 1980).

With analytical methods such as x-ray fluorescence (XRF), proton-induced x-ray emission (PIXE), and instrumental neutron activation analysis (INAA), many metals can be simultaneously analyzed without destroying the sample matrix. Of these, XRF and PIXE have good sensitivity and are frequently used to analyze nickel in environmental samples containing low levels of nickel such as air, rain, snow, and soil (Adamo et al. 1996; EPA 1999; Hansson et al. 1988; Landsberger et al. 1983; Nygren 2002; Schroeder et al. 1987; Sweet et al. 1993; Wiersema et al. 1984). The Texas Air Control Board, which uses XRF in its network of air monitors, reported a mean minimum detectable value of 6 ng nickel/m^3 (Wiersema et al. 1984). In the EPA method IO-3.3, detection limits of 0.18 and 1.89 ng/m^3 are reported in the analysis of

nickel contained in fine (ca. 2.5 μm) and coarse (>10 μm) particulate matter (PM), respectively, collected on Teflon filters (EPA 1999). A detection limit of 30 ng/L was obtained using PIXE with a nonselective preconcentration step (Hansson et al. 1988). Lower detection limits of 2.37 ng/m^3 are reported for the EPA method IO-3.6 based on dichotomous sampling for 24 hours using a Teflon filter at a sampling rate of 0.9 m^3/hour (EPA 1999). Energy dispersive x-ray analysis, in conjunction with a four-step metal extraction technique, has been used to measure the speciation of nickel in soils (Adamo et al. 1996). In these techniques, the sample (e.g., air particulates collected on a filter) is irradiated with a source of x-ray photons or protons. The excited atoms emit their own characteristic energy spectrum, which is detected with an x-ray detector and multichannel analyzer. INAA and neutron activation analysis (NAA) with prior nickel separation and concentration have poor sensitivity and are rarely used (Schroeder et al. 1987; Stoeppler 1984).

There are other standardized analytical methods for quantifying airborne nickel. These techniques utilize an extraction procedure to isolate nickel and other trace metals from PMs collected on air sampler filters. The extraction methods typically involve the use of hot nitric acid or microwave digestion techniques, for example as described in EPA Method IO-3.1 (EPA 1999). The extracted metals are commonly analyzed using instrumental techniques as described in EPA test methods IO-3.2 (atomic absorption, furnace technique), IO-3.4 (ICP-AES), and IO-3.5 (ICP-MS) (EPA 1999), providing limits of detection for concentrations of nickel in air ranging between 0.02 and 0.10 ng/m^3 (Table 7-2; Vousta and Samara 2002). Use of trace-metal-free acids and sample extraction methods that are designed to exclude contamination of samples from adventitious metals can yield detection limits for determining airborne nickel concentrations down to 0.013–0.02 ng/m^3 when using ICP-MS techniques (EPA 1999; Magari et al. 2002).

Contamination and loss are the main concerns when determining trace metals (Christensen 1995). Nickel-containing knives and needles should be avoided when collecting specimens. A study that compared the effects of using different dissecting tools on trace metal analysis did not report significant differences in the nickel content of fish or mussel samples dissected with stainless steel, lexan, titanium, or Teflon-coated instruments (Iyengar 1986). Contamination can result from impurities in reagents or laboratory apparatus and laboratory dust. Losses may also occur when the analyte adsorbs onto container walls. When collecting air samples on filters, one should be aware that filter material can contain high and variable trace metal concentrations. Glass fiber filters may contain <80 ng/cm^2 of nickel. Silver membrane, cellulose, and polystyrene filters may contain ≈100 ng/cm^2 of nickel (Schroeder et al. 1987).

Table 7-2. Analytical Methods for Determining Nickel in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air, airborne particulates	Collection on cellulose acetate filter; digestion with concentrated nitrated and perchloric acids	ICP-AES; NIOSH 7300	1 μg/ sample	105% at 2.5 μg; 97% at 1 mg	NIOSH 1994b
Air, airborne particulates	Collection on glass or quartz fiber filter; microwave or hot acid digestion Method IO-3.1	AAS, graphite furnace; Method IO-3.2	0.10 ng/m^3	No data	EPA 1999
Air, airborne particulates	Collection on Teflon (fine PM) and Nucleopore (coarse PM) membrane filter	XRF; Method IO-3.3	0.18 ng/m^3 (fine PM); 1.89 ng/m^3 (coarse PM)	No data	EPA 1999
Air, airborne particulates	Collection on glass or quartz fiber filter; microwave or hot acid digestion Method IO-3.1	ICP-AES; Method IO-3.4	3.1 ng/m^3	96.4%	EPA 1999
Air, airborne particulates	Collection on glass or quartz fiber filter; microwave or hot acid digestion Method IO-3.1	ICP-MS; Method IO-3.5	0.02 ng/m^3	101.7% at 20 μg/L; 102.3% at 100 μg/L	EPA 1999
Air, airborne particulates	Collection on PCTE or Teflon filters, or Kapton impaction surface	PIXE; Method IO-3.6	2.37 ng/m^3	No data	EPA 1999
Air, airborne $Ni(CO)_4$	Collection on low-Ni charcoal sorbent tube; ultrasonic digestion with nitric acid	Graphite furnace AAS; NIOSH 6007	0.01 μg/ sample	93% at 5 to 121 μg/m^3	NIOSH 1994b
Water	Acid digestion in mixture of nitric, sulfuric, and perchloric acids	Electro-thermal AAS; Method 11	0.2 μg Ni/L fluids	98% at 5 μg Ni/L; 97% at 8 μg Ni/L	IARC 1986
Drinking, domestic, surface water; industrial waste water	Filter and acidify sample	ICP-AES; Method D1976	15 μg/L	92%	ASTM 2000
Drinking water, surface water, groundwater	Filter and acidify sample	ICP-MS; Method D5673	4 μg/L	104%	ASTM 2000

Table 7-2. Analytical Methods for Determining Nickel in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, waste water	Acid digestion	AAS, direct aspiration; Method 249.1	0.04 mg/L	100% at 0.20 mg Ni/L; 97% at 1.0 mg Ni/L; 93% at 5.0 mg Ni/L	EPA 1983
	Acid digestion; sample solutions should contain 0.5% HNO_3	AAS, direct aspiration; Method 249.2	1 μg/L	100%	EPA 1983
	Filter and acidify sample (dissolved Ni); digest in nitric acid (total recoverable Ni)	ICP-AES; Method 200.7	5 μg/L	Accuracy: 6.7% at 30 μg/L; 8.3% at 60 g/L; 2.0% at 120 g/L	EPA 1983, 1994; Martin et al. 1992
	Filter and acidify sample (dissolved Ni); digest in nitric acid (total recoverable Ni)	ICP-MS; Method 200.8	0.5 μg/L	100.1% at 100 μg/L	EPA 1994
	Acid digestion	AAS, graphite furnace; Method 7521	1 μg/L	No data	EPA 2002
	Digestion with nitric and hydrochloric acids	ICP-AES; Method 6010C	10 μg/L	98% at 250 μg/L; 92% at 60 μg/L; 93% at 30 μg/L	EPA 2002
Marine water	Acidified with nitric acid, undissolved material removed	STPGFAA; Method 200.12	1.8 μg/L	92% at 15 μg/L; 93% at 37.5 μg/L	EPA 1997b
Snow	Samples acidified with nitric acid	ICP-MS	0.7 pg/L	95%	Barbante et al. 2002
Soil, sediment, sludge, solid waste	Digestion with nitric and hydrochloric acids; Method 3050	ICP-AES; Method 6010B	10 μg/L	98% at 250 μg/L; 93% at 50 μg/L	EPA 1986b EPA 2002
Soil, sediment, sludge, solid waste	Digestion with nitric and hydrochloric acids; Method 3050	AAS, direct aspiration; Method 7520	0.04 mg/L	100% at 0.2 mg/L; 97% at 1.0 mg/L; 93% at 5.0 mg/L	EPA 1986b

Table 7-2. Analytical Methods for Determining Nickel in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil (total nickel)	Digest with nitric acid; oxidize with hydrogen peroxide at 450 °C to destroy organic matter; digest with sulfuric and hydrofluoric acids, followed by digestion with nitric, sulfuric, and perchloric acids	AAS	0.02 μg/mL	No data	Baker and Amacher 1982
Soil (DPTA extractable)	Shake soil with 0.005 *M* DPTA extraction solution for 2 hours	AAS	No data	No data	Baker and Amacher 1982
Soil (acid extractable)	Shake soil with 0.1 *N* hydrochloric acid for 5 minutes; complete 3 times	AAS	No data	No data	Baker and Amacher 1982
Soil and sediment	Sample is heated to 110 °C in a mixture of hydrochloric, nitric, perchloric, and hydrofluoric acids and evaporated to dryness, and then treated with aqua regia	ICP-AES	3 ppm	92–114%	USGS 2002
	Sample is heated to 110 °C in a mixture of hydrochloric, nitric, perchloric, and hydrofluoric acids and evaporated to dryness, and then treated with aqua regia	ICP-MS	0.16 ppm	91–104%	USGS 2002
Food	Wet oxidation with sulfuric acid, complexation with ammonium tetramethylene-dithiocarbamate followed by extraction with methyl butyl ketone[a]	AAS; Method 17	20 μg/kg	No data	IARC 1986
Edible tissues	Samples were homogenized, mixed with magnesium nitrate solution (6.67%), lyophilized, dry ashed twice, and dissolved in hydrochloric acid	AAS	0.15 ppm	101%	Coleman et al. 1992

Table 7-2. Analytical Methods for Determining Nickel in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Samples were homogenized then solubilized using atmospheric pressure microwave digestion in nitric acid	ICP-MS	7.0 ng/g	52–96%[b]	Melnyk et al. 2003

[a]The digestion procedure is not satisfactory for fats and oils. For these substances, sulfuric acid and 50% hydrogen peroxide should be used.

[b]Percent recoveries of nickel in food samples spiked at 2 times the limit of detection (LOD) of nickel were given as: rice cereal, 94%; fatty food, 95%; beverage, 93%; duplicate diet 1, 52%; and duplicate diet 2, 90%. In food samples spiked with nickel at 5 times the LOD, the percent recoveries were given as: fatty food, 96%; beverage, 94%; duplicate diet 1, 81%; and duplicate diet 2, 81%

AAS = atomic absorption spectrometry; DPTA = diethylenetriamine pentaacetic acid; HNO_3 = nitric acid; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; Ni = nickel; $Ni(CO)_4$ = nickel carbonyl; NIOSH = National Institute for Occupational Safety and Health; PCTE = polycarbonate track etched; PIXE = proton induced x-ray emission spectroscopy; PM = particulate matter; STPGFAA = stabilized temperature graphite furnace atomic absorption; XRF = x-ray fluorescence

Trace metals in blanks of different filter types and in different filters of the same type may vary from 5 to 20% (Brzezinska-Paudyn et al. 1986).

Some investigators have characterized the forms of nickel in an environmental sample by using successively stronger solvents. Each fraction solubilized is subsequently analyzed for nickel by atomic absorption or other procedures. In air, where the speciation of nickel is less complex, a method of sequential selective leaching has been developed to determine the amount of nickel in four phase categories of a dust sample, namely, soluble nickel, sulfidic nickel, metallic nickel, and refractory nickel oxides (Zatka et al. 1992). Soluble nickel salts, mostly nickel sulfates, are leached at pH 4; sulfidic nickel is next solubilized with a peroxide-citrate solution; and metallic nickel is oxidized with bromine. The residue consists of refractory nickel oxides. Wong and Wu (1991) used an adsorptive stripping voltammetry method to determine different forms of nickel in air at a nickel manufacturing facility. The method distinguished between metallic nickel ions and nickel oxides. The results showed that speciation of nickel from several samples taken at the same location were highly variable. Although it is important to characterize the nickel contained in an environmental sample, methods that determine nickel speciation are difficult and not in widespread use.

Analytical methods and detection limits for standard methods of determining nickel in environmental media are reported in Table 7-2. If the determination of dissolved nickel is required, samples should be filtered with a 0.45-μm membrane filter.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of nickel is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of nickel.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Nickel concentrations in hair, nails, blood, or urine are elevated in exposed individuals. A correlation has been established between nickel levels in urine, plasma, and feces in occupationally exposed workers and nickel levels in air (Angerer and Lehnert 1990; Bernacki et al. 1978; Hassler et al. 1983). If the identity of the nickel compounds to which workers are exposed is known, nickel levels in urine and plasma can be used as a biomarker for nickel exposure (Sunderman 1993). Available analytical methods can determine the nickel levels in these media in both unexposed and occupationally exposed persons. Also, reference values for nickel measured in urine and blood in individuals exposed to low levels of nickel are needed to establish norms for the general population (Christensen 1995).

Methods for determining exposure of individuals through the assessment of plasma or urine levels of nickel are adequate, but further method development is needed to determine nickel speciation in biological media. Also, development of assays that make use of biological markers, such as changes in gene expression in blood cells or protein levels in serum, as measured with gene or protein arrays would be useful not only in providing an alternative method for assessing nickel exposure in occupational and public populations, but also in providing information on biological effects to nickel exposures.

Effect. There are no unique biomarkers of effect for nickel.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining total nickel in environmental media are well developed and adequate. Standardized methods are available from several sources including EPA (EPA 1983, 1986b, 1999, 2002). Most analytical methods measure total nickel content. Sequential extraction techniques are sometimes used to determine the nature of nickel in particles, e.g., they are exchangeable, adsorbed, easily reducible, or organically bound (Adamo et al. 1995; Lottermoser 2002; Rudd et al. 1988; Rybicka 1989). There is a need for more development in this area and the adoption of standard methods for determining nickel species or forms of nickel in various media.

7.3.2 Ongoing Studies

Information on ongoing research studies involving sample collection and the characterization and quantification of nickel was derived from a search of Federal Research in Progress (FEDRIP 2003) and are summarized in Table 7-3.

Table 7-3. Ongoing Studies on Analytical Methods for Quantifying Nickel[a]

Investigator	Affiliation	Research description	Sponsor
Vincent, JH	University of Michigan	Develop a smaller and lighter sampling instrument to assess the occupational exposure of people to aerosol fractions most relevant to ill-health	NIH
Fiedler, NL	University of Medicine/Dentistry New Jersey	Develop a smaller and lighter sampling instrument to assess the occupational exposure of people to aerosol fractions most relevant to ill-health	NIH
Odom, JW	Auburn University	Develop analytical techniques for determining total and extractable heavy metals in Alabama soils and plant materials and assess the normal occurrence of metals in select soil profiles	Hatch
McBride, MB	Cornell University	Develop methods to measure chemical lability of heavy metals in soils and soil materials, comparing labilities to solubility and plant availability and determine the forms that metals take in mineral soils over long terms	USDA
Ramachandran, G	University of Minnesota, Twin Cities	Develop an improved exposure and dose assessment method for epidemiologic research on occupational cancer that accounts for the uncertainties in exposure reconstruction due to sparse data, relevant dose, and exposures to multiple chemicals	NIH

[a] FEDRIP 2003

NIH = National Institutes of Health; USDA = U.S. Department of Agriculture

8. REGULATIONS AND ADVISORIES

ATSDR has derived an intermediate-duration inhalation minimal risk level (MRL) of 0.0002 mg Ni/m^3 for nickel. This MRL is based on a NOAEL of 0.06 mg Ni/m^3 and a LOAEL of 0.11 mg Ni/m^3 for chronic active lung inflammation in rats exposed to nickel sulfate 6 hours/day, 5 days/week for 13 weeks (NTP 1996c). The MRL was derived by dividing the $NOAEL_{HEC}$ of 0.0052 mg Ni/m^3 by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustments and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of $9x10^{-5}$ mg Ni/m^3 for nickel. This MRL is based on a NOAEL of 0.03 mg Ni/m^3 and a LOAEL of 0.06 mg Ni/m^3 for chronic active lung inflammation and bronchialization in rats exposed to nickel sulfate 6 hours/day, 5 days/week for 2 years (NTP 1996c). The MRL was derived by dividing the $NOAEL_{HEC}$ of 0.0027 mg Ni/m^3 by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustments and 10 for human variability).

EPA (IRIS 2003) derived an oral reference dose (RfD) of 0.02 mg/kg/day for nickel soluble salts. The RfD was based on a NOAEL of 5 mg/kg/day and a LOAEL of 50 mg/kg/day for decreased body weight and organ weight in rats exposed to dietary nickel for 2 years (Ambrose et al. 1976). The NOAEL was divided by an uncertainty factor of 300 (10 for animal to human extrapolation, 10 to protect sensitive individuals, and 3 for inadequacies in the reproductive toxicity studies).

The Department of Health and Human Services (NTP 2002) has determined that metallic nickel may reasonably be anticipated to be a carcinogen and that nickel compounds are known to be human carcinogens. Similarly, IARC classified metallic nickel in group 2B (possibly carcinogenic to humans) and nickel compounds in group 1 (carcinogenic to humans). EPA has classified nickel refinery dust and nickel subsulfide in Group A (human carcinogen) (IRIS 2003). Other nickel compounds have not been classified by the EPA. Based on the occupational data, inhalation unit risk levels of $2.4x10^{-4}$ $(\mu g/m^3)^{-1}$ and $4.8x10^{-4}$ $(\mu g/m^3)^{-1}$ were derived for nickel refinery dust and nickel subsulfide, respectively (IRIS 2003).

In an attempt to reduce the prevalence of nickel sensitivity, the European Union has passed a directive to restrict the use of nickel beginning in February 1996 (Delescluse and Dinet 1994). The directive forbids the use of nickel in objects introduced into pierced ears and other parts of the human body during epithelialization of the wound. It forbids the use of nickel in products placed in direct and prolonged

contact with the skin (e.g., earrings, watches, clothing accessories). The use of nickel is also forbidden in accessories that are plated with another metal, except if the plating is strong enough to restrict liberation of nickel to <0.5 $\mu g/cm^2$/week during a normal use of 2 years.

National and state guidelines and regulations regarding exposure to nickel and its compounds are summarized in Table 8-1.

Table 8-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 1990
	Nickel compounds	Group 1[a]	
	Nickel, metallic	Group 2B[b]	
WHO	Air quality guideline		WHO 2000
	Nickel unit risk	3.8×10^{-5} $(\mu g/m^3)^{-1}$	
	Drinking water guideline		WHO 1998
	Nickel	0.02 mg/L	
NATIONAL			
Regulations and Guidelines:			
a. Air:			
ACGIH	TLV (8-hour TWA)		ACGIH 2003
	Nickel, elemental (as Ni)	1.5 mg/m^3	
	Nickel, soluble inorganic compounds	0.1 mg/m^3	
	Nickel, insoluble inorganic compounds	0.2 mg/m^3	
	Nickel subsulfide (as Ni)	0.1 mg/m^3	
	Nickel carbonyl (as Ni)	0.05 ppm	
EPA	Chemical accident prevention provisions; toxic end points		EPA 2003b 40 CFR 68, Appendix A
	Nickel carbonyl	0.00067 mg/L	
	Hazardous air pollutant pursuant to Section 112 of the Clean Air Act	Nickel	EPA 2003j 40 CFR 61.01
	Regulated toxic substance and threshold quantity for accidental release prevention under Section 112(r) of the Clean Air Act		EPA 2003a 40 CFR 68.130
	Nickel carbonyl	1,000 pounds	
NIOSH	REL (10-hour TWA)		NIOSH 2003a, 2003b
	Nickel[c]	0.015 mg/m^3	
	IDLH	10 mg/m^3	
	Nickel carbonyl[c]	0.001 ppm	
	IDLH	2 ppm	
U.S. NRC	Occupational values		U.S. NRC 2003 10 CFR 20, Appendix B
	Oral ingestion for Class D[d]	ALI (µCi)	
	^{56}Ni	1.0×10^3	
	^{57}Ni	2.0×10^3	
	^{59}Ni	2.0×10^4	
	^{63}Ni	9.0×10^3	
	^{65}Ni	8.0×10^3	
	^{66}Ni (LLI wall)	4.0×10^2	
	^{66}Ni	5.0×10^2	

Table 8-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
U.S. NRC	Occupational values	ALI	DAC	U.S. NRC 2003
	Inhalation[e] for Class D[d]	(µCi)	(µCi/mL)	10 CFR 20,
	^{56}Ni	2.0×10^{3}	8.0×10^{-7}	Appendix B
	^{57}Ni	5.0×10^{3}	2.0×10^{-6}	
	^{59}Ni	4.0×10^{3}	2.0×10^{-6}	
	^{63}Ni	2.0×10^{3}	7.0×10^{-7}	
	^{65}Ni	2.0×10^{4}	1.0×10^{-5}	
	^{66}Ni (LLI wall)	2.0×10^{3}	7.0×10^{-7}	
	Occupational values	ALI	DAC	U.S. NRC 2003
	Inhalation[e] for Class W[f]	(µCi)	(µCi/mL)	10 CFR 20,
	^{56}Ni	1.0×10^{3}	5.0×10^{-7}	Appendix B
	^{57}Ni	3.0×10^{3}	1.0×10^{-6}	
	^{59}Ni	7.0×10^{3}	3.0×10^{-6}	
	^{63}Ni	3.0×10^{3}	1.0×10^{-6}	
	^{65}Ni	3.0×10^{4}	1.0×10^{-5}	
	^{66}Ni	6.0×10^{2}	3.0×10^{-7}	
	Occupational values	ALI	DAC	U.S. NRC 2003
	Inhalation[e] for vapors	(µCi)	(µCi/mL)	10 CFR 20,
	^{56}Ni	1.0×10^{3}	5.0×10^{-7}	Appendix B
	^{57}Ni	6.0×10^{3}	3.0×10^{-6}	
	^{59}Ni	2.0×10^{3}	8.0×10^{-7}	
	^{63}Ni	8.0×10^{2}	3.0×10^{-7}	
	^{65}Ni	2.0×10^{4}	7.0×10^{-6}	
	^{66}Ni	3.0×10^{3}	1.0×10^{-6}	
OSHA	PEL (8-hour TWA) for general industry			OSHA 2003a 29 CFR 1910.1000, Table Z-1
	Nickel, metal and insoluble compounds (as Ni)	1.0 mg/m^3		
	Nickel, soluble compounds (as Ni)	1.0 mg/m^3		
	Nickel carbonyl	0.007 mg/m^3		
	PEL (8-hour TWA) for construction industry			OSHA 2003e 29 CFR 1926.55, Appendix A
	Nickel, metal and insoluble compounds (as Ni)	1.0 mg/m^3		
	Nickel, soluble compounds (as Ni)	1.0 mg/m^3		
	Nickel carbonyl	0.007 mg/m^3		
	PEL (8-hour TWA) for shipyard industry			OSHA 2003d 29 CFR 1915.1000
	Nickel, metal and insoluble compounds (as Ni)	1.0 mg/m^3		
	Nickel, soluble compounds (as Ni)	1.0 mg/m^3		
	Nickel carbonyl	0.007 mg/m^3		
OSHA	Highly hazardous chemicals, toxics, and reactives			OSHA 2003b,f 29 CFR 1926.64, 29 CFR 1910.119, Appendix A
	Nickel carbonyl			
	Threshold quantity	150 pounds		

Table 8-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Drinking water health advisories		EPA 2002
	1-day (10-kg child)	1.0 mg/L	
	10-day (10-kg child)	1.0 mg/L	
	DWEL[g]	0.7 mg/L	
	Lifetime[h]	0.1 mg/L	
	Effluent guidelines and standards; toxic pollutants pursuant to Section 307(a)(1) of the Clean Water Act	Nickel and compounds	EPA 2003f 40 CFR 401.15
	National primary drinking water regulations; best technology and treatment techniques for nickel	Ion exchange, lime softening, and reverse osmosis	EPA 2003l 40 CFR 141.62
	Pollutant of initial focus in the Great Lakes Water Quality Initiative	Nickel	EPA 2003s 40 CFR 132, Table 6
c. Food			
FDA	Bottled drinking water		FDA 2003a
	Nickel	0.1 mg/L	21 CFR 165.110
	Generally recognized as safe as a direct human food ingredient with no limitation other than current good manufacturing practices	Nickel	FDA 2003b 21 CFR 184.1537
	Indirect food additives; components of paper and paper-board	Nickel	FDA 2003c 21 CFR 176.180
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2003
	Nickel subsulfide	A1[i]	
EPA	Carcinogenicity classification		IRIS 2003
	Nickel	Not evaluated	
	Nickel refinery dust	A[j]	
	Nickel carbonyl	B2[k]	
	Nickel subsulfide	A[j]	
	RfD		IRIS 2003
	Nickel	0.02 mg/kg/day	
	Nickel refinery dust	No data	
	Nickel carbonyl	No data	
	Nickel subsulfide	No data	
EPA	Community right-to-know; release reporting; effective date of reporting for nickel	01/01/87	EPA 2003r 40 CFR 372.65
	Criteria for municipal solid waste landfills; hazardous constituent	Nickel	EPA 2003c 40 CFR 258, Appendix II

Table 8-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	Emergency planning and notification			EPA 2003g 40 CFR 355, Appendix A
	Nickel carbonyl			
	Reportable quantity	10 pounds		
	Threshold planning quantity	1 pound		
	Land disposal restrictions; universal treatment standards			EPA 2003i 40 CFR 268.48
	Nickel			
	Waste water	3.98 mg/L		
	Non-waste water	11 mg/L TCLP		
	Reportable quantity; designated as a hazardous substance			EPA 2003d 40 CFR 302.4
	Nickel[l]	Not assigned		
	Nickel compounds[m]	Not assigned		
	Nickel carbonyl[l,n]	10 pounds		
	Standards for owners and operators of hazardous waste treatment, storage, and disposal facilities; health-based limits for exclusion of waste-derived residues; residue concentration limit			EPA 2003o 40 CFR 266, Appendix VII
	Nickel	7×10^{1} mg/kg		
	Standards for the management of specific hazardous waste and hazardous waste management facilities; risk specific dose			EPA 2003n 40 CFR 266, Appendix V
	Nickel	2.4×10^{-1} µg/m^3		
	Nickel refinery dust	2.4×10^{-1} µg/m^3		
	Nickel subsulfide	4.8×10^{-1} µg/m^3		
	Standards for the use or disposal of sewage sludge; pollutant limits (risk specific concentration)			EPA 2003q 40 CFR 503.43
	Nickel	2.0 µg/m^3		
U.S. NRC	Effluent concentrations for Class D[d]	Air (µCi/mL)	Water (µCi/mL)	U.S. NRC 2003 10 CFR 20, Appendix B
	^{56}Ni	3.0×10^{-9}	2.0×10^{-5}	
	^{57}Ni	7.0×10^{-9}	2.0×10^{-5}	
	^{59}Ni	5.0×10^{-9}	3.0×10^{-4}	
	^{63}Ni	2.0×10^{-9}	1.0×10^{-4}	
	^{65}Ni	3.0×10^{-8}	1.0×10^{-4}	
	^{66}Ni (LLI wall)	2.0×10^{-9}	6.0×10^{-6}	

Table 8-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	Effluent concentrations for Class W[f]	Air (µCi/mL)	U.S. NRC 2003 10 CFR 20, Appendix B
	^{56}Ni	$2.0x10^{-9}$	
	^{57}Ni	$4.0x10^{-9}$	
	^{59}Ni	$1.0x10^{-8}$	
	^{63}Ni	$4.0x10^{-9}$	
	^{65}Ni	$4.0x10^{-8}$	
	^{66}Ni	$4.0x10^{-10}$	
U.S. NRC	Effluent concentrations for Vapors	Air (µCi/mL)	U.S. NRC 2003 10 CFR 20, Appendix B
	^{56}Ni	$2.0x10^{-9}$	
	^{57}Ni	$9.0x10^{-9}$	
	^{59}Ni	$3.0x10^{-9}$	
	^{63}Ni	$1.0x10^{-9}$	
	^{65}Ni	$2.0x10^{-8}$	
	^{66}Ni	$4.0x10^{-9}$	
	Release to sewers for Class D[d]	Monthly average concentration (µCi/mL)	U.S. NRC 2003 10 CFR 20, Appendix B
	^{56}Ni	$2.0x10^{-4}$	
	^{57}Ni	$2.0x10^{-4}$	
	^{59}Ni	$3.0x10^{-3}$	
	^{63}Ni	$1.0x10^{-3}$	
	^{65}Ni	$1.0x10^{-3}$	
	^{66}Ni	$6.0x10^{-5}$	
NTP	Carcinogenicity		NTP 2002
	Nickel, metallic	Reasonably anticipated to be human carcinogens	
	Nickel compounds	Known human carcinogens	
STATE			
a. Air	No data		
b. Water			
Arizona	Drinking water guideline		HSDB 2003
	Nickel, elemental	150 µg/L	
Massachusetts	Drinking water guideline		HSDB 2003
	Nickel and nickel compounds	100 µg/L	
Maine	Drinking water guideline		HSDB 2003
	Nickel and nickel compounds	150 µg/L	
Minnesota	Drinking water guideline		HSDB 2003
	Nickel and nickel compounds	100 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Nickel

Agency	Description	Information	Reference
STATE *(cont.)*			
c. Food	No data		
d. Other	No data		

[a]Group 1: carcinogenic to humans
[b]Group 2B: possibly carcinogenic to humans
[c]Carcinogen
[d]Class D: refers to the retention (clearance half-times of <10 days) for all compounds except those given for W.
[e]The ALIs and DACs for inhalation are given for an aerosol with an activity median aerodynamic diameter (AMAD) of 1 μm and for class D and W of radioactive material, which refers to their retention (clearance half-times of <10 days and 10–100 days, respectively) in the pulmonary region of the lung.
[f]Class W: refers to the retention (clearance half-times of 10–100 days) for sulfides, oxides, hydroxides, halides, nitrates, and stannic phosphate.
[g]DWEL: a lifetime exposure concentration protection of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from drinking water.
[h]Lifetime: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for a lifetime of exposure. The Lifetime health advisory is based on exposure of a 70-kg adult consuming 2 L water/day.
[i]A1: confirmed human carcinogen
[j]A: human carcinogen
[k]B2: probable human carcinogen
[l]designated as a hazardous substances pursuant to Section 307(a) of the Clean Water Act,
[m]designated as a hazardous substances pursuant to Section 3001 of RCRA
[n]designated as a hazardous substances pursuant to Section 112 of the Clean Air Act

ACGIH = American Conference of Governmental Industrial Hygienists; ALI = annual limits on intake; CFR = Code of Federal Regulations; DAC = derived air concentration; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; LLI = lower large intestine; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfD = reference dose; TCLP = toxicity characteristic leachate procedure; TLV = threshold limit values; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; U.S. NRC = Nuclear Regulatory Commission; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Activity Median Aerodynamic Diameter (AMAD)—The median of the distribution of radiolabelled particles with varying activities and aerodynamic diameters. The aerodynamic diameter takes into account both the density of the particle and the aerodynamic drag.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

10. GLOSSARY

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Mass Median Aerodynamic Diameter (MMAD)—The median of the distribution of particles with varying mass concentrations and aerodynamic diameters. The aerodynamic diameter takes into account both the density of the particle and the aerodynamic drag.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation

either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

10. GLOSSARY

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level (NOAEL)/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Nickel
CAS Number: 7440-02-0
Date: September 2003
Profile Status: Final Draft for Public Comment Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 38
Species: F344 Rats

Minimal Risk Level: 0.0002 [ ] mg/kg/day [x] mg/m^3

Reference: NTP 1996c. Toxicology and carcinogenesis of nickel sulfate hexahydrate (CAS No. 10101-97-0) in F344/N rats and B6C3F1 mice (inhalation studies). U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

Experimental design: Groups of 10 male and 10 female F344/N rats were exposed to 0.12, 0.25, 0.5, 1.0, or 2.0 mg/m^3 nickel sulfate hexahydrate (0.03, 0.06, 0.11, 0.22, or 0.44 mg Ni/m^3, as calculated by study authors) for 6 hours/day, 5 days/week for 13 weeks. The MMAD (and sigma g) values reported in Table K1 of the paper were 2.31 (2.1), 2.11 (2.7), 3.08 (2.9), 1.81 (2.2), and 2.01 (2.0) for the 0.03, 0.06, 0.11, 0.22, and 0.44 mg Ni/m^3 concentrations, respectively. End points examined included body weight gain, clinical observations, hematology, and organ weights, and microscopic examinations of the following organs were completed: adrenal gland, bone, brain, clitoral gland, epididymis, oviduct, esophagus, heart, large intestine, small intestine, kidneys, larynx, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary, preputial gland, prostate, salivary gland, seminal vesicle, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, bladder, and uterus.

Effects noted in study and corresponding doses: No exposure related deaths, alterations in body weight gain, or clinical signs were observed. A number of hematological alterations were observed in female rats—increased hematocrit, hemoglobin, and erythrocyte concentrations at 0.22 mg Ni/m^3 and higher; increased reticulocytes at 0.03 mg Ni/m^3 and higher; increased leukocyte levels at 0.11 mg Ni/m^3 and higher; increased segmented neutrophils at 0.06 mg Ni/m^3 and higher; and increased lymphocytes at 0.22 mg Ni/m^3 and higher—the study authors noted that these alterations are consistent with chronic inflammation, hyperplasia of lymph nodes, and mild dehydration. Significant alterations in lung weights were observed at 0.06 mg Ni/m^3 and higher. Lung lesions consisted of minimal alveolar macrophage hyperplasia at 0.03–0.11 mg Ni/m^3, mild to moderate macrophage hyperplasia at 0.22 and 0.44 mg Ni/m^3, interstitial infiltrates at 0.22 mg Ni/m^3 and higher in males and 0.11 mg Ni/m^3 and higher in females, and chronic active inflammation characterized by slight thickening of alveolar septae due to an increase in monnuclear inflammatory cells, and few neutrophils and fibroblasts in the intersitium. Hyperplasia of bronchial and mediastinal lymph nodes was observed at 0.22 mg Ni/m^3 and higher and atrophy of the olfactory epithelium was observed at 0.22 and 0.44 mg Ni/m^3.

The minimal alveolar macrophage hyperplasia observed at 0.03–0.11 mg Ni/m^3 was not considered an adverse health effect because the slight changes in the number of macrophages were considered to be part of the normal physiologic response to inhaled particles and it is not believed to compromise the lung's ability to clear foreign matter.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

The NOAEL of 0.06 mg/m^3 for chronic active inflammation in rats is the basis of the intermediate-duration inhalation MRL for nickel.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
The exposure concentration was adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days). A regional deposited dose ratio (RDDR) of 0.474 for the pulmonary region was used to extrapolate from particle deposition in rats to deposition in humans. The RDDR was calculated using EPA's software for calculating RDDRs. The following parameters were used: particle size (MMAD) of 2.11 μm and geometric standard deviation (sigma g) of 2.7; default human body weight (70 kg), minute volume (13 L) and pulmonary surface area (54 m^2); default female F344 rat body weight (0.124 kg), minute volume (101.3 mL), and pulmonary surface area (0.34 m^2).

$NOAEL_{ADJ}$= 0.06 mg Ni/m^3 x 6 hours/24 hours x 5 days/7 days = 0.011 mg Ni/m^3
$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x RDDR = 0.011 mg Ni/m^3 x 0.474 = 0.0052 mg Ni/m^3

Other additional studies or pertinent information which lend support to this MRL: The identification of the lung as the most sensitive target of nickel toxicity is supported by a number of acute-, intermediate-, and chronic-duration studies of nickel sulfate, nickel subsulfide, and nickel oxide in rats and mice (Benson et al. 1995a, 1995b; Horie et al. 1985; NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1990; Tanaka et al. 1988). In these studies, respiratory effects, in particular chronic lung inflammation, was observed at the lowest LOAEL values. Three other inhalation studies have examined the toxicity of nickel sulfate. Benson et al. (1995a) observed mild alveolitis in rats exposed to 0.11 mg Ni/m^3 6 hours/day, 5 days/week for 6 months; 4 months after exposure termination, alveolitis was still present in the nickel-exposed rats. Minimal alveolar macrophage hyperplasia was observed at 0.03 mg Ni/m^3; this was not observed 4 months after exposure termination. In mice exposed to nickel sulfate (6 hours/day, 5 days/week for 13 weeks), chronic lung inflammation and fibrosis were observed at 0.44 mg Ni/m^3; minimal alveolar hyperplasia was observed at 0.11 mg Ni/m^3 and higher (NTP 1996c). Similarly, Benson et al. (1995a) reported minimal alveolar macrophage hyperplasia and interstitial pneumonia in mice exposed to 0.22 mg Ni/m^3.

Similar studies in which rats and mice were exposed to nickel subsulfide (NTP 1996b) or nickel oxide (1996a) confirm that the lungs are the principal target of nickel toxicity following inhalation exposure. Comparison of the NOAEL and LOAEL values identified in the NTP studies of nickel sulfate (NTP 1996c), nickel subsulfide (NTP 1996b), and nickel oxide (NTP 1996a) demonstrate that nickel sulfate is more toxic than nickel subsulfide and nickel oxide. In rats, the NOAEL and LOAEL values for chronic lung inflammation were 0.06 and 0.11 mg Ni/m^3 for nickel sulfate (NTP 1996c), 0.11 and 0.22 mg Ni/m^3 for nickel subsulfide (NTP 1996b), and 2.0 and 3.9 mg Ni/m^3 for nickel oxide (NTP 1996a). Atrophy of the nasal olfactory epithelium was observed at 0.22 and 0.44 mg Ni/m^3 as nickel sulfate (NTP 1996c) and

nickel subsulfide (NTP 1996b), respectively. Similar effects were observed in mice. For nickel sulfate and nickel subsulfide, the LOAEL values in mice were higher than the LOAELs identified in rats; the LOAEL for chronic inflammation following exposure to nickel oxide was the same in rats and mice.

Agency Contact (Chemical Managers): Mike Fay, Sharon Wilbur, and Henry Abadin

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Nickel
CAS Number:	7440-02-0
Date:	September 2003
Profile Status:	Final Draft for Public Comment
Route:	[x] Inhalation [ ] Oral
Duration:	[ ] Acute [ ] Intermediate [x] Chronic
Graph Key:	77
Species:	F344 Rats

Minimal Risk Level: 9×10^{-5} [ ] mg/kg/day [x] mg/m^3

Reference: NTP 1996c. Toxicology and carcinogenesis of nickel sulfate hexahydrate (CAS No. 10101-97-0) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program.

Experimental design: Groups of male and female F344 rats were exposed to 0.12, 0.25, or 0.5 mg/m^3 nickel sulfate hexahydrate (0, 0.03, 0.06, or 0.11 mg Ni/m^3 as calculated by study authors) 6 hours/day, 5 days/week for 2 years. The mean MMAD and sigma g values (reported in Table K2 of the paper) were 2.50 (sigma g of 2.38), 2.24 (2.21), and 2.25 (2.08) for the 0.03, 0.06, and 0.11 mg Ni/m^3 concentrations, respectively. End points examined included body weight gain, clinical observations, hematology, and organ weights. Microscopic examinations of the following organs were completed: adrenal gland, bone, brain, clitoral gland, epididymis, oviduct, esophagus, heart, large intestine, small intestine, kidneys, larynx, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary, preputial gland, prostate, salivary gland, seminal vesicle, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, bladder, and uterus.

Effects noted in study and corresponding doses: No significant alterations in survival, body weight, or the occurrence of clinical signs were observed. The only treatment-related changes noted were in the respiratory tract. Lung lesions consisted of chronic active inflammation, hyperplasia of alveolar macrophages, alveolar proteinosis, and fibrosis at 0.06 and 0.11 mg Ni/m^3. The combined incidences of chronic active inflammation in the male and female rats were 28/106, 24/106, 91/106, and 98/107 in the 0, 0.03, 0.06, and 0.11 mg Ni/m^3 groups, respectively. The chronic inflammation consisted of multifocal, minimal to mild accumulation of macrophages, neutrophils, and cellular debris within the alveolar spaces. No significant alterations in the malignant tumors were observed in the lungs. Significant increases in the incidence of lymphoid hyperplasia of the bronchial lymph nodes and atrophy of the olfactory epithelium were observed at 0.11 mg Ni/m^3.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

The NOAEL of 0.03 mg/m^3 for chronic active inflammation and lung fibrosis in rats is the basis of the chronic inhalation MRL for nickel.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment

[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
No.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:
The exposure concentration was adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days). A regional deposited dose ratio (RDDR) of 0.506 for the pulmonary region was used to extrapolate from a deposited dose in rats to a deposited dose in humans. The RDDR was calculated using EPA's software for calculating RDDRs. The following parameters were used: particle size (MMAD) of 2.5 μm and geometric standard deviation (sigma g) of 2.38; default human body weight (70 kg), minute volume (13 L) and pulmonary surface area (54 m^2); default female F344 rat body weight (0.229 kg), minute volume (167.3 mL), and pulmonary surface area (0.34 m^2).

$NOAEL_{ADJ}$= 0.03 mg Ni/m^3 x 6 hours/24 hours x 5 days/7 days = 0.0054 mg Ni/m^3
$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x RDDR = 0.0054 mg Ni/m^3 x 0.506 = 0.0027 mg Ni/m^3

Other additional studies or pertinent information which lend support to this MRL: The identification of the lung as the most sensitive target of nickel toxicity is supported by a number of acute-, intermediate-, and chronic-duration studies of nickel sulfate, nickel subsulfide, and nickel oxide in rats and mice (Benson et al. 1995a, 1995b; Horie et al. 1985; NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1990; Tanaka et al. 1988). In these studies, respiratory effects, in particular chronic lung inflammation, was observed at the lowest LOAEL values. One other inhalation study has examined the toxicity of nickel sulfate. Chronic active lung inflammation was observed in mice exposed to 0.11 or 0.22 mg Ni/m^3 6 hours/day, 5 days/week for 2 years (NTP 1996c); no respiratory tract effects were observed at 0.06 mg Ni/m^3. Chronic-duration studies (all studies involved 6 hour/day, 5 day/week exposures) with different nickel compounds have also found inflammatory lung effects at in rats exposed to 0.11 mg Ni/m^3 as nickel subsulfide for 2 years (NTP 1996b), rats exposed to 0.7 mg Ni/m^3 as nickel subsulfide for 78 weeks (Ottolenghi et al. 1990), mice exposed to 0.44 mg Ni/m^3 as nickel subsulfide for 2 years (NTP 1996b), rats exposed to 0.2 mg Ni/m^3 as nickel oxide for 2 years (NTP 1996a), and mice exposed to 1 mg Ni/m^3 as nickel oxide for 2 years (NTP 1996a).

Agency Contact (Chemical Managers): Mike Fay, Sharon Wilbur, and Henry Abadin

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, and chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods: acute (<15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

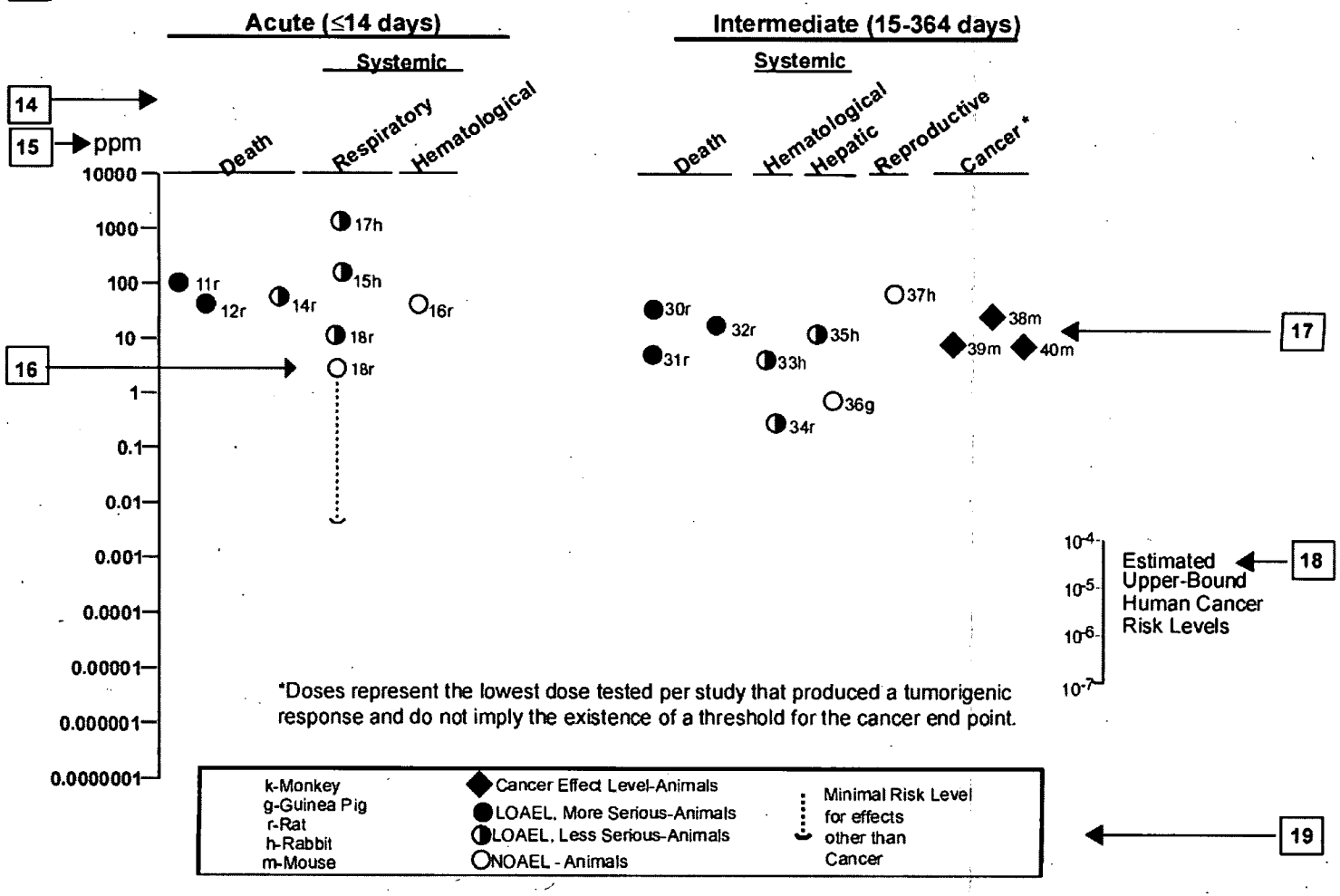
1 → **TABLE 3-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et.al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 →
[a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/NA/IMCO	Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level

ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFO	mixed function oxidase
mg	milligram
mL	milliliter

mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit

pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

APPENDIX C

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result