DRAFT
TOXICOLOGICAL PROFILE FOR VANADIUM

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

September 2009

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.

This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

UPDATE STATEMENT

A Toxicological Profile for Vanadium was released in 1992. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-62
Atlanta, Georgia 30333

This page is intentionally blank.

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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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; more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information. 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 toxic 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
Division of Toxicology and Environmental Medicine
1600 Clifton Road, N.E.
Mail Stop F-62
Atlanta, Georgia 30333

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of 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. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs 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.

Howard Frumkin, M.D., Dr. P.H.
Director, National Center for Environmental Health/Agency for Toxic Substances and Disease Registry

Thomas R. Frieden, M.D., M.P.H.
Administrator, Agency for Toxic Substances and Disease Registry

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: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Jessilynn Taylor, M.S., CDR USPHS
Sam Keith, M.S., CHP
Larry Cseh, M.S.A., R.S., CPT USPHS
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Lisa Ingerman, Ph.D., DABT
Lara Chappell, Ph.D.
Jennifer Rhoades, B.A.
Amy Hueber, M.L.S.
SRC, Inc., North Syracuse, NY

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 Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

This page is intentionally blank.

PEER REVIEW

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

1. Janusz Z. Byczkowski, Ph.D., DABT, Independent Consultant, Fairborn, Ohio;

2. David Dorman, Ph.D., D.V.M., DABT, Associate Dean for Research and Graduate Studies, North Carolina State University, Raleigh, North Carolina; and

3. Anna Fan, Ph.D., DABT, Chief, Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland/Sacramento, California.

These experts collectively have knowledge of vanadium'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.

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.

This page is intentionally blank.

CONTENTS

DISCLAIMER ii
UPDATE STATEMENT iii
FOREWORD v
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 VANADIUM? 1
1.2 WHAT HAPPENS TO VANADIUM WHEN IT ENTERS THE ENVIRONMENT? 2
1.3 HOW MIGHT I BE EXPOSED TO VANADIUM? 3
1.4 HOW CAN VANADIUM ENTER AND LEAVE MY BODY? 4
1.5 HOW CAN VANADIUM AFFECT MY HEALTH? 5
1.6 HOW CAN VANADIUM AFFECT CHILDREN? 6
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO VANADIUM? 6
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO VANADIUM? 7
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 7
1.10 WHERE CAN I GET MORE INFORMATION? 8

2. RELEVANCE TO PUBLIC HEALTH 11
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO VANADIUM IN THE UNITED STATES 11
2.2 SUMMARY OF HEALTH EFFECTS 12
2.3 MINIMAL RISK LEVELS (MRLs) 13

3. HEALTH EFFECTS 25
3.1 INTRODUCTION 25
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 25
3.2.1 Inhalation Exposure 26
3.2.1.1 Death 26
3.2.1.2 Systemic Effects 27
3.2.1.3 Immunological and Lymphoreticular Effects 41
3.2.1.4 Neurological Effects 41
3.2.1.5 Reproductive Effects 41
3.2.1.6 Developmental Effects 42
3.2.1.7 Cancer 42
3.2.2 Oral Exposure 44
3.2.2.1 Death 44
3.2.2.2 Systemic Effects 44
3.2.2.3 Immunological and Lymphoreticular Effects 64
3.2.2.4 Neurological Effects 64
3.2.2.5 Reproductive Effects 65
3.2.2.6 Developmental Effects 65
3.2.2.7 Cancer 66

3.2.3 Dermal Exposure 66
3.2.3.1 Death 66
3.2.3.2 Systemic Effects 66
3.2.3.3 Immunological and Lymphoreticular Effects 66
3.2.3.4 Neurological Effects 66
3.2.3.5 Reproductive Effects 66
3.2.3.6 Developmental Effects 66
3.2.3.7 Cancer 66
3.3 GENOTOXICITY 66
3.4 TOXICOKINETICS 72
3.4.1 Absorption 72
3.4.1.1 Inhalation Exposure 72
3.4.1.2 Oral Exposure 73
3.4.1.3 Dermal Exposure 73
3.4.2 Distribution 73
3.4.2.1 Inhalation Exposure 73
3.4.2.2 Oral Exposure 74
3.4.2.3 Dermal Exposure 77
3.4.2.4 Other Routes of Exposure 77
3.4.3 Metabolism 77
3.4.4 Elimination and Excretion 77
3.4.4.1 Inhalation Exposure 77
3.4.4.2 Oral Exposure 78
3.4.4.3 Dermal Exposure 78
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models 78
3.5 MECHANISMS OF ACTION 80
3.5.1 Pharmacokinetic Mechanisms 80
3.5.2 Mechanisms of Toxicity 82
3.5.3 Animal-to-Human Extrapolations 82
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS 82
3.7 CHILDREN'S SUSCEPTIBILITY 83
3.8 BIOMARKERS OF EXPOSURE AND EFFECT 85
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Vanadium 86
3.8.2 Biomarkers Used to Characterize Effects Caused by Vanadium 87
3.9 INTERACTIONS WITH OTHER CHEMICALS 87
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 87
3.11 METHODS FOR REDUCING TOXIC EFFECTS 88
3.11.1 Reducing Peak Absorption Following Exposure 88
3.11.2 Reducing Body Burden 88
3.11.3 Interfering with the Mechanism of Action for Toxic Effects 89
3.12 ADEQUACY OF THE DATABASE 90
3.12.1 Existing Information on Health Effects of Vanadium 90
3.12.2 Identification of Data Needs 92
3.12.3 Ongoing Studies 99

4. CHEMICAL AND PHYSICAL INFORMATION 101
4.1 CHEMICAL IDENTITY 101
4.2 PHYSICAL AND CHEMICAL PROPERTIES 101

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 107
5.1 PRODUCTION 107

5.2 IMPORT/EXPORT 113
5.3 USE 113
5.4 DISPOSAL 113
6. POTENTIAL FOR HUMAN EXPOSURE 115
6.1 OVERVIEW 115
6.2 RELEASES TO THE ENVIRONMENT 117
6.2.1 Air 118
6.2.2 Water 123
6.2.3 Soil 123
6.3 ENVIRONMENTAL FATE 124
6.3.1 Transport and Partitioning 124
6.3.2 Transformation and Degradation 127
6.3.2.1 Air 127
6.3.2.2 Water 128
6.3.2.3 Sediment and Soil 128
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 129
6.4.1 Air 129
6.4.2 Water 131
6.4.3 Sediment and Soil 133
6.4.4 Other Environmental Media 136
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 139
6.6 EXPOSURES OF CHILDREN 142
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 144
6.8 ADEQUACY OF THE DATABASE 145
6.8.1 Identification of Data Needs 145
6.8.2 Ongoing Studies 148

7. ANALYTICAL METHODS 149
7.1 BIOLOGICAL MATERIALS 151
7.2 ENVIRONMENTAL SAMPLES 153
7.3 ADEQUACY OF THE DATABASE 153
7.3.1 Identification of Data Needs 157
7.3.2 Ongoing Studies 157

8. REGULATIONS, ADVISORIES, AND GUIDELINES 159

9. REFERENCES 165

10. GLOSSARY 201

APPENDICES
A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS A-1
B. USER'S GUIDE B-1
C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS C-1
D. INDEX D-1

This page is intentionally blank.

LIST OF FIGURES

3-1. Levels of Significant Exposure to Vanadium and Compounds - Inhalation 34

3-2. Levels of Significant Exposure to Vanadium and Compounds - Oral..... 56

3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 81

3-4. Existing Information on Health Effects of Vanadium and Compounds 91

6-1. Frequency of NPL Sites with Vanadium Contamination 116

This page is intentionally blank.

LIST OF TABLES

2-1. Lung Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/day, 5 Days/week for 6 or 13 Days, 3 Months, or 2 Years 17

2-2. Hematological Effects in Rats Exposed to Ammonium Metavanadate for 4 Weeks 23

3-1. Levels of Significant Exposure to Vanadium and Compounds - Inhalation 28

3-2. Incidence of Lung Tumors in Rats and Mice Exposed to Vanadium Pentoxide for 2 Years 43

3-3. Levels of Significant Exposure to Vanadium and Compounds - Oral 45

3-4. Genotoxicity of Vanadium and Compounds *In Vitro* 67

3-5. Genotoxicity of Vanadium and Compounds *In Vivo* 70

3-6. Vanadium Elimination Half-Times in Various Organs in Rats Exposed to 8.2 mg Vanadium/kg/day for 1 Week 76

4-1. Chemical Identity of Vanadium and Compounds 102

4-2. Physical and Chemical Properties of Vanadium and Compounds 104

5-1. Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy) 108

5-2. Facilities that Produce, Process, or Use Vanadium Compounds 110

5-3. Current U.S. Manufacturers of Vanadium and Selected Vanadium Compounds 112

6-1. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy) 119

6-2. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium Compounds 121

6-3. Vanadium Levels in Food 137

6-4. Estimated Daily Vanadium Intake 140

7-1. Analytical Methods for Determining Vanadium in Biological Materials 152

7-2. Analytical Methods for Determining Vanadium in Environmental Samples 154

8-1. Regulations, Advisories, and Guidelines Applicable to Vanadium and Compounds 161

This page is intentionally blank.

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about vanadium and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Vanadium has been found in at least 319 of the 1,699 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which vanadium is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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 vanadium, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS VANADIUM?

Description	Vanadium is a naturally occurring element. It is widely distributed in the earth's crust at an average concentration of approximately 100 mg/kg. Vanadium is found in about 65 different minerals. Depending on its form, vanadium can be a gray-white metal or light gray or white lustrous powder. Pure vanadium is a bright white, soft, and ductile metal.

Uses	
• **Vanadium metal**	Vanadium is used in producing rust-resistant, spring, and high-speed tool steels. It is an important carbide stabilizer in making steels.
• **Vanadium pentoxide**	Vanadium pentoxide is used in ceramics and as a catalyst as well as in the production of superconductive magnets.
• **Vanadyl sulfate and sodium metavanadate**	Vanadyl sulfate and sodium metavanadate have been used in dietary supplements.

For more information on the physical and chemical properties of vanadium and its production, disposal and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO VANADIUM WHEN IT ENTERS THE ENVIRONMENT?

Sources	Vanadium occurs naturally in soil, water, and air. Natural sources of atmospheric vanadium include continental dust, marine aerosol, and volcanic emissions. Releases of vanadium to the environment are mainly associated with industrial sources, especially oil refineries and power plants using vanadium rich fuel oil and coal. Global human-made atmospheric releases of vanadium has been estimated to be greater than vanadium releases due to natural sources. Natural releases to water and soil are far greater overall than human-made releases to the atmosphere.

Break down	Vanadium cannot be destroyed in the environment. It can only change its form or become attached or separated from airborne particulate, soil, particulate in water, and sediment.
• **Air**	Vanadium particles in the air settle to the ground or are washed out of the air by rain. Smaller particles, such as those emitted from oil-fueled power plants, may stay in the air for longer times and are more likely to be transported farther away from the site of release.
• **Water and soil**	The transport and partitioning of vanadium in water and soil is influenced by many factors including acidity of the water or soil and the presence of particulates. Vanadium can either be dissolved in water as dissolved ions or may become adsorbed to particulate matter.

1.3 HOW MIGHT I BE EXPOSED TO VANADIUM?

Food–primary source of exposure	Most foods have naturally occurring low concentrations of vanadium. Seafood generally contains higher concentrations of vanadium than meat from land animals. Daily intakes of vanadium from food ranging from 0.01 to 0.02 mg have been reported. Average vanadium concentrations in tap water are approximately 0.001 mg/L. Assuming that you drink approximately 2 L of water a day, a daily intake of approximately 0.002 mg of vanadium from tap water can be estimated for adults. Vanadium also may be found in various commercial nutritional supplements and multivitamins in amounts ranging from 0.0004 to 12.5 mg, depending on the serving size recommended by the manufacturer. Consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed intakes from food and water. Populations in areas with high levels of residual fuel oil consumption may also be exposed to above-background levels of vanadium, both from increased particulate deposition upon food crops and soil in the vicinity of power plants.

Air	Most people take in very little vanadium from breathing. The general population may also be exposed to airborne vanadium through inhalation, particularly in areas where use of residual fuel oils for energy production is high. Individuals exposed to cigarette smoke may also be exposed to higher than background levels of vanadium. Approximately 0.0004 mg of vanadium is given off by in the smoke of one cigarette.
Water and soil	Vanadium concentrations in surface water can range from approximately 0.04 to 220 μg/L depending on geographical location.

For more information on how you might be exposed to vanadium, see Chapter 6.

1.4 HOW CAN VANADIUM ENTER AND LEAVE MY BODY?

Enter your body	
• **Inhalation**	Some of the vanadium you breathe will enter your body through your lungs; however, we do not know how much will enter.
• **Ingestion**	A small amount of vanadium in food and water (3–20%) will enter your body through the digestive tract. The vanadium compounds you are exposed to will determine how much is absorbed.
• **Dermal contact**	We do not know how much vanadium will enter your body through your skin. It is likely that very little will pass through the skin.

For more information about how vanadium enters and leaves your body, see Chapter 3.

1.5 HOW CAN VANADIUM AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Workers • **Inhalation**	Breathing air with vanadium pentoxide can result in coughing which can last a number of days after exposure.
Laboratory animals • **Inhalation**	Damage to the lungs, throat, and nose have been observed in rats and mice exposed to vanadium pentoxide.
Humans • **Oral**	Nausea, mild diarrhea, and stomach cramps have been reported in people taking sodium metavanadate or vanadyl sulfate for the experimental treatment of diabetes. Stomach cramps were also reported in a study of people taking about 13 mg vanadium/day.
Laboratory animals • **Oral**	A number of effects have been found in rats and mice ingesting several vanadium compounds. The effects include: • Decreases in number of red blood cells • Increased blood pressure • Mild neurological effects
Cancer	Lung cancer has been found in mice exposed to vanadium pentoxide. The International Agency for Research on Cancer (IARC) has determined that vanadium is possibly carcinogenic to humans.

For more information on health effects in people and animals after breathing, eating, or touching vanadium, see Chapter 3.

1.6 HOW CAN VANADIUM AFFECT CHILDREN?

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

Effects in children	The health effects seen in children from exposure to toxic levels of vanadium are expected to be similar to the effects seen in adults. We do not know if children will be more sensitive to vanadium toxicity than adults.
Birth defects	We do not know whether vanadium can cause birth defects in people. Studies in animals exposed during pregnancy have shown that vanadium can cause decreases in growth and increases in the occurrence of birth defects. These effects are usually observed at levels which cause effects in the mother.

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

Food	Vanadium is a naturally occurring element that is widely distributed in the environment. It is found in many foods, typically in small amounts. You cannot avoid exposure to vanadium. Exposure to the levels of vanadium that are naturally present in food and water are not considered to be harmful.
Consumer products	Consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed intakes from food and water. You should check with your physician before taking supplements containing vanadium to determine if such supplements are appropriate for you. As a precaution, such products should have child-proof caps or should be kept out of reach of children so that children will not accidentally ingest them.

Air	Individuals exposed to cigarette smoke may also be exposed to higher-than-background levels of vanadium. Avoiding exposure to cigarette smoke may reduce exposure of you and your family to vanadium.

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

Detecting exposure	All people have small amounts of vanadium in their bodies. It can be measured in many tissues and fluids including blood, urine, and hair.
Measuring exposure	Measurements of vanadium concentrations in blood and urine can tell you whether you have been exposed to larger-than-normal amounts of vanadium. Blood and urinary vanadium levels are considered the most reliable indicators of occupational exposure to vanadium. Measuring the concentration of vanadium in breathing air, drinking water, and food can help in determining how much vananium you are exposed to. Measuring vanadium levels in hair is not a good indicator of occupational or environmental exposure to vanadium.

For more information on ways to tell whether you have been exposed to vanadium see 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. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but cannot be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as "not-to-exceed" levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically 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 vanadium include the following:

Workplace air	OSHA set a legal limit of 0.5 mg/m^3 for vanadium pentoxide respirable dust averaged over an 8-hour work day. A limit of 0.1 mg/m^3 for vanadium pentoxide fume has also been established.

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 that result 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 toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological 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/

This page is intentionally blank.

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO VANADIUM IN THE UNITED STATES

Vanadium is the 22nd most abundant element in the earth's crust with an average concentration of 100 ppm. It exists in oxidation states ranging from -1 to +5 with 3+, 4+, and 5+ being the most common oxidation states. Vanadium is primarily used in the production of rust-resistant, spring, and high-speed tool steels; vanadium pentoxide is used in ceramics. Vanadium is released to the environment by continental dust, marine aerosols, volcanic emissions, and the combustion of coal and petroleum crude oils. It is naturally released into water and soil as a result of weathering of rock and soil erosion. Ambient air concentrations of vanadium are low, with urban areas having higher concentrations. Average vanadium concentrations were 3.0–3.7 ng/m^3 in urban areas of Illinois; in rural areas, the vanadium concentrations were 0.8–1.2 ng/m^3. Higher vanadium levels have been measured in the eastern United States due to the high density of oil fired power plants using vanadium-rich residual fuel oil. An average vanadium air concentration of 620 ng/m^3 was measured in Eastern cities compared to 11 ng/m^3 in cities throughout the United States. Vanadium residence time in the environment is inversely related to the particle size. In water, vanadium is converted from trivalent forms to pentavalent forms. The levels of vanadium in surface water range from 0.04 to 104 µg/L. Vanadium levels of 1.2–1.0 µg/L were measured in tap water samples collected in several U.S. states.

Food is the primary route of exposure for the general population; foods with the highest vanadium content include ground parsley, freeze-dried spinach, wild mushrooms, and oysters. Vanadium in food is mainly ingested as VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2-} (vanadate, V^{5+}). Estimates of dietary vanadium intake range from 0.09 to 0.34 µg/kg/day in adults. Humans are potentially exposed to a variety of vanadium compounds, the most common being vanadium pentoxide, sodium metavanadate, sodium orthovanadate, vanadyl sulfate, and ammonium metavanadate. Organic anthropogenic vanadium compounds, such as bis(maltolato)oxyvanadium (IV) or vanadyl acetyl acetonate, are used in the treatment of diabetes and cancer; these compounds have different toxicokinetic properties than inorganic vanadium compounds and are not discussed in this toxicological profile.

Although there is some evidence to suggest that vanadium is an essential nutrient, a functional role for vanadium in humans has not been established; increases in abortion rates and decreased milk production have been observed in vanadium-deprived goats. Vanadium mimics insulin and stimulates cell proliferation and differentiation. In animal models, particularly streptozotoxin-induced diabetes in rats,

vanadium has been shown to normalize blood glucose and lipid levels, improve insulin sensitivity, and prevent or reverse secondary complications such as cardiomyopathy, cataract development, and impaired antioxidant status.

2.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to vanadium primarily through oral (ingestion of vanadium in food) and inhalation routes of exposure. Based on occupational exposure studies, human experimental studies, and studies in laboratory animals, the respiratory tract following inhalation exposure and the gastrointestinal tract, hematological system, and developing organism following oral exposure are the primary targets of toxicity.

Adverse respiratory effects have been reported in humans and animals exposed to vanadium compounds at concentrations much higher than those typically found in the environment. Although the available data in humans are limited, signs of airway irritation (e.g., coughing, wheezing, sore throat) have been reported in subjects acutely exposed to 0.6 mg vanadium/m^3 and in workers exposed to vanadium pentoxide dust. These effects have persisted for days to weeks after exposure termination and are often not associated with alterations in lung function. Studies in laboratory animals provide strong support that the respiratory tract is the most sensitive target following inhalation exposure to vanadium. A variety of lung lesions including alveolar/bronchiolar hyperplasia, inflammation, and fibrosis have been observed in rats and mice exposed to vanadium pentoxide; the severity of the lesions is related to concentration and duration. The lung effects have been observed following acute exposure to 0.56 mg vanadium/m^3 and chronic exposures to 0.28 mg vanadium/m^3 and have been observed after 2 days of exposure. Longer duration exposures also result in inflammation and hyperplasia in the larynx and hyperplasia in nasal goblet cells. These histological alterations result in restrictive impairments in lung function; respiratory distress is observed at vanadium pentoxide concentrations of $\geq$4.5 mg vanadium/m^3.

Other sensitive targets of vanadium toxicity include the gastrointestinal system following oral exposure and hematological system following inhalation or oral exposure. Symptoms of gastrointestinal irritation (diarrhea, cramps, nausea) have been observed in humans following bolus administration of sodium metavanadate or vanadyl sulfate; it appears that with repeated exposure, humans develop a tolerance to these effects. Diarrhea has also been observed in rats and mice orally exposed to lethal doses of vanadium. Microcytic erythrocytosis (evidenced by decreases in hematocrit, hemoglobin, and mean cell volume and increases in reticulocytes and nucleated erythrocytes) has been observed in rats exposed to

1.1 mg vanadium/m^3 as vanadium pentoxide for at least 4 days. Hematological effects, including decreases in erythrocyte levels, decreases in hemoglobin, and increases in reticulocytes have also been observed in rats orally exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate for 4 weeks.

Information on the potential of vanadium to induce developmental effects in humans is limited, but developmental effects have been observed in laboratory animals. Decreases in pup growth have been observed at maternal doses of ≥2.1 mg vanadium/kg/day. At higher doses, decreases in pup survival and gross, skeletal, and visceral malformations and anomalies have been reported; marked decreases in maternal body weight are also observed at these dose levels.

No studies have examined the carcinogenic potential of vanadium in humans. An increase in lung carcinoma incidence has been observed in mice chronically exposed to vanadium pentoxide; there is also marginal evidence for lung cancer in male rats (incidence of carcinoma was higher than historical controls but not concurrent controls). Carcinogenicity has not been adequately assessed in laboratory animals following oral exposure. One study classified vanadium pentoxide in group 2B (possibly carcinogenic to humans) based on inadequate evidence in humans and sufficient evidence in animals. The Department of Health and Human Services and EPA have not classified carcinogenicity of vanadium.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for vanadium. 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 types of 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.

Inhalation MRLs

Acute-Duration Inhalation MRL

- An MRL of 0.0008 mg vanadium/m^3 has been derived for acute-duration inhalation exposure (14 days or less) to vanadium pentoxide dust.

Data on acute toxicity of vanadium in humans are limited to an experimental study in which a small number of subjects were exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). A persistent cough lasting for 8 days developed in two subjects exposed to 0.6 mg vanadium/m^3; at 0.1 mg vanadium/m^3, a productive cough without any subjective complaints or impact on work or home activities were observed in five subjects. The available studies in laboratory animals focused on potential respiratory tract effects. Impaired lung function, characterized as airway obstructive changes (increased resistance and decreased airflow), was observed in monkeys exposed to 2.5 or 1.7 mg vanadium/m^3 as vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992); the highest no-observed-adverse-effect level (NOAEL) for this effect was 0.34 mg vanadium/m^3. In female rats exposed to 0.56 mg vanadium/m^3 6 hours/day, 5 days/week for 13 days, minimal inflammation and histiocytic infiltration were observed (NTP 2002). Alveolar and bronchiolar epithelial hyperplasia and inflammation were observed in the lungs of mice similarly exposed to 1.1 mg vanadium/m^3 as vanadium pentoxide (NTP 2002). Although the Knecht et al. (1985, 1992) or NTP (2002) studies did not include examination of potential end points outside of the respiratory tract, longer-duration studies have identified the respiratory tract as the most sensitive target of toxicity (NTP 2002). The NTP (2002) rat study was selected as the basis of the acute-duration inhalation MRL.

In the NTP (2002) study, groups of male and female F344 rats received whole-body exposure to 0, 1, 2, or 4 mg vanadium pentoxide/m^3 (0, 0.56, 1.1, or 2.2 mg vanadium/m^3) as particulate aerosols 6 hours/day, 5 days/week. On days 6 and 13, 10 rats/group were killed and a histopathological examination of the lungs was conducted. Four rats per group were killed for examination of the onset and extent of lung lesions after 1, 2, 5, 10, or 16 days of exposure. Hyperplasia of alveolar epithelium and bronchiole epithelium were observed in 100% of the female rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days. Significant increases in the incidence of histiocytic infiltrate and inflammation were observed in rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days and in rats exposed to 0.56 mg vanadium/m^3 for 13 days. A significant increase in fibrosis was observed in rats exposed to 2.2 mg vanadium/m^3 for

13 days. No histopathological alterations were observed in the four female rats killed after 1 day of exposure; by day 2, inflammation and histiocytic infiltrates (increased number of alveolar macrophages) were observed in the rats exposed to 2.2 mg vanadium/m^3. Hyperplasia of the alveolar and bronchiolar epidthelium was first observed on day 5 in rats exposed to 1.1 or 2.2 mg vanadium/m^3.

A benchmark dose (BMD) approach was considered for derivation of the acute-duration inhalation MRL; however, the fit was not considered adequate due to the limited amount of information from the study on the shape of the exposure-response curve for lung inflammation; more information regarding the BMD analysis is presented in Appendix A. A NOAEL/lowest-observed-adverse-effect level (LOAEL) approach was used to derive the MRL. The LOAEL of 0.56 mg vanadium/m^3 for lung inflammation was selected as the point of departure for the MRL. This LOAEL was converted to a human equivalent concentration ($LOAEL_{HEC}$) of 0.073 mg vanadium/m^3 (see Appendix A for more information on the calculation of the $LOAEL_{HEC}$) and divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human extrapolation using dosimetric adjustments, and 10 for human variability), resulting in an acute-duration inhalation MRL of 0.0008 mg vanadium/m^3.

Intermediate-Duration Inhalation MRL

The available data on the toxicity of vanadium following intermediate-duration inhalation exposure are limited to several rat and mouse studies (NTP 2002) involving exposure to vanadium pentoxide for 6 hours/day, 5 days/week. These studies demonstrate that the respiratory tract is the most sensitive target of toxicity. Signs of respiratory distress (rapid respiration, difficulty breathing) have been observed in rats exposed to 4.4 mg vanadium/m^3 as vanadium pentoxide for at least 4 weeks (NTP 2002). A 3-month exposure resulted in increased incidences of lung lesions in rats and mice and nasal lesions in rats. Lung effects included alveolar and bronchiolar epithelial hyperplasia, histiocytic infiltrates, inflammation, and fibrosis. A NOAEL of 0.56 mg vanadium/m^3 was identified in both species. At 1.1 mg vanadium/m^3, epithelial hyperplasia and inflammation (male rats and female mice only) were observed. In mice, the severity of the lesions was graded as minimal. In rats, the epithelial hyperplasia was graded as mild in males and minimal to mild in females and the inflammation was graded as mild. These data suggest that at a given air concentration, rats are more sensitive than mice based on the severity of the lesions. In both species, the severity of the lesions increased with increasing concentrations. Significant alterations in pulmonary function suggestive of a restrictive disease were observed in rats exposed to 2.2 or 4.4 mg vanadium/m^3; lung function tests were not performed in mice. Nasal effects in rats included hyperplasia and squamous metaplasia of the respiratory epithelium and inflammation. The NOAEL and LOAEL for

nasal effects were 2.2 and 4.5 mg vanadium/m^3 in males and 1.1 and 2.2 mg vanadium/m^3 in females. In addition to the respiratory tract effects, mild microcytic erythrocytosis was observed in rats exposed to ≥1.1 mg vanadium/m^3.

The lowest LOAEL identified in intermediate-duration studies is 1.1 mg vanadium/m^3 for lung epithelial hyperplasia and inflammation in rats exposed 6 hours/day, 5 days/week for 13 weeks (NTP 2002); the NOAEL for these effects is 0.56 mg vanadium/m^3. However, this NOAEL is the same as the LOAEL for lung inflammation in rats exposed for 13 days (NTP 2002). As summarized in Table 2-1, lung inflammation was observed in rats exposed to 0.56 mg vanadium/m^3 for 6 days (not significant), 13 days, and 2 years. Although the three studies were conducted for the National Toxicology Program (NTP), the 13-week study was conducted at a different laboratory using the same strain of rats and vanadium pentoxide dusts with similar particles sizes as the acute and chronic studies. An explanation for the inconsistent findings is not apparent from the available data. Because an intermediate-duration inhalation MRL based on the NOAEL identified in the 13-week study would be higher than the acute-duration inhalation MRL, the database is not considered adequate for derivation of an intermediate-duration inhalation MRL. However, it would be expected that the acute-duration inhalation MRL would be protective of intermediate-duration exposure to vanadium.

Chronic-Duration Inhalation MRL

- An MRL of 0.0001 mg vanadium/m^3 has been derived for chronic-duration inhalation exposure (1 year or longer) to vanadium pentoxide dust.

Two-year rat and mouse studies conducted by NTP (2002) examined the chronic toxicity of inhaled vanadium pentoxide 6 hours/day, 5 days/week for 2 years. At the lowest concentration tested in rats (0.28 mg vanadium/m^3), lung (increases in the incidence of alveolar and bronchiolar epithelial hyperplasia), larynx (degeneration and hyperplasia of the epiglottis epithelium), and nasal (goblet cell hyperplasia in respiratory epithelium) effects were observed. Similar lung and larynx effects were observed in mice at the lowest concentration tested (0.56 mg vanadium/m^3). The nasal effects observed in mice exposed to 0.56 mg vanadium/m^3 included goblet cell hyperplasia in the respiratory epithelium and nasal olfactory epithelial atrophy and hyaline degeneration. In addition to these effects, a significant increase in alveolar/bronchiolar carcinoma incidence was also observed in mice exposed to ≥0.56 mg vanadium/m^3. In male rats, an increased combined incidence of alveolar/bronchiolar adenoma or carcinoma was also observed; however, the incidence was not significantly higher than concurrent

Table 2-1. Lung Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/day, 5 Days/week for 6 or 13 Days, 3 Months, or 2 Years

	mg vanadium/m^3						
Air concentration	0	0.28	0.56	1.1	2.2	4.5	9.0
			6-Day study				
Alveolar hyperplasia	0/10		0/10	10/10[a] (1.1)[b]	8/10[a] (1.4)		
Bronchiole hyperplasia	1/10 (1.0)		0/10	10/10[a] (1.7)	10/10[a] (1.8)		
Histiocytic infiltrate	2/10 (1.0)		6/10 (1.3)	10/10[a] (1.4)	10/10[a] (1.8)		
Inflammation	0/10		3/10 (1.0)	10/10[a] (1.5)	10/10[a] (2.5)		
			13-Day study				
Alveolar hyperplasia	0/10		3/10 (1.0)	10/10[a] (1.0)	10/10[a] (2.0)		
Bronchiole hyperplasia	0/10		0/10	10/10[a] (1.0)	10/10[a] (1.8)		
Histiocytic infiltrate	0/10		10/10[a] (1.3)	10/10[a] (1.9)	10/10[a] (2.2)		
Inflammation	0/10		8/10 (1.3)	10/10[a] (1.7)	10/10[a] (2.0)		
Fibrosis	0/10		0/10	0/10	6/10[a] (1.5)		
			3-Month study (males)				
Epithelial hyperplasia	0/10		0/10	10/10[a] (2.0)	10/10[a] (3.0)	10/10[a] (3.6)	10/10[a] (3.3)
Inflammation	0/10		0/10	9/10[a] (1.0)	10/10[a] (1.0)	10/10 (1.6)	10/10[a] (2.1)
Fibrosis	0/10		0/10	2/10 (1.0)	10/10[a] (1.9)	10/10[a] (3.2)	10/10 (3.1)
			3-Month study (females)				
Epithelial hyperplasia	0/10		0/10	10/10[a] (1.3)	10/10[a] (2.9)	10/10[a] (3.5)	10/10[a] (3.2)
Inflammation	0/10		0/10	0/10	10/10[a] (1.0)	10/10[a] (1.9)	10/10[a] (1.2)
Fibrosis	0/10		0/10	0/10	10/10[a] (1.0)	10/10[a] (2.9)	10/10[a] (3.2)

Table 2-1. Lung Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/day, 5 Days/week for 6 or 13 Days, 3 Months, or 2 Years

	mg vanadium/m^3						
Air concentration	0	0.28	0.56	1.1	2.2	4.5	9.0
	2-Year study (males)						
Alveolar hyperplasia	7/50 (2.3)	24/49[a] (2.0)	34/48[a] (2.0)	49/50[a] (3.3)			
Bronchiole hyperplasia	3/50 (2.3)	17/49[a] (2.2)	31/48[a] (1.8)	49/50[a] (3.3)			
Inflammation	5/50 (1.6)	8/49 (1.8)	24/48[a] (1.3)	42/50[a] (2.4)			
Fibrosis	7/50 (1.4)	7/49 (2.0)	16/48[a] (1.6)	38/50[a] (2.1)			
Histiocyte infiltration	22/50 (1.3)	40/49[a] (2.0)	45/48[a] (2.3)	50/50[a] (3.3)			
	2-Year study (females)						
Alveolar hyperplasia	4/49 (1.0)	8/49 (1.8)	21/50[a] (1.2)	50/50[a] (3.1)			
Bronchiole hyperplasia	6/49 (1.5)	5/49 (1.6)	14/50[a] (1.3)	48/50[a] (3.0)			
Inflammation	10/49 (1.5)	10/49 (1.1)	14/50 (1.2)	40/50[a] (1.7)			
Fibrosis	19/49 (1.4)	7/49[a] (1.3)	12/50 (1.6)	32/50[a] (1.4)			
Histiocyte infiltration	26/49 (1.4)	35/49[a] (1.3)	44/50[a] (2.0)	50/50[a] (1.9)			

[a]$p \leq 0.05$
[b]Average severity grade of lesions in affected animals: 1=minimal; 2=mild, 3=moderate; 4=marked

Source: NTP 2002

controls, but was higher than historical controls. Because the rat study identified a lower LOAEL for lung, larynx, and nasal effects, it was selected as the basis of a chronic-duration inhalation MRL.

In the NTP (2002) study, groups of 50 male and 50 female F344 rats were exposed to 0, 0.5, 1, or 2 mg vanadium pentoxide/m^3 (0, 0.28, 0.56, and 1.1 mg vanadium/m^3) 6 hours/day, 5 days/week for 104 weeks. No significant alterations in survival or body weight gain were observed in the vanadium-exposed rats. Alveolar histiocytic infiltrates were observed in males and females exposed to ≥0.28 mg vanadium/m^3. Significant increases in the incidence of hyperplasia of the alveolar and bronchiolar epithelium were observed in males exposed to ≥0.28 mg vanadium/m^3 and females exposed to ≥0.56 mg vanadium/m^3. Squamous metaplasia was observed in alveolar epithelium of males and females exposed to 1.1 mg vanadium/m^3 and in the bronchiolar epithelium of males exposed to 1.1 mg vanadium/m^3. Chronic inflammation was observed in males exposed to 0.56 or 1.1 mg vanadium/m^3 and females exposed to 1.1 mg vanadium/m^3 and interstitial fibrosis was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.28 or 1.1 mg vanadium/m^3. An increased incidence of brownish pigment in alveolar macrophages was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.56 or 1.1 mg vanadium/m^3; this effect was considered to be of little biological relevance. Chronic inflammation, degeneration and hyperplasia of the epiglottis were observed in the larynx of males and females exposed to ≥0.28 mg vanadium/m^3; squamous metaplasia of the epiglottis respiratory epithelium was also observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3. Goblet cell hyperplasia of the nasal respiratory epithelium was observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3.

BMD analyses of the incidence data for alveolar and bronchiolar epithelial hyperplasia, chronic inflammation of the larynx, degeneration of epiglottis respiratory epithelium, and hyperplasia of nasal respiratory epithelial goblet cells in male rats were used to determine the point of departure for the MRL. As described in greater detail in Appendix A, the $BMCL_{10}$ values for these effects were 0.09, 0.10, 0.07, 0.04, and 0.16 mg vanadium/m^3, respectively.

These $BMCL_{10}$ values were converted to a human equivalent concentrations (as described in detail in Appendix A); the $BMCL_{HEC}$ values were 0.008, 0.017, 0.005, 0.003, and 0.012 mg vanadium/m^3 for alveolar epithelial hyperplasia, bronchiolar epithelial hyperplasia, chronic inflammation of the larynx, degeneration of epiglottis respiratory epithelium, and hyperplasia of nasal respiratory epithelial goblet cells, respectively. The $BMCL_{HEC}$ of 0.003 mg vanadium/m^3 for degeneration of epiglottis respiratory epithelium was selected as the point of departure. This value was divided by an uncertainty factor of

30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability), resulting in a chronic-duration inhalation MRL of 0.0001 mg vanadium/m^3.

Oral MRLs

Acute-Duration Oral MRL

Gastrointestinal effects (diarrhea, cramps, nausea, and vomiting) have been observed in diabetic patients administered vanadyl sulfate or sodium metavanadate capsules as a supplement to their diabetes treatment (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). The gastrointestinal effects subsided within the first couple of weeks of exposure. The concentrations in the capsules ranged from 16 to 24 mg and daily doses ranged from 0.35 to 0.66 mg vanadium/kg/day. A small number of studies in laboratory animals have examined the acute toxicity of vanadium following oral exposure. Significant increases in reticulocyte levels in peripheral blood and polychromatophilic erythroblasts in the bone marrow were observed in rats exposed to 27.72 mg vanadium/kg/day as ammonium metavanadate in drinking water for 2 weeks (Zaporowska and Wasilewski 1989). The remaining nonlethality studies reported developmental effects in the offspring of rats and mice administered 7.5–8.4 mg vanadium/kg/day via gavage during gestation (Paternain et al. 1987, 1990; Sanchez et al. 1991). The observed developmental effects included decreases in fetal growth, increases in resorptions, and gross, visceral, and skeletal malformations and anomalies.

Although the human studies identified the lowest LOAEL values, they were not considered suitable as the basis of an MRL. These studies used a small number of diabetic subjects (5–10 subjects per study) and no control group. The lowest LOAEL identified in an animal study is 7.5 mg vanadium/kg/day for developmental effects (Paternain et al. 1990). In this study, significant increases in early resorptions, decreases in fetal body weight and length, and increases in the incidence of soft tissue anomalies/ malformations (hematomas in facial area, neck, and dorsal area, cleft palate), and skeletal defects (delayed ossification of supraoccipital bone, carpus, tarsus, and sternebrae) were observed in the offspring of Swiss mice administered via gavage 7.5 mg vanadium/kg/day as vanadyl sulfate on gestation days 6–15. This dose was also associated with significant decreases in maternal body weight gain (during gestation days 6–15, the dams gained 46% less weight than controls); no significant alterations in food intake were observed. Because 7.5 mg vanadium/kg/day is a serious LOAEL in the dams (ATSDR defines serious effects as those that evoke failure in a biological system and can lead to morbidity or mortality), this study is not suitable for derivation of an acute-duration oral MRL. It is ATSDR's policy to not use a LOAEL for serious health effects as the basis of an MRL.

Intermediate-Duration Oral MRL

- An MRL of 0.01 mg vanadium/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to vanadium.

Two human studies have examined the oral toxicity of vanadium. No significant alterations in hematological parameters, liver function (as measured by serum enzymes), cholesterol and triglyceride levels, kidney function (as measured by blood urea nitrogen), body weight, or blood pressure were observed in subjects administered via capsule 0.12 or 0.19 mg vanadium as ammonium vanadyl tartrate or vanadyl sulfate for 6–12 weeks (Dimond et al. 1963; Fawcett et al. 1997). Studies in laboratory animals have identified several sensitive effects including alterations in erythrocyte and reticulocyte levels, increased blood pressure, neurobehavioral alterations, and developmental toxicity. The lowest LOAEL identified in an intermediate-duration study was 0.12 mg vanadium/kg/day for increases in blood pressure observed in rats exposed to sodium metavanadate in drinking water for 210 days (Boscolo et al. 1994); several other studies by these investigators have reported similar effects at higher doses (Carmagnani et al. 1991, 1992). However, other studies have not found significant alterations in blood pressure at higher doses (Bursztyn and Mekler 1993; Sušić and Kentera 1986, 1988). Significant decreases in erythrocyte levels have been observed in rats exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate in drinking water for 4 weeks (Zaporowska et al. 1993); at higher concentrations, decreases in hemoglobin and increases in reticulocyte levels have been observed (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993). However, other intermediate-duration studies have not found significant alterations at doses as high as 9.7 mg vanadium/kg/day (Dai et al. 1995; Mountain et al. 1953). At 1.72 mg vanadium/kg/day, impaired performance on neurobehavioral tests (open field and active avoidance tests) was observed in rats exposed to administered sodium metavanadate for 8 weeks (Sanchez et al. 1998). No other studies have examined the neurotoxic potential of vanadium. As with acute-duration exposure, the developing organism is a sensitive target of vanadium toxicity. Decreases in pup body weight and length were observed in the offspring of rats administered 2.1 mg vanadium/kg/day as sodium metavanadate for 14 days prior to mating and throughout gestation and lactation (Domingo et al. 1986). At higher doses (6, 10, or 12 mg vanadium/kg/day), decreases in pup survival, and increases in the occurrence of gross, visceral, or skeletal malformations and anomalies were observed (Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001).

The animal database suggests that the most sensitive targets of vanadium toxicity are blood pressure, erythroctyes, nervous system, and the developing organism with LOAEL values of 0.12, 1.18, 1.72, and

2.1 mg vanadium/kg/day, respectively. Two approaches for derivation of an intermediate-duration oral MRL were considered. In the first approach, the NOAEL of 0.12 mg vanadium/kg/day identified in the Fawcett et al. (1997) study was used as the point of departure for the MRL. The Fawcett et al. (1997) study was selected over the Dimond et al. (1963) study, which identified a slightly higher NOAEL (0.19 mg vanadium/kg/day) because more subjects (six subjects in Dimond study compared to 15–16 subjects in Fawcett study) were examined and the results of the study are described in greater detail. In the Fawcett et al. (1997) study, groups of men and women enrolled in a weight training program for at least 1 year were administered capsules containing 0 (11 men and 4 women) or 0.12 mg vanadium/kg/day as vanadyl sulfate trihydrate (12 men and 4 women) for 12 weeks. Fasting blood samples were collected at 0 and 12 weeks and analyzed for hematological (erythrocyte count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, platelet count, and total and differential leukocyte count) and serum chemistry (cholesterol, high density lipoprotein, triglycerides, albumin, total protein, total and direct bilirubin, alkaline phosphatase, alanine amino-transferase) parameters. Body weight and blood pressure were measured at weeks 4, 8, and 12. No significant alterations in blood pressure, body weight, or hematological or clinical chemistry parameters were found. Using the NOAEL of 0.12 mg vanadium/kg/day and an uncertainty factor of 10 for human variability, the MRL would be 0.01 mg vanadium/kg/day.

Several animal studies were also considered as the basis of an MRL. Although an increase in blood pressure was observed at the lowest adverse effect level (0.12 mg vanadium/kg/day; Boscolo et al. 1994), this end point was not selected as the basis for an intermediate-duration oral MRL. This effect has not been consistently observed among rat studies and no alterations in blood pressure were observed in a study of healthy adults exposed to 0.12 mg vanadium/kg/day for 12 weeks (Fawcett et al. 1997). The next highest LOAEL of 1.18 mg vanadium/kg/day for a decrease in erythrocyte levels in rats (Zaporowski et al. 1993) was considered as the principal study for the MRL. In the Zaporowski et al. (1993) study, groups of 2-month-old male and female Wistar rats (15–16/sex/group) were exposed to ammonium metavanadate in drinking water for 4 weeks at doses of 0, 1.18, and 4.93 mg vanadium/kg/day (males) or 1.50 and 6.65 mg vanadium/kg/day (females). No alterations in behavior or motor activity were observed. A significant decrease in water consumption (14% less than controls) was observed in males exposed to 4.93 mg vanadium/kg/day. No significant alterations in body weight gain were observed. As summarized in Table 2-2, alterations in erythrocyte, hemoglobin, hematocrit, and reticulocyte levels were observed. This study identified a minimal LOAEL of 1.18 mg vanadium/kg/day for decreases in erythrocyte and hematocrit levels in male rats. The alteration in erythrocyte levels was considered minimally adverse because the magnitude of the change was small (approximately 11%). Dividing this

Table 2-2. Hematological Effects in Rats Exposed to Ammonium Metavanadate for 4 Weeks

	Dose (mg vanadium/kg/day)		
Males	0	1.18	4.93
Erythrocytes ($x10^{12}/dm^3$)	8.32	7.38[a]	7.47[b]
Hemoglobin (mmol/L)	9.37	8.94	8.65[a]
Hematocrit (L)	0.48	0.47[b]	0.47[a]
Reticulocytes (%)	2.55	2.64	3.82[b]
Females	0	1.50	6.65
Erythrocytes ($x10^{12}/dm^3$)	8.24	7.38[c]	7.12[c]
Hemoglobin (mmol/L)	9.41	8.76	8.72[a]
Hematocrit (L)	0.48	0.47	0.47
Reticulocytes (%)	2.55	2.91	3.64[b]

[a]Significantly different from control group ($p<0.01$)
[b]Significantly different from control group ($p<0.05$)
[c]Significantly different from control group ($p<0.001$)

Source: Zaporowska et al. 1993

minimal LOAEL by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) results in an MRL of 0.004 mg vanadium/kg/day.

Although an MRL based on the Zaporwska et al. (1993) rat study would be approximately 3 times lower than an MRL based on the Fawcett et al. (1997) human study, the Fawcett et al. (1997) study was selected as the basis of the intermediate-duration oral MRL because greater confidence was given to an MRL based on a reliable human study. Thus, the intermediate-duration oral MRL is 0.01 mg vanadium/kg/day.

Chronic-Duration Oral MRL

No studies examining the chronic toxicity of vanadium in humans were identified. Although several laboratory animal studies have examined chronic toxicity, most tested low doses and did not find effects. No adverse effects were observed in rats and mice exposed to 0.7 or 4.1 mg vanadium/kg/day, respectively, as vanadyl sulfate in drinking water for 2–2.5 years (Schroeder et al. 1970; Schroeder and Balassa 1967). In rats exposed to 28 mg vanadium/kg/day as vanadyl sulfate in drinking water, a 20% decrease in body weight gain was observed; no alterations in lungs, heart, liver, or kidneys histopathology, hematological parameters, or blood pressure were observed at 19 mg vanadium/kg/day (Dai and McNeill 1994; Dai et al. 1994a, 1994b). Because the most sensitive target of vanadium toxicity following chronic-duration oral exposure have not been identified, the animal studies that mostly identified free-standing NOAEL values were not considered suitable for derivation of an MRL.

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 vanadium. 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.

Elemental vanadium does not occur in nature; however, vanadium compounds exist in over 50 different mineral ores and in association with fossil fuels. It has six oxidation states (1-, 0, 2+, 3+, 4+, and 5+) of which 3+, 4+, and 5+ are the most common. The toxicologically significant compounds are vanadium pentoxide (V_2O_5), sodium metavanadate ($NaVO_3$), sodium orthovanadate (Na_3VO_4), vanadyl sulfate ($VOSO_4$), and ammonium vanadate (NH_4VO_3). Vanadium pentoxide dust is usually encountered in occupational settings, and humans would be exposed via the inhalation route. Organic vanadium compounds, such as bis(maltolato)oxyvanadium (IV), bis(ethylmaltolato)oxyvanadium (IV), and vanadyl acetyl acetonate, have been synthesized for use in the treatment of diabetes and cancer. Because these compounds likely have different toxicokinetic properties from inorganic vanadium compounds, they are not included in this toxicological profile.

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

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.

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

No studies were located regarding death in humans after inhalation exposure to vanadium.

Increases in mortality have been observed in several studies of laboratory animals exposed to vanadium pentoxide. Deaths occurred in rabbits exposed to 114 mg vanadium/m^3 for 1 hour, but not in rabbits exposed to 43 mg vanadium/m^3 (Sjöberg 1950). Exposure to 18 mg vanadium/m^3 as vanadium pentoxide resulted in death in three of five rats exposed for 6 days (NTP 2002). Intermediate-duration exposure resulted in deaths in rats exposed to 9 mg vanadium/m^3 and mice exposed to 18 mg vanadium/m^3 (NTP

2002). A decrease in survival was observed in mice chronically exposed to 2.2 mg vanadium/m^3 (NTP 2002). The LOAEL values are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Although a number of studies have reported respiratory effects in humans exposed to vanadium, in particular vanadium pentoxide, very few provide reliable quantitative exposure data. In an experimental study, persistent coughing lasting 8 days after exposure termination was observed in two subjects exposed to 0.6 mg vanadium/m^3 for 8 hours; no alterations in lung function (lung function parameters assessed: forced vital capacity, 0.5 and 1 second forced expiratory volume, maximal expiratory flow, 200–1,200 cc flow rate, maximal midexpiratory time, and forced inspiratory vital capacity) were observed (Zenz and Berg 1967). At 0.1 mg vanadium/m^3, five subjects reported productive coughing without other subjective complaints, alterations in lung function, or changes in daily activities; this concentration level was considered a NOAEL. Workers exposed to a range of vanadium pentoxide dust levels for as little as 1 day (Levy et al. 1984; Musk and Tees 1982; Thomas and Stiebris 1956; Zenz et al. 1962) or as long as ≥6 years (Irsigler et al. 1999; Lewis 1959; NIOSH 1983; Sjöberg 1956; Vintinner et al. 1955; Wyers 1946), show mild respiratory distress, such as cough, wheezing, chest pain, runny nose, or sore throat. One study of chronically-exposed workers showed increased neutrophils in the nasal mucosa (Kiviluoto 1980; Kiviluoto et al. 1979b, 1981a). More severe pathology has not been reported. Symptoms are reversible within days or weeks after exposure ceases. Data were not located to assess the relationship of exposure level or duration to severity of response. Chest x-rays and pulmonary function tests were normal in most cases. Chronic effects were infrequently reported. In a study of 40 vanadium pentoxide workers with persistent respiratory symptoms (Irsigler et al. 1999), 12 were found to have bronchial hyperresponsiveness to inhaled histamine or exercise challenge. No significant alterations in baseline lung function were found. The mean urine vanadium level (assessed via spot urine samples) in the hyperresponsive group was 52.7 μg/g creatinine compared to 30.7 μg/g creatinine in 12 matched subjects with persistent respiratory symptoms and without bronchial hyperreactivity; statistical comparisons of the two groups were not made. Five to 23 months after removal from exposure, bronchial hyperreactivity was still present in nine of the subjects, although the response was less severe in five of them and more severe in one subject.

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rabbit	1 d 7 hr/d (NS)				114 (2/4 died)	Sjoberg 1950 VANADIUM PENTOXIDE	
Systemic								
2	Monkey (Cynomolgus)	6 hr (NS)	Resp	0.34 M	2.5 M (impaired lung function)		Knecht et al. 1985 VANADIUM PENTOXIDE	
3	Monkey (Cynomolgus)	6 hr	Resp	0.28 M	1.7 M (impaired lung function)		Knecht et al. 1992 VANADIUM PENTOXIDE	
4	Rat (Fischer- 344)	6 hr/d 5 d/wk 6 or 13 d	Resp		0.56 F[b] (histiocytic infiltrate and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
5	Mouse (B6C3F1)	6 hr/d 5 d/wk 6 or 13 d	Resp		1.1 F (hyperplasia of alveolar and bronchiole epithelium and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
INTERMEDIATE EXPOSURE								
Death								
6	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d				18 M (3/5 males died)	NTP 2002 VANADIUM PENTOXIDE	
7	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo				9 (7/10 males and 3/10 females died)	NTP 2002 VANADIUM PENTOXIDE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
8	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d				18 M (5/5 males died)	NTP 2002 VANADIUM PENTOXIDE	
Systemic								
9	Monkey (Cynomolgus)	6 hr/d 5 d/wk 26 wk	Resp		0.62 M (audible wheezing and coughing in 3/8 monkeys)		Knecht et al. 1992 VANADIUM PENTOXIDE	
10	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d	Resp	1.1	2.2 (localized inflammatory response)		NTP 2002 VANADIUM PENTOXIDE	
			Bd Wt	4.5	9 (12-13% decreased body weight gain)	9 (25-40% decreased body weight gain)		
11	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo	Resp	0.56	1.1 (epithelial hyperplasia and inflammation in lungs)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	4.5				
			Gastro	4.5				
			Musc/skel	4.5				
			Hepatic	4.5				
			Renal	4.5				
			Dermal	4.5				
			Bd Wt	4.5		9 (30-60% decreased body weight gain)		

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
12	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d	Resp	1.1	2.2 (lung inflammation)		NTP 2002 VANADIUM PENTOXIDE	
			Bd Wt	9		18 (28% decreased body weight gain)		
13	Mouse (B6C3F1)	6 hr/d 5 d/wk 3 mo	Resp	0.56	1.1 (lung inflammation and epithelial hyperplasia)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	9				
			Gastro	9				
			Hepatic	9				
			Renal	9				
			Bd Wt	4.5 F	9 F (12% decreased body weight gain)			
Immuno/ Lymphoret								
14	Rat (Fischer- 344)	6 hr/d 5 d/wk 16 d			2.2 (decr phagocytosis and incr bactericidal activity)		NTP 2002 VANADIUM PENTOXIDE	
15	Mouse (B6C3F1)	6 hr/d 5 d/wk 16 d		18			NTP 2002 VANADIUM PENTOXIDE	
Reproductive								
16	Rat (Fischer- 344)	6 hr/d 5 d/wk 3 mo		9 M 2.2 F	4.5 F (increased estrous cycle length)		NTP 2002 VANADIUM PENTOXIDE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
17	Mouse (B6C3F1)	6 hr/d 5 d/wk 3 mo		2.2 M 9 F	4.5 M (decreased epididymal spermatozoa motility)		NTP 2002 VANADIUM PENTOXIDE	
CHRONIC EXPOSURE								
Death								
18	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr				2.2 M (decreased survival in males)	NTP 2002 VANADIUM PENTOXIDE	
Systemic								
19	Rat (Fischer- 344)	6 hr/d 5 d/wk 2 yr	Resp		0.28[c] (hyperplasia of alveolar and bronchiolar epithelium, degeneration and hyperplasia of epiglottis epithelium, and goblet cell hyperplasia in nasal respiratory epithelium)		NTP 2002 VANADIUM PENTOXIDE	
			Cardio	1.1				
			Gastro	1.1				
			Musc/skel	1.1				
			Hepatic	1.1				
			Renal	1.1				
			Bd Wt	1.1				

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)		LOAEL Serious (mg V/m³)		Reference Chemical Form	Comments
20	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr	Resp		0.56	(hyperplasia and chronic inflammation in lungs; squamous metaplasia of epiglottis epithelium and nasal respiratory epithelium; atrophy and degeneration of nasal olfactory epithelium)			NTP 2002 VANADIUM PENTOXIDE	
			Cardio	2.2						
			Gastro	2.2						
			Hepatic	2.2						
			Renal	2.2						
			Dermal	2.2						
			Bd Wt	0.56	1.1	(15-20% decreased body weight gain)	2.2	(20-29% decreased body weight gain)		
Cancer										
21	Rat (Fischer- 344)	6 hr/d 5 d/wk 2 yr					0.28 M	(lung tumor incidence higher than historical controls)	NTP 2002 VANADIUM PENTOXIDE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/m³)	LOAEL Less Serious (mg V/m³)	LOAEL Serious (mg V/m³)	Reference Chemical Form	Comments
22	Mouse (B6C3F1)	6 hr/d 5 d/wk 2 yr				0.56 (alveolar/bronchiolar carcinoma)	NTP 2002 VANADIUM PENTOXIDE	

a The number corresponds to entries in Figure 3-1

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 0.0008 mg vanadium/m3; concentration adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the Regional Deposited Dose Ratio (RDDR) of 0.732 for the thoracic region, and divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to human with dosimetric adjustment, and 10 for human variability).

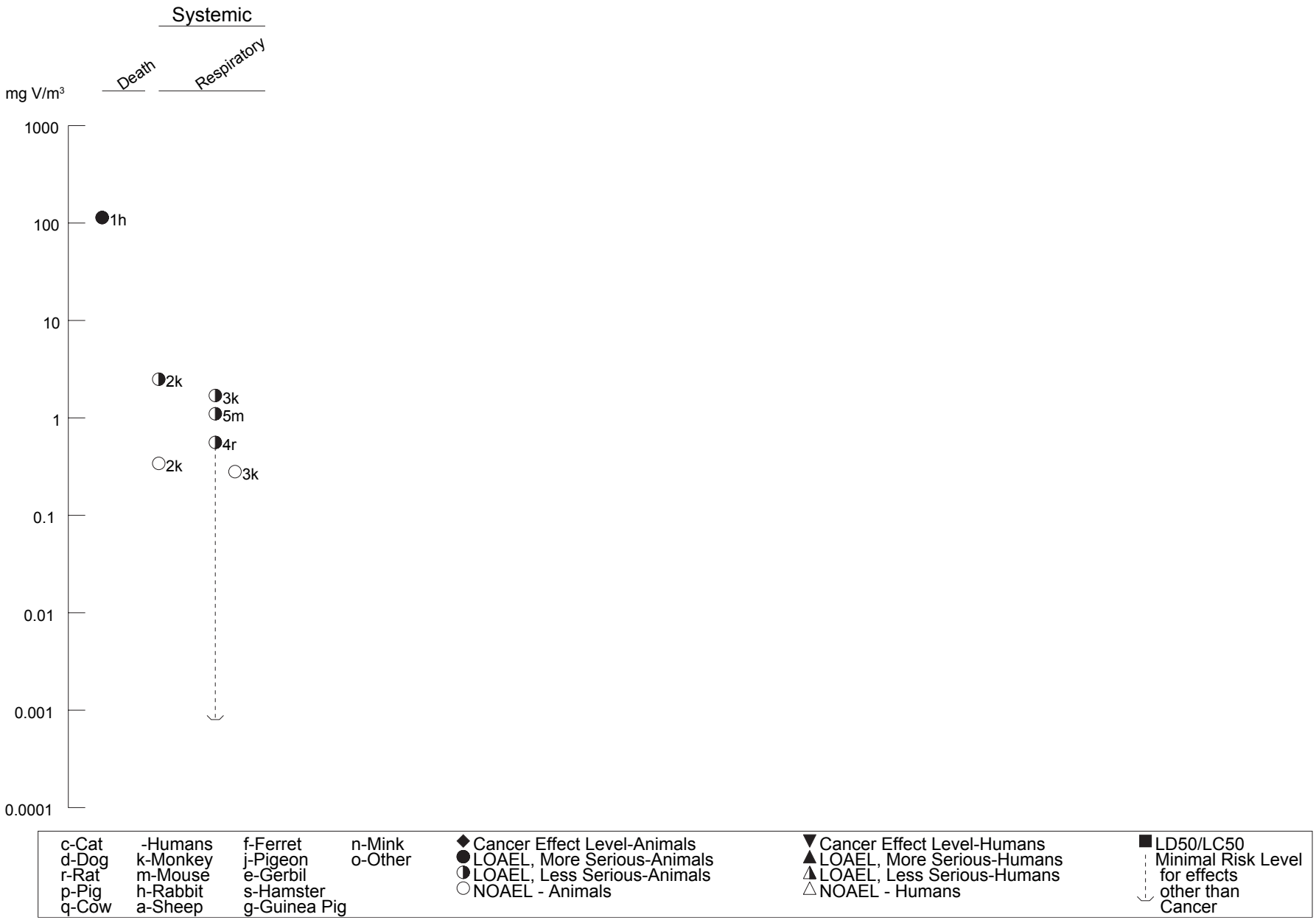
c Used to derive a chronic-duration inhalation MRL of 0.0001 mg vanadium/m3 calculated using benchmark dose analysis. The BMCL10 of 0.04 mg vanadium/m3 was adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days), multiplied by the RDDR of 0.423 for the extrathoracic region, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gastro = gastrointestinal hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); yr = year(s)

DRAFT FOR PUBLIC COMMENT

Figure 3-1 Levels of Significant Exposure to Vanadium - Inhalation

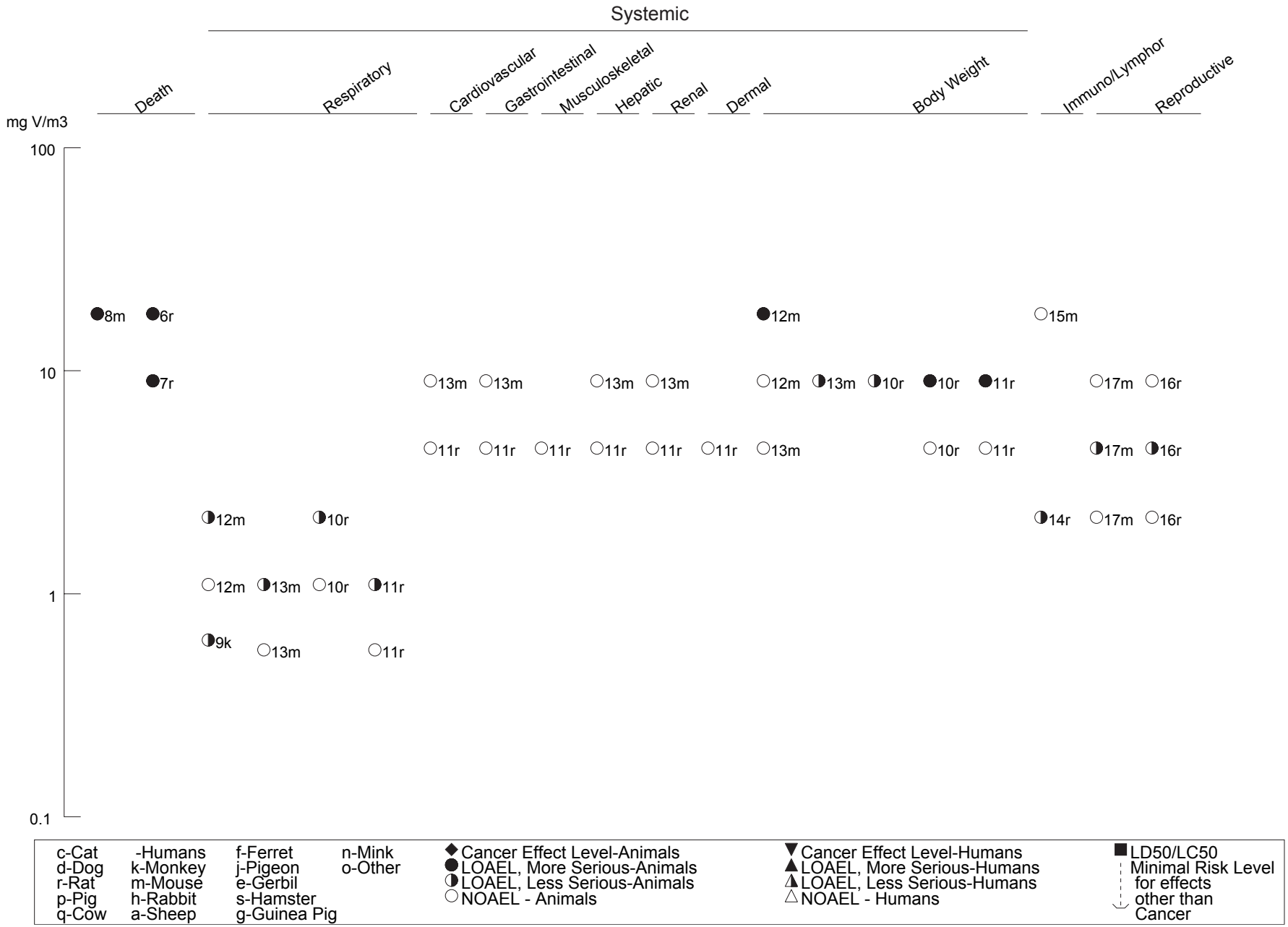
Acute (≤14 days)



DRAFT FOR PUBLIC COMMENT

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

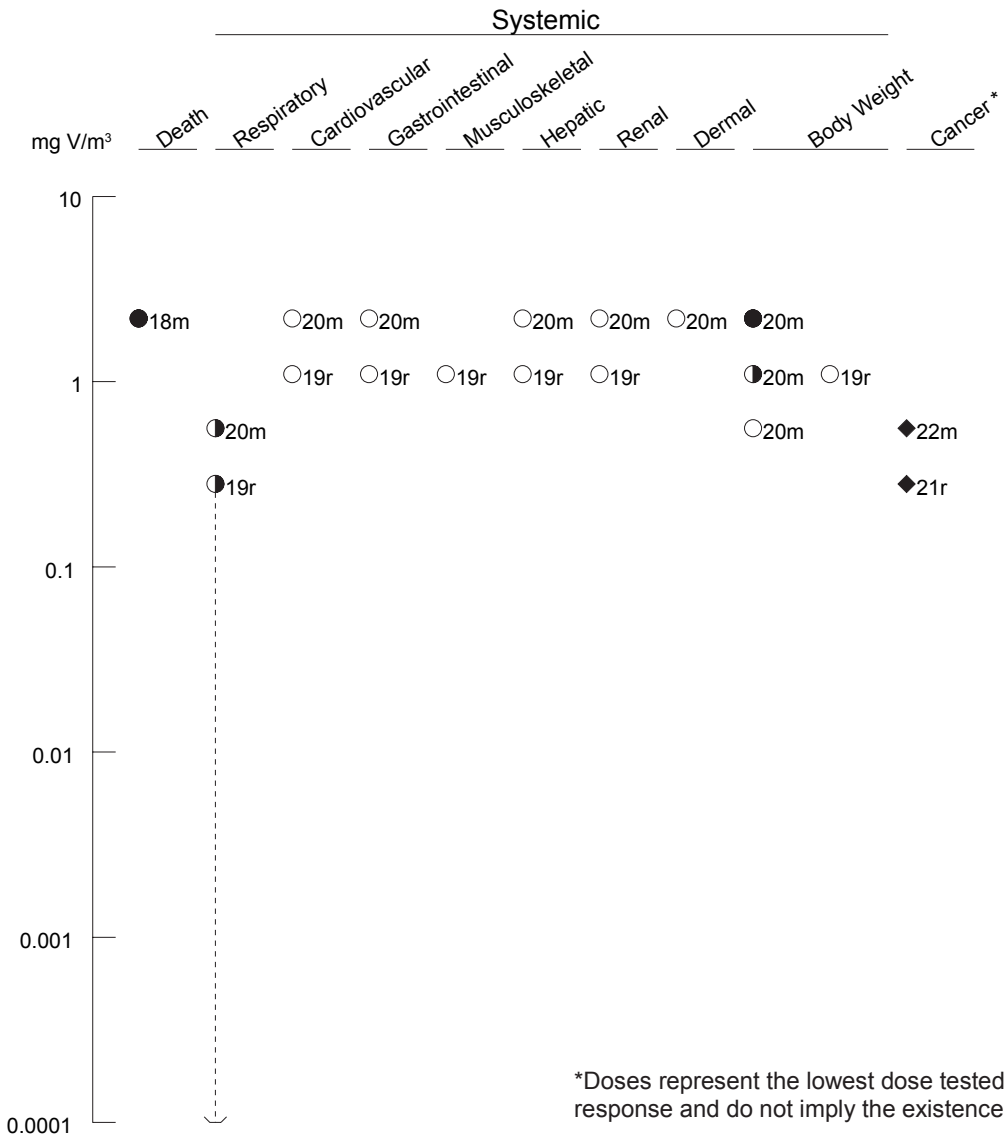
Intermediate (15-364 days)



DRAFT FOR PUBLIC COMMENT

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

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

DRAFT FOR PUBLIC COMMENT

Animal data support the human findings and provide additional evidence that vanadium compounds are respiratory toxicants. Signs of respiratory distress, impaired lung function, increased pulmonary reactivity, and histological alterations in the lungs, larynx, and nasal cavity have been observed in laboratory animals. Rapid respiration during the exposure period was observed in rats exposed to 9.0 mg vanadium/m^3 as vanadium pentoxide for 16 days or 4.5 mg vanadium/m^3 for 4 weeks. In rats exposed to 9.0 mg vanadium/m^3 for 9 weeks, abnormal respiration was also observed during periods between vanadium exposures (NTP 2002). Audible wheezing and coughing were observed in monkeys exposed to 0.62 mg vanadium/m^3 for 6 hours; respiratory symptoms were not observed at 0.14 or 0.028 mg vanadium/m^3 as vanadium pentoxide (Knecht et al. 1992).

Decreases in pulmonary function were observed in rats exposed to ≥2.2 mg vanadium/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 2002). Exposure to 2.2 or 4.5 mg vanadium/m^3 resulted in alterations characterized as restrictive based on reduced lung compliance, changes in breathing measurements, impaired capacity to diffuse carbon monoxide, reduced static and dynamic lung volumes, and exaggerated airflow. The changes in breathing mechanics, static lung volumes, and forced expiratory maneuvers observed at 9.0 mg vanadium/m^3 were suggestive of an obstructive lung disease; however, the investigators noted that these alterations may have been due to the deteriorating condition of the rats rather than an obstructive disease. Increased pulmonary resistance was observed in monkeys 1 day after a 6-hour exposure to 2.8 mg vanadium/m^3 (Knecht et al. 1985). Pulmonary reactivity, as evidenced by an obstructive pattern of impaired pulmonary function, was also observed in monkeys following a 6-hour exposure to 1.7 mg vanadium/m^3 as vanadium pentoxide (Knecht et al. 1992); an increase in the total number of inflammatory cells present in the lungs was also observed. A similar degree of pulmonary reactivity was observed when the monkeys were re-challenged with methacholine following a 26-week exposure to 0.28 mg vanadium/m^3 (6 hours/day, 5 days/week). Pulmonary reactivity was not significantly affected by a provocation challenge with 0.28 mg vanadium/m^3 before or after the 26-week exposure (Knecht et al. 1992).

NTP (2002) conducted a series of studies to evaluate the toxicity of vanadium pentoxide in rats and mice exposed 6 hours/day, 5 days/week for acute, intermediate, and chronic durations. Histological alterations were observed in the lungs, larynx, and nose. In the lungs, hyperplasia of alveolar and bronchiolar epithelium occurred at 1.1 mg vanadium/m^3 in rats and mice exposed for 6, 13, or 90 days, 0.28 mg vanadium/m^3 in rats exposed for 2 years, and 0.56 mg vanadium/m^3 in mice exposed for 2 years. Lung inflammation and histiocytic infiltration (alveolar macrophages) were observed at similar concentrations in the acute, intermediate, and chronic duration studies. Fibrosis was also observed in rats exposed to

2.2 mg vanadium/m^3 for 13 or 90 days or 0.28 mg vanadium/m^3 for 2 years and in mice exposed to 1.1 mg vanadium/m^3 for 2 years. In both species, the severity of the lung lesions increased with increasing exposure duration and vanadium pentoxide exposure level. NTP (2002) also conducted several studies to examine the time course of the lung lesions. In rats exposed to 2.2 mg vanadium/m^3, histiocytic infiltrates and inflammation were observed after 2 days of exposure and alveolar and bronchiolar epithelial hyperplasia were first observed after 5 days of exposure to 1.1 or 2.2 mg vanadium/m^3. In rats exposed to 0.56 mg vanadium/m^3, hyperplasia was only observed in a few animals after 542 days of exposure; however, at the end of the 2-year study, there was a significant increase in the incidence at this exposure level. In mice, lung lesions were not observed after 1 or 2 days of exposure. Bronchiolar epithelial hyperplasia and inflammation were observed after 5 days of exposure to 2.2 mg vanadium/m^3. At the lower exposure levels, lung lesions were observed after 12 days of exposure to 1.1 mg vanadium/m^3 and 54 days of exposure to 0.56 mg vanadium/m^3.

The nasal effects observed in rats consisted of hyperplasia and squamous metaplasia of respiratory epithelium at 2.2 mg vanadium/m^3 for 13 weeks, inflammation at 9.0 mg vanadium/m^3 for 13 weeks, and goblet cell hyperplasia of the respiratory epithelium at 0.28 mg vanadium/m^3 for 2 years. In mice exposed to vanadium pentoxide for 2 years, the nasal effects included suppurative inflammation at 1.1 mg vanadium/m^3, olfactory epithelium atrophy at 0.56 mg vanadium/m^3, hyaline degeneration of olfactory and respiratory epithelium at 0.56 mg vanadium/m^3, and squamous metaplasia of respiratory epithelium at 0.56 mg vanadium/m^3. Chronic exposure also resulted in damage to the larynx; degeneration and hyperplasia of the epiglottis epithelium were observed in rats exposed to 0.28 mg vanadium/m^3 and squamous metaplasia of epiglottis epithelium was observed in rats exposed to 1.1 mg vanadium/m^3 and mice exposed to 0.56 mg vanadium/m^3.

Cardiovascular Effects. Workers exposed chronically to vanadium pentoxide dusts at incompletely documented exposure levels had normal blood pressure values (Vintinner et al. 1955). No other cardiovascular parameters were investigated in this study, but another study revealed normal electrocardiograms in vanadium workers (Sjöberg 1950).

No significant alterations in heart rate, blood pressure, or electrocardiogram readings were observed in rats exposed to 4.5 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks (NTP 2002). Decreases in heart rate and blood pressure were found in rats exposed to 9.0 mg vanadium/m^3; however, this was attributed to the poor condition of the animals rather than a direct cardiotoxic effect. No histological alterations were observed in the hearts of rats exposed to 4.5 or 1.1 mg vanadium/m^3

6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Gastrointestinal Effects. No gastrointestinal complaints were reported by subjects exposed to 0.6 or 0.1 mg vanadium/m^3 vanadium pentoxide dusts for 8 hours (Zenz and Berg 1967). Workers exposed to vanadium in oil-burner ashes also did not show gastrointestinal symptoms (Sjöberg 1950). One study found that workers exposed chronically to vanadium dusts in factories sometimes complained of nausea and vomiting (Levy et al. 1984), but these symptoms can have a number of causes (such as exposure to other substances) and cannot be directly attributed to the vanadium. No histological alterations were observed in the gastrointestinal tract of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively, (NTP 2002).

Hematological Effects. No hematological alterations were observed in humans following acute (Zenz and Berg 1967) or occupational exposure (Kiviluoto et al. 1981a; Sjöberg 1950; Vintinner et al. 1955) to vanadium dusts.

During the first 23 days of a 13-week study, minimal erythrocyte microcytosis (as evidenced by decreases in hematocrit values, hemoglobin, mean cell volume, and mean cell hemoglobin) was observed in rats exposed to vanadium pentoxide 6 hours/day, 5 days/week (NTP 2002). The alterations in hematocrit and hemoglobin were observed after 4 days of exposure to 1.1 mg vanadium/m^3, mean cell volume and mean cell hemoglobin were decreased after 23 or 90 days of exposure to 2.2 mg vanadium/m^3. At 13 weeks, the microcytosis was replaced by erythrocytosis (as evidenced by increases in hemoglobin, hematocrit, nucleated erythrocytes, and reticulocytes) in rats exposed to 4.5 or 9.0 mg vanadium/m^3.

Musculoskeletal Effects. Muscular strength was not altered in one study of workers exposed to vanadium pentoxide (Vintinner et al. 1955). No significant histological alterations were observed in the bone or muscle following a 13-week or 2-year exposure of rats to 9.0 or 1.1 mg vanadium/m^3 as vanadium pentoxide, respectively, or mice to 9.0 or 2.2 mg vanadium/m^3, respectively.

Hepatic Effects. Workers exposed chronically to 0.01–0.5 mg/m^3 of vanadium dusts had normal serum levels of four enzymes (serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase) that are commonly used to detect possible liver damage (Kiviluoto et al. 1981a).

Significant increases in serum ALT levels were observed in rats exposed to 4.5 mg vanadium/m^3 6 hours/day, 5 days/week for 13 weeks (NTP 2002). However, this alteration was not considered to be biologically relevant because it was not associated with histological alterations in the liver. No histological alterations were observed in the livers of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Renal Effects. Workers exposed chronically to 0.01–0.5 mg/m^3 of vanadium dusts had normal serum levels of electrolytes, creatinine, and urea, suggesting no alterations in renal function (Kiviluoto et al. 1981b). Workers in other studies of chronic exposure to vanadium had normal urine levels of substances used to detect kidney disease (casts, protein levels, urea) (Sjöberg 1950; Vintinner et al. 1955).

Significant increases in serum urea nitrogen concentration were observed in male rats exposed to 4.5 mg vanadium/m^3 for 13 weeks and females exposed to 2.2 mg vanadium/m^3 for 23 days (but not after 13 weeks of exposure) (NTP 2002). However, because decreases in total protein and creatinine concentration were also observed, the urea nitrogen alteration was attributed to decreased body weight rather than an effect on renal clearance. A decrease in overnight urine volumes and increase in urine specific gravity were observed in rats exposed to 2.2 mg vanadium/m^3 for 13 weeks (NTP 2002). No alterations in urine volume or specific gravity were observed in urine samples collected after a 16-hour water deprivation period, suggesting that the alterations observed in the overnight urine sample were reflective of dehydration rather than altered kidney function. No histological alterations were observed in the kidneys of rats exposed to 4.5 or 1.1 mg vanadium/m^3 as vanadium pentoxide 6 hours/day, 5 days/week for 13 weeks or 2 years, respectively, or mice exposed to 9.0 or 2.2 mg vanadium/m^3 for 13 weeks or 2 years, respectively (NTP 2002).

Dermal Effects. No increases in the occurrence of dermatitis were observed in vanadium pentoxide workers (Vintinner et al. 1955); increases in skin rashes were observed in some workers (NIOSH 1983). No histological alterations of the skin were observed in rats and mice following intermediate- or chronic-duration exposure to vanadium pentoxide (NTP 2002).

Ocular Effects. Workers chronically exposed to vanadium dusts in factories had slight to moderate eye irritation (Levy et al. 1984; Lewis 1959; Sjöberg 1950; Thomas and Stiebris 1956; Vintinner et al. 1955). Brief exposure to vanadium dust can also cause conjunctivitis (Zenz et al. 1962).

Body Weight Effects. Workers exposed to vanadium ore dust reported weight loss (Vintinner et al. 1955). Significant decreases in body weight gain have been observed in rats and mice exposed to vanadium pentoxide (6 hours/day, 5 days/week) for intermediate or chronic durations (NTP 2002). The LOAELs were 9.0 mg vanadium/m^3 for rats exposed for 16 or 90 days, 18 mg vanadium/m^3 for mice exposed for 16 days, 9.0 mg vanadium/m^3 for mice exposed for 90 days, and 1.1 mg vanadium/m^3 for mice exposed for 2 years. At lower concentrations, the decreases were within 10% of the controls. Marked decreases in body weight gain (approximately 30% or higher) were observed at lethal concentrations.

3.2.1.3 Immunological and Lymphoreticular Effects

The only human data located found that workers chronically exposed to unspecified levels of vanadium dusts in factories showed no significant signs of allergic reactions on the skin or in the respiratory system (Sjöberg 1950). This, however, cannot be considered to be an adequate evaluation of immunological function. Systemic immunity was evaluated in rats and mice exposed to vanadium pentoxide 6 hours/day, 5 days/week for 16 days (NTP 2002). Significant decreases in *in vitro* phagocytosis and increases *in vivo* bactericidal activity were observed in rats exposed to ≥2.2 mg vanadium/m^3. No adverse effect on the response to *Klebsiella pneumoniae* or to the influenza virus were observed in mice exposed to 18 mg vanadium/m^3.

3.2.1.4 Neurological Effects

Most workers exposed to vanadium dusts did not report major adverse neurological signs (Sjöberg 1956; Vintinner et al. 1955). However, some workers complained of dizziness, depression, headache, or tremors of the fingers and arms (Levy et al. 1984; Vintinner et al. 1955), which may or may not have been specifically due to vanadium exposure. No histological alterations were observed in the nervous system following a 13-week or 2-year exposure of rats to 4.5 or 1.1 mg vanadium/m^3, respectively, or mice to 9.0 or 2.2 mg vanadium/m^3, respectively (NTP 2002). Because the NTP (2002) study did not assess neurological function, these NOAELs are not listed in Table 3-1 or Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding the reproductive effects in humans after inhalation exposure to vanadium. There are limited data on the potential reproductive toxicity of vanadium in animals following

inhalation exposure. No histological alterations were observed in rats exposed to 9.0 mg vanadium/m^3 as vanadium pentoxide for 3 months or 1.1 mg vanadium/m^3 for 2 years or in mice exposed to 9.0 mg vanadium/m^3 for 3 months or 2.2 mg vanadium/m^3 for 2 years (NTP 2002). No significant alterations in sperm count, motility, or concentration were observed in rats exposed to 9.0 mg vanadium/m^3 for 3 months (NTP 2002). In females exposed to 4.5 mg vanadium/m^3 as vanadium pentoxide for 3 months, significant increases in estrous cycle length were observed (NTP 2002); at 9.0 mg vanadium/m^3, the number of cycling females was significantly reduced. No studies examined reproductive function.

3.2.1.6 Developmental Effects

No studies were located regarding the developmental effects in humans or animals after inhalation exposure to vanadium.

3.2.1.7 Cancer

No studies were located regarding the carcinogenicity in humans after inhalation exposure to vanadium. NTP (2002) examined the carcinogenic potential of vanadium in rats and mice exposed to vanadium pentoxide 6 hours/day, 5 days/week for 2 years. Increases in the incidence of alveolar/bronchiolar adenoma, carcinoma, or the combined incidences of adenoma and carcinoma were observed in male rats. As indicated in Table 3-2, the incidences of these tumors were not statistically different from controls; however, the incidence of adenomas at 0.28 mg vanadium/m^3 and combined incidence of adenoma and carcinoma at 0.56 or 1.1 mg vanadium/m^3 were greater than historical control levels. Due to the rarity of these tumors, NTP considered the increases in adenoma and carcinoma observed in male rats to be related to vanadium pentoxide exposure. In female rats, no significant increases in lung tumors were observed. In the 0.28 mg vanadium/m^3 group, the incidence of alveolar/bronchiolar adenoma exceeded the historical control range. NTP (2002) noted that this may be related to vanadium pentoxide exposure; however, because it was only observed at the lowest vanadium pentoxide concentration, a clear relationship between lung neoplasms and vanadium pentoxide could not be determined in female rats. In male mice, significant increases in the incidence of alveolar/bronchiolar carcinoma and the combined incidence of alveolar/bronchiolar adenoma and carcinoma were observed at 0.56, 1.1, and 2.2 mg vanadium/m^3; an increased incidence of alveolar/bronchiolar adenoma was observed at 1.1 mg vanadium/m^3. In female mice, the incidences of alveolar/bronchiolar adenoma or carcinoma and the combined incidence of adenoma and carcinoma were significantly elevated in the 0.56, 1.1, and 2.2 mg vanadium/m^3 groups. As presented in Table 3-2, the tumor incidences in the male and female mice were not concentration-related. Based on vanadium lung burden studies in female rats and mice exposed to vanadium pentoxide, NTP

Table 3-2. Incidence of Lung Tumors in Rats and Mice Exposed to Vanadium Pentoxide for 2 Years[a]

	Concentration (mg vanadium/m^3)			
	0	0.28	0.56	1.1
Rats				
Male				
Alveolar/bronchiolar adenoma, multiple	0/50	2/49	0/48	0/50
Alveolar/bronchiolar adenoma (includes multiple)[b]	4/50	8/49	5/48	6/50
Alveolar/bronchiolar carcinoma, multiple	0/50	1/49	0/48	0/50
Alveolar/bronchiolar carcinoma (includes multiple)[c]	0/50	3/49	1/48	3/50
Alveolar/bronchiolar adenoma or carcinoma[d]	4/50	10/49	6/48	9/50
Female				
Alveolar/bronchiolar adenoma	0/49	3/49	1/50	0/50
Alveolar/bronchiolar carcinoma	0/49	0/49	0/50	1/50
Alveolar/bronchiolar adenoma or carcinoma	0/49	3/49	1/50	1/50
Mice	0	0.56	1.1	2.2
Male				
Alveolar/bronchiolar adenoma, multiple	1/50	1/50	11/50[e]	5/50
Alveolar/bronchiolar adenoma (includes multiple)	13/50	16/50	26/50[e]	15/50
Alveolar/bronchiolar carcinoma, multiple	1/50	10/50[e]	16/50[e]	13/50[e]
Alveolar/bronchiolar carcinoma (includes multiple)	12/50	29/50	30/50	35/50
Alveolar/bronchiolar adenoma or carcinoma	22/50	42/50[e]	43/50[e]	43/50[e]
Female	0	0.28	0.56	1.1
Alveolar/bronchiolar adenoma, multiple	0/50	3/50	5/50[e]	6/50[e]
alveolar/bronchiolar adenoma (includes multiple)	1/50	17/50[e]	23/50[e]	19/50[e]
Alveolar/bronchiolar carcinoma, multiple	0/50	9/50[e]	5/50[e]	5/50[e]
Alveolar/bronchiolar carcinoma (includes multiple)	0/50	23/50[e]	18/50[e]	22/50[e]
Alveolar/bronchiolar adenoma or carcinoma	1/50	32/50[e]	35/50[e]	32/50[e]

[a]Animals were exposed for 6 hours/day, 5 days/week
[b]Historical incidence for 2-year studies with controls given NTP-2000 diet (mean ±standard deviation): 4.2±3.5%, range 0–12%; with inhalation chamber controls given NIH-07 diet: 1.7±2.4%, range 0–10%
[c]Historical incidence for NTP-2000: diet 0.4±0.8%, range 0–2%; NIH-07 diet: 0.8±1.2%, range 0–10%
[d]Historical incidence for NTP-2000: diet 4.5±3.9%, range 0–14%; NIH-07 diet: 2.5±2.6%, range 0–10%
[e]$p \leq 0.01$

Source: NTP 2002

(2002) estimated that the total vanadium lung "doses" were 130, 175, and 308 μg vanadium in rats exposed to 0.28, 0.56, or 1.1 mg vanadium/m^3 for 540 days and 153, 162, and 225 μg vanadium in mice exposed to 0.56, 1.1, or 2.2 mg vanadium/m^3 for 553 days. In both species, the similarity of the total dose at the two lower concentrations (total lung doses of 130 and 175 μg vanadium in rats exposed to 0.28 and 0.56 mg vanadium/m^3 and 153 and 162 μg vanadium in mice exposed to 0.56 and 1.1 mg vanadium/m^3) provides a partial explanation for the flat dose-response curve for lung tumors. NTP (2002) also suggested that the differences in lung tumor responses between the rats and mice may be due to finding that mice received considerably more vanadium on a body weight basis than rats.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to vanadium.

The 14-day LD_{50} values for sodium metavanadate are 41 mg vanadium/kg in rats and 31.2 mg vanadium/kg in mice (Llobet and Domingo 1984). Deaths have been reported in rat dams exposed to 17 mg vanadium/kg/day as sodium orthovanadate on gestation days 6–15 (Sanchez et al. 1991) and in rats exposed to 22.06 or 24.47 mg vanadium/kg/day as ammonium metavanadate for 4 weeks (Zaporowska and Wasilewski 1989, 1990). Although the cause of death was not determined, marked decreases in body weight, food intake, and water consumption and increases in the occurrence of diarrhea were observed in animals dying early. Chronic exposures of up to 19 mg vanadium/kg as vanadyl sulfate in food or water did not affect mortality in rats or mice (Dai et al. 1994a, 1994b; Schroeder and Balassa 1967; Schroeder et al. 1970).

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

No studies were located regarding musculoskeletal or dermal/ocular effects in humans or animals following oral exposure to vanadium.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to vanadium. Rats receiving sodium metavanadate in the drinking water for 3 months had

Table 3-3 Levels of Significant Exposure to Vanadium - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat	1 d 1 x/d (GW)				41 (LD50)	Llobet and Domingo 1984 SODIUM METAVANADATE	
2	Mouse	once (GW)				31 (LD50)	Llobet and Domingo 1984 SODIUM METAVANADATE	
3	Mouse (Swiss)	Gd 6-15 (G)				17 F (17/19 dams died)	Sanchez et al. 1991 SODIUM ORTHOVANADATE	
Systemic								
4	Rat (Wistar)	2 wk (W)	Hemato		27.72 M (increased reticulocytes, increased polychromatophilic erythroblasts in bone marrow)		Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
			Bd Wt	27.65 F				
5	Mouse (Swiss)	Gd 6-15 (G)	Bd Wt			7.5 F (46% decrease in maternal weight gain)	Paternain et al. 1990 VANADYL SULFATE	
Developmental								
6	Rat	Gd 6-14 (G)		4.2	8.4 (facial hemorrhages)		Paternain et al. 1987 SODIUM METAVANADATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
7	Mouse (Swiss)	Gd 6-15 (G)			7.5 F (increased early resorptions, decreased fetal growth, increased soft tissue and skeletal defects)		Paternain et al. 1990 VANADYL SULFATE	
8	Mouse (Swiss)	Gd 6-15 (G)		4.2	8.3 (decreased number of ossified sacrococcygeal vertebrae)		Sanchez et al. 1991 SODIUM ORTHOVANADATE	
INTERMEDIATE EXPOSURE								
Death								
9	Rat (Wistar)	4 or 8 wk (W)				24.47 M (10/32 animals died by week 4)	Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
10	Rat (Wistar)	4 wk (W)				22.06 M (12/20 rats died)	Zaporowska and Wasilewski 1990 AMMONIUM METAVANADATE	
Systemic								
11	Human	45-68 d (C)	Hemato	0.19			Dimond et al. 1963 AMMONIUM VANADYL TARTRATE	
			Hepatic	0.19				
			Renal	0.19				

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
12	Human	daily 12 wk (C)	Cardio	0.12			Fawcett et al. 1997 VANADYL SULFATE	
			Hemato	0.12[b]				
			Hepatic	0.12				
			Bd Wt	0.12				
13	Rat (Wistar)	10 wk (F)	Hemato	1 F	2.1 F (decreased hemoglobin and hematocrit, increased reticulocyte)		Adachi et al. 2000 SODIUM METAVANADATE	
			Bd Wt	2.1 F				
14	Rat (Swiss)	60 d (G)	Cardio		31 M (decreased aorta diameter)		Akgun-Dar et al. 2007 VANADYL SULFATE	
			Metab	31 M				
15	Rat (Sprague-Dawley)	210 d (W)	Resp	4.7 M			Boscolo et al. 1994 SODIUM METAVANADATE	
			Cardio		0.12 M (increased blood pressure)			
			Hepatic	4.7 M				

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Rat (Sabra)	4 wk (W)	Cardio	22 M			Bursztyn and Mekler 1993 SODIUM METAVANADATE	
			Metab	22 M				
17	Rat (Sprague-Dawley)	7 mo (W)	Cardio		12 M (increased blood pressure and heart rate)		Carmagnani et al. 1991 SODIUM METAVANADATE	
18	Rat (Sprague-Dawley)	7 mo (W)	Cardio		1.2 M (increased blood pressure)		Carmagnani et al. 1992 SODIUM METAVANADATE	
19	Rat (Wistar)	12 wk (W)	Hemato	9.7 M			Dai et al. 1995 AMMONIUM METAVANADATE	
			Bd Wt	9.7 M				
20	Rat (Wistar)	12 wk (W)	Hemato	7.6 M			Dai et al. 1995 VANADYL SULFATE	
			Bd Wt	7.6 M				
21	Rat (Sprague-Dawley)	Gd 0- Ld 21 (F)	Bd Wt		6 F (19% decrease in maternal body weight gain)		Elefant and Keen 1987 SODIUM METAVANADATE	
22	Rat (Wistar)	60 d (G)	Bd Wt	31 M			Jain et al. 2007 VANADYL SULFATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
23	Rat (Wistar)	75 or 103 d (F)	Hemato	6.6 M			Mountain et al. 1953 VANADIUM PENTOXIDE	
			Bd Wt	6.6 M		30 M (53% decrease in body weight gain)		
24	Rat (Sprague-Dawley)	8 wk (G)	Bd Wt	3.42 M	6.84 M (10% decrease in body weight gain)		Sanchez et al. 1998 SODIUM METAVANADATE	
25	Rat (Wistar)	6 wk (W)	Hemato		8.35 M (increased erythrocyte levels)		Scibior 2005 SODIUM METAVANADATE	
			Bd Wt	8.35 M				
26	Rat (Wistar)	6 wk (W)	Hemato		10.69 M (decreased erythrocyte and hemoglobin levels)		Scibior et al. 2006 SODIUM METAVANADATE	
27	Rat (Long- Evans)	2 mo (F)	Cardio		10 M (increased ventricular pressure)		Susic and Kentera 1986 AMMONIUM METAVANADATE	
28	Rat (Sprague-Dawley)	7.4 wk (W)	Metab	13 M			Yao et al. 1997 VANADYL SULFATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
29	Rat (Wistar)	4 or 8 wk (W)	Hemato		24.47 M (decreased erythroctyes, increased reticulocytes)		Zaporowska and Wasilewski 1989 AMMONIUM METAVANADATE	
30	Rat (Wistar)	4 wk (W)	Hemato		22.06 M (decreased erythrocyte, increased reticulocyte)		Zaporowska and Wasilewski 1990 AMMONIUM METAVANADATE	
31	Rat (Wistar)	4 wk (W)	Hemato		19.73 M (decreased hemoglobin and erythrocyte and increased reticulocyte)		Zaporowska and Wasilewski 1991 AMMONIUM METAVANADATE	
32	Rat (Wistar)	4 wk (W)	Gastro		19.73 (diarrhea)		Zaporowska and Wasilewski 1992a AMMONIUM METAVANADATE	
			Hemato		19.73 M (decreased hemoglobin and erythrocyte and increased reticulocyte)			
33	Rat (Wistar)	4 wk (W)	Hemato		12.99 M (decreased hemoglobin and erythrocyte and increased reticulocyte)		Zaporowska and Wasilewski 1992b AMMONIUM METAVANADATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
34	Rat (Wistar)	4 wk (W)	Hemato		1.18 M (decreased erythrocyte levels)		Zaporowska et al. 1993 AMMONIUM METAVANADATE	
			Bd Wt	4.93 M				
35	Rabbit (NS)	24, 129, or 171 d (W)	Hemato		1.8 (decreased erythrocyte levels)		Kasibhatla and Rai 1993 Not Reported	
Immuno/ Lymphoret								
36	Rat (Wistar)	10 wk (F)		1 F	2.1 F (decreased B-cell, IgG, and IgM levels)		Adachi et al. 2000 SODIUM METAVANADATE	
Neurological								
37	Rat (Sprague-Dawley)	8 wk (G)			1.72 M (impaired performance on neurobehavioral tests)		Sanchez et al. 1998 SODIUM METAVANADATE	
38	Rat (Sprague-Dawley)	daily 8 wk (GW)			6.84 M (impaired response in active avoidance tests)		Sanchez et al. 1999 SODIUM METAVANADATE	
Reproductive								
39	Rat (Sprague-Dawley)	60 d (GW)		8.4			Domingo et al. 1986 SODIUM METAVANADATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL: Less Serious (mg V/kg/day)	LOAEL: Serious (mg V/kg/day)	Reference Chemical Form	Comments
40	Rat (Wistar)	60 d (G)			31 M (decreased fertility, sperm count, and motility)		Jain et al. 2007 VANADYL SULFATE	
41	Rat (Sprague-Dawley)	M: 70 d F:14 d premating, mating, gestation, lactation (W)			10 M (decreased fertility) 12 F (decreased fertility)		Morgan and El-Tawil 2003 AMMONIUM METAVANADATE	
42	Mouse (Swiss)	64 d (W)		17 M	25 M (decreased fertility and spermatozoa count)		Llobet et al. 1993 SODIUM METAVANADATE	
Developmental								
43	Rat (Sprague-Dawley)	60 d (G)			2.1 (reduced pup weight and length)		Domingo et al. 1986 SODIUM METAVANADATE	
44	Rat (Sprague-Dawley)	Gd 0- Ld 21 (F)				6 (decreased pup survival and body weight)	Elefant and Keen 1987 SODIUM METAVANADATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
45	Rat (Sprague-Dawley)	M: 70 d F:14 d premating, mating, gestation, lactation (W)			10 M (decreased viability, increased gross, skeletal and visceral anomalies, decreased pup body weight)		Morgan and El-Tawil 2003 AMMONIUM METAVANADATE	
					12 F (decreased viability, increased gross, skeletal and visceral anomalies, decreased pup body weight)			
46	Rat (Wistar)	Gd 19- Ld 25, pups exposed until pnd 100 (W)				10 (decreased pup survival)	Poggioli et al. 2001 VANADYL SULFATE	
CHRONIC EXPOSURE								
Death								
47	Rat	2.5 yr (W)		0.7			Schroeder et al. 1970 VANADYL SULFATE	
48	Mouse	2 yr (F)		4.1			Schroeder and Balassa 1967 VANADYL SULFATE	
49	Mouse	2.5 yr (W)		0.54			Schroeder and Mitchner 1975 VANADYL SULFATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
Systemic								
50	Rat (Wistar)	52 wk (W)	Resp	19 M			Dai and McNeill 1994; Dai et al. 1994a, 1994b VANADYL SULFATE	
			Cardio	19 M				
			Hemato	19 M				
			Hepatic	19 M				
			Renal	19 M				
			Bd Wt	17 M	28 M (20% decrease in body weight gain)			
			Metab	19 M				
51	Rat	2.5 yr (W)	Renal	0.7			Schroeder et al. 1970 VANADYL SULFATE	
			Bd Wt	0.7				
52	Mouse	2 yr (F)	Resp	4.1			Schroeder and Balassa 1967 VANADYL SULFATE	
			Cardio	4.1				
			Hemato	4.1				
			Renal	4.1				
			Bd Wt	4.1				
53	Mouse	2.5 yr (W)	Bd Wt	0.54			Schroeder and Mitchner 1975 VANADYL SULFATE	

DRAFT FOR PUBLIC COMMENT

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

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg V/kg/day)	LOAEL Less Serious (mg V/kg/day)	LOAEL Serious (mg V/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
54	Mouse	2 yr (F)		4.1			Schroeder and Balassa 1967 VANADYL SULFATE	

a The number corresponds to entries in Figure 3-2

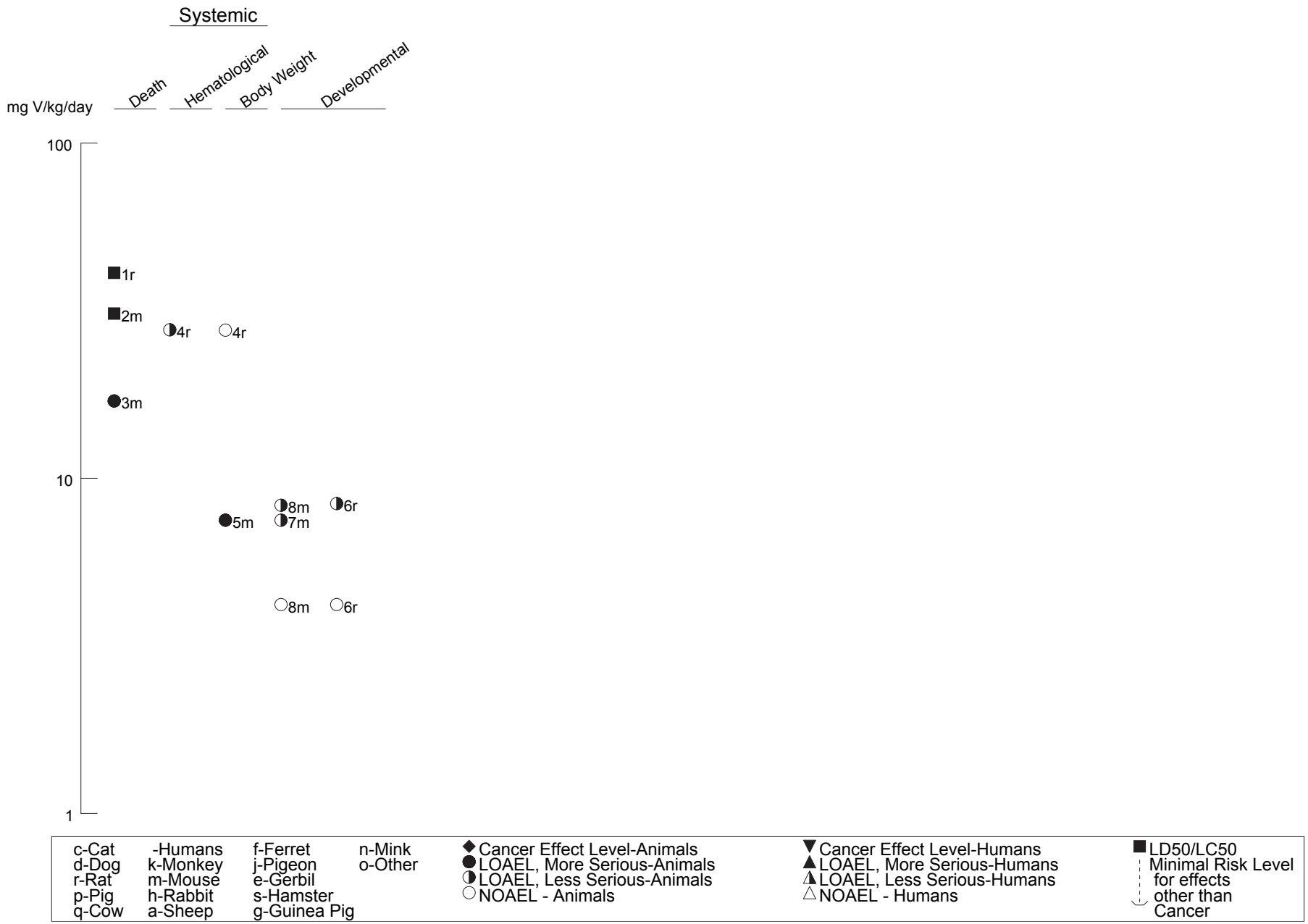
b Used to derive an intermediate-duration oral MRL of 0.01 mg vanadium/kg/day; dose divided by an uncertainty factor of 10 for human variability.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; pnd = post-natal day; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

DRAFT FOR PUBLIC COMMENT

Figure 3-2 Levels of Significant Exposure to Vanadium - Oral

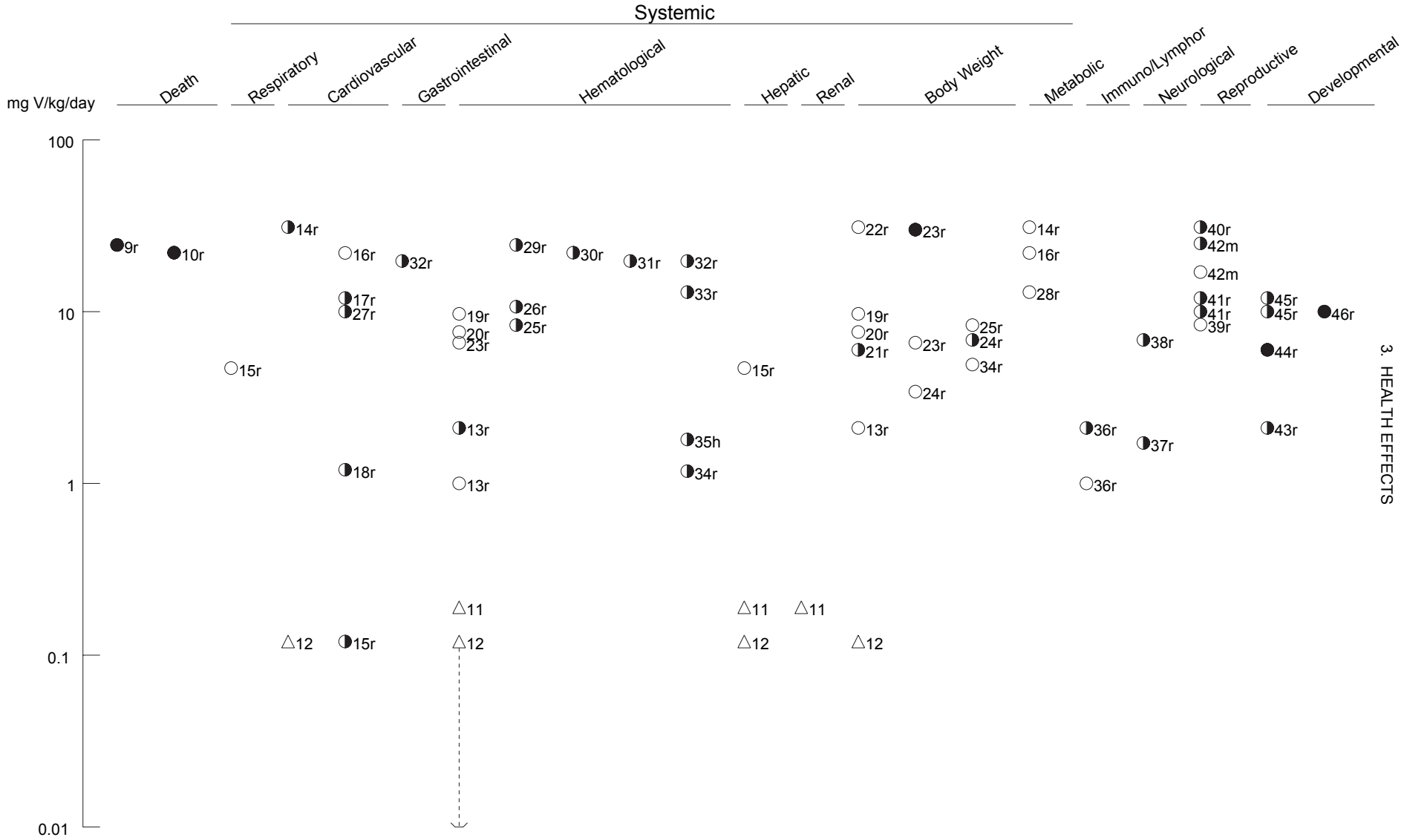
Acute (≤14 days)



DRAFT FOR PUBLIC COMMENT

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

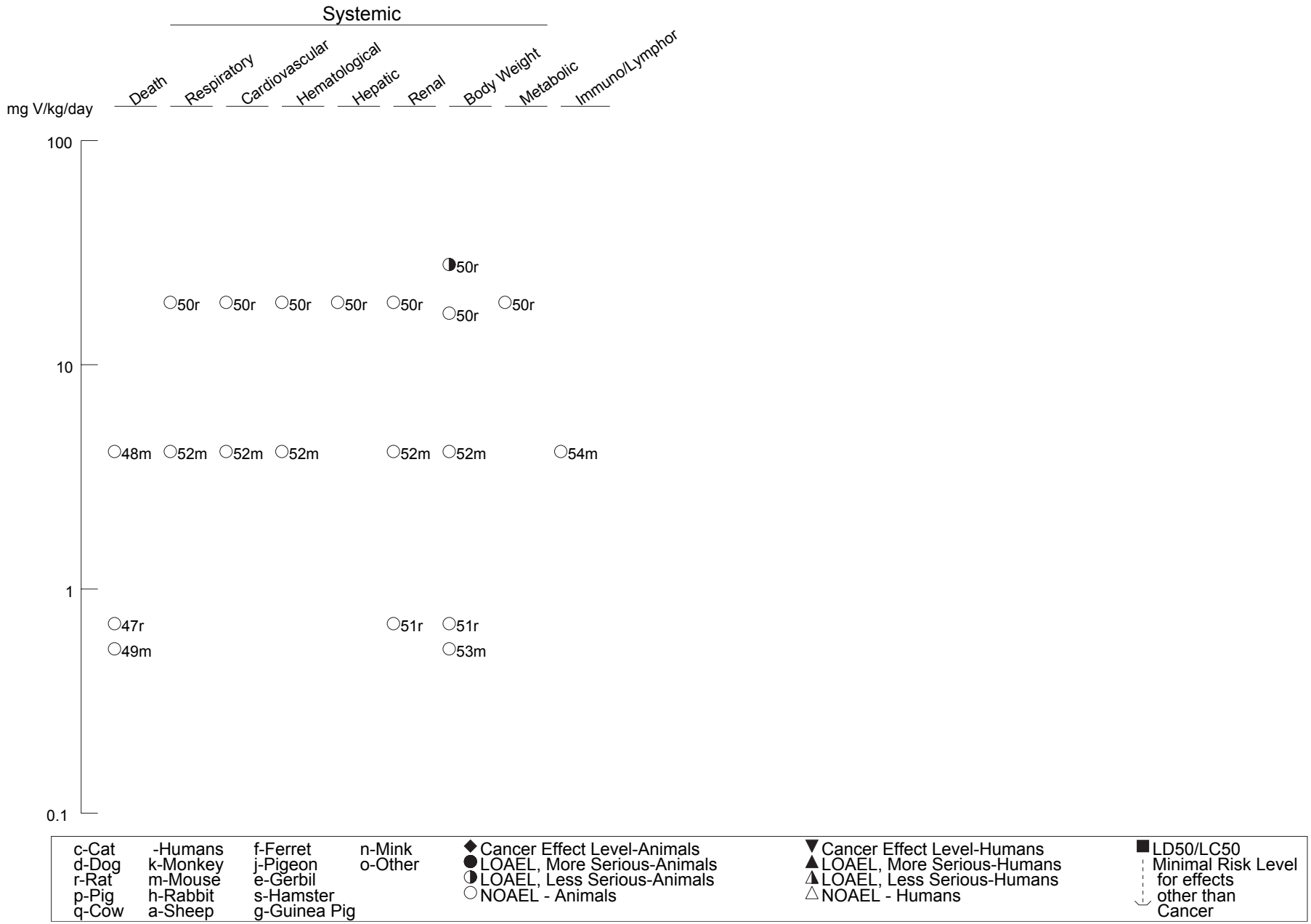
Intermediate (15-364 days)



DRAFT FOR PUBLIC COMMENT

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

Chronic (≥365 days)



DRAFT FOR PUBLIC COMMENT

mononuclear cell infiltration, mostly perivascular, in the lungs; the investigators noted that the effects were more evident at the highest dose level (3.5 mg vanadium/kg/day), but incidence data were not reported (Domingo et al. 1985).

Cardiovascular Effects. No significant alterations in systolic or diastolic blood pressure were observed in adults exposed to 0.12 mg vanadium/kg/day as vanadyl sulfate for 4, 8, or 12 weeks via capsules taken at mealtime (Fawcett et al. 1997).

Several studies have examined the effects of vanadium on blood pressure in laboratory animals. The results are inconsistent; however, differences in the methods used to measure blood pressure and the strains of rats tested complicate cross study comparisons. Significant increases in systolic, diastolic, and/or mean blood pressure were observed in Sprague-Dawley rats exposed to 0.12–12 mg vanadium/kg/day as sodium metavanadate in drinking water for 180–210 days (measured in femoral artery of anesthetized rats; Boscolo et al. 1994), in Sprague-Dawley rats exposed to 1.2–12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (measured in the aorta of anesthetized rats; Carmagnani et al. 1991, 1992), and Long-Evans rats exposed to 10 mg vanadium/kg/day as ammonium vanadate in the diet for 60 days (measured in ventricle of anesthetized rats; Sušić and Kentera 1986). In contrast, no alterations in blood pressure were observed in rats exposed to 10 mg vanadium/kg/day as ammonium vanadate in the diet for 60 days (Long-Evans rats, measured in femoral artery; Sušić and Kentera 1986), 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks (Sabra rats, measured via tail cuff; Bursztyn and Mekler 1993), 32 mg vanadium/kg/day as vanadyl sulfate in drinking water for 52 weeks (Wistar rats, measured via tail cuff; Dai and McNeill 1994), or 63 mg vanadium/kg/day as sodium metavanadate in the diet for 24 weeks (Long-Evans rats, measured via tail cuff or femoral artery; Sušić and Kentera 1988). Studies in compromised animals have also found alterations in blood pressure. Increases in arterial blood pressure (measured via tail cuff) were observed in salt-induced hypertensive rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks compared to hypertensive controls (Bursztyn and Mekler 1993). Similar increases in blood pressure (measured via tail cuff) were observed in uninephrectomized rats exposed to 6 mg vanadium/kg/day as sodium metavanadate in the diet for 18 weeks (Sušić and Kentera 1988) or 5 mg vanadium/kg/day as sodium orthovanadate in the diet (Steffen et al. 1981). Alterations in the renin-angiotensin-aldosterone system and alterations in urinary excretion of electrolytes observed in the Boscolo et al. (1994) study provide suggestive evidence that altered renal function may play a role in vanadium-induced hypertension. Significant increases in plasma renin activity, plasma aldosterone levels, and increases in kallikrein (enzyme that releases vasodilating kinins from plasma proteins), and

kininases I and II activities were observed in rats exposed to 1.2 or 4.7 mg vanadium/kg/day as sodium metavanadate in the drinking water for 7 months.

Other alterations in the cardiovascular system included significant decreases in aorta diameter and the aorta tunica intima thickness in rats administered 31 mg vanadium/kg/day as vanadyl sulfate via gavage for 60 days (Akgün-Dar et al. 2007) and an increase in heart rate in rats exposed to 12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Carmagnani et al. 1991, 1992), but not in rats exposed to ≤4.7 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Boscolo et al. 1994; Carmagnani et al. 1992) or 10 mg vanadium/kg/day as ammonium vanadate in the diet for 2 months (Sušić and Kentera 1986).

Gastrointestinal Effects. The limited data available for assessing gastrointestinal effects suggest that exposure to vanadium may cause mild gastrointestinal irritation. Intestinal cramping and diarrhea were observed in subjects exposed to an average dose of 0.19 mg vanadium/kg/day as ammonium vanadyl tartrate administered via capsules for 45–68 days (Dimond et al. 1963). Several clinical studies investigating the efficacy and mechanism of action of sodium metavanadate and vanadyl sulfate for the treatment of diabetes mellitus have found mild gastrointestinal effects (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). Mild diarrhea was reported by 4/10 insulin- and noninsulin-dependent diabetes patients administered 0.66 mg vanadium/kg/day as sodium metavanadate as capsules administered 3 times/day (0.26 mg vanadium/kg at breakfast and lunch and 0.13 mg vanadium/kg at dinner) for 14 days (Goldfine et al. 1995); another subject reported nausea and vomiting that subsided when the dose was decreased to 0.13 mg vanadium/kg 3 times/day. In another study of eight noninsulin dependent diabetics administered 0.35 mg vanadium/kg/day as vanadyl sulfate as capsules 2 times/day for 4 weeks, diarrhea and abdominal cramps were reported during the first week of treatment, but not reported thereafter (Boden et al. 1996). Similarly, insulin-independent diabetics reported diarrhea and abdominal discomfort during the first 2 weeks of exposure to vanadyl sulfate (Cusi et al. 2001). The initial dose of 0.2 mg vanadium/kg/day administered presumably as capsules 2 times/day was increased every 2–3 days and reached 0.6 mg vanadium/kg/day by week 2. Several animal studies have reported diarrhea in rats exposed to ≥8.35 mg vanadium/kg/day as sodium metavanadate or ammonium metavanadate (Ścibior 2005; Zaporowska and Wasilewski 1989, 1990, 1992a); the diarrhea was often observed at doses associated with marked decreases in food intake and water consumption.

Hematological Effects. No alterations in reticulocyte or platelet counts (Dimond et al. 1963) or erythrocyte, hemoglobin, hematocrit, or platelet levels (Fawcett et al. 1997) were observed in adults

exposed to 0.19 mg vanadium/kg/day as ammonium vanadyl tartrate for 6–10 weeks or 0.12 mg vanadium/kg/day as vanadyl sulfate for 12 weeks, respectively.

A series of studies conducted by Zaporowska and associates examined the hematotoxicity of ammonium metavanadate administered in drinking water to rats for acute or intermediate durations. A 2-week exposure to 27.72 mg vanadium/kg/day resulted in significant increases in reticulocyte levels and increases in the percentage of polychromatophilic erythroblasts in the bone marrow in male rats (Zaporowska and Wasilewski 1989); a nonsignificant increase in erythrocytes was also observed at this dose level. Exposures to 12.99–24.47 mg vanadium/kg/day for 4 weeks resulted in decreases in erythrocyte levels and hemoglobin levels and increases in reticulocyte levels (Zaporowska and Wasilewski 1989, 1990, 1991, 1992a, 1992b). However, death and decreases in body weight gain, food intake, and water consumption were also observed at these dose levels. Similar effects were observed in rats exposed to 8.35 or 10.69 mg vanadium/kg/day as sodium metavanadate for 6 weeks (Ścibior 2005; Ścibior et al. 2006). One study in this series tested lower concentrations which did not result in frank toxicity. Significant decreases in erythrocyte and hematocrit levels were observed in rats exposed to 1.18 or 4.93 mg vanadium/kg/day as ammonium metavanadate for 4 weeks (Zaporowska et al. 1993); significant increases in reticulocyte levels were observed at 4.93 mg vanadium/kg/day. The decreases in erythrocyte levels were small (approximately 11% less than controls) and not dose-related. Decreases in hemoglobin and hematocrit and increases in reticulocytes were observed in rats exposed to 2.1 mg vanadium/kg/day as sodium metavanadate for 10 weeks (Adachi et al. 2000a) and decreases in erythrocyte counts were observed in rabbits exposed to 1.8 mg vanadium/kg/day of an unknown metavanadate compound for 24 days (Kasbhatla and Rai 1993). However, other investigators have not found hematological alterations in rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate for 1 year (Dai and McNeill 1994), 9.7 mg vanadium/kg/day as ammonium metavanadate for 12 weeks (Dai et al. 1995), 7.6 mg vanadium/kg/day as vanadyl sulfate for 12 weeks (Dai et al. 1995), or 6.6 mg vanadium/kg/day as vanadium pentoxide for 10–15 weeks (Mountain et al. 1953). As suggested by Ścibior et al. (2006), the differences may be due to the duration of exposure, compound administered, or age of the animals.

Hepatic Effects. No significant alterations in serum AST, cholesterol, triglyceride, phospholipid, and/or bilirubin levels were observed in humans administered, via capsules, 0.19 mg vanadium/kg as ammonium vanadyl tartrate for 45–68 days (Dimond et al. 1963) or 0.12 mg vanadium/kg/day as vanadyl sulfate for 12 weeks (Fawcett et al. 1997).

Several studies in laboratory animals examining cholesterol and triglyceride levels (Adachi et al. 2000a; Dai et al. 1994a) or serum enzyme levels (ALT or AST) (Adachi et al. 2000a; Dai et al. 1994b; Yao et al. 1997) have not found biologically relevant alterations. The highest NOAEL values for these effects are 13 mg vanadium/kg/day (Yao et al. 1997) following intermediate-duration exposure and 19 mg vanadium/kg/day following chronic-duration exposure (Dai et al. 1994a, 1994b). No histological alterations were observed in the livers of rats exposed to 3.5 mg vanadium/kg/day as sodium metavanadate in drinking water for 3 months (Domingo et al. 1985), 4.7 mg vanadium/kg/day as sodium metavanadate in drinking water for 210 days (Boscolo et al. 1994), or 19 mg vanadium/kg/day as vandyl sulfate in drinking water for 1 year (Dai et al. 1994b).

Renal Effects. Humans given 0.19 mg vanadium/kg as ammonium vanadyl tartrate capsules for 45–68 days did not show any changes in urinalysis for albumin, hemoglobin, or formed elements. Blood urea nitrogen levels were also unchanged (Dimond et al. 1963).

There are limited data on the renal toxicity of vanadium compounds. Narrowing of the lumen of the proximal tubules was observed in rats exposed to 4.7 or 12 mg vanadium/kg/day as sodium metavanadate in drinking water for 7 months (Boscolo et al. 1994; Carmagnani et al. 1991); however, neither study reported the incidence of the lesion or statistical significance. Similarly, corticomedullar micro-hemorrhagic foci were observed in the kidneys of rats exposed to sodium metavanadate in drinking water for 3 months (Domingo et al. 1985); the investigators noted that the effect was more evident at the highest dose (3.5 mg vanadium/kg/day), but incidence data or statistical analyses were not included in the paper. This study also found significant increases in serum total protein, urea, and uric acid levels in rats exposed to 3.5 mg vanadium/kg/day. No statistically significant increases in the incidence of histological alterations were observed in rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate in drinking water for 1 year (Dai et al. 1994b). No histological alterations were observed in the kidneys of rats exposed to 0.7 mg vanadium/kg/day (Schroeder et al. 1970) as vanadyl sulfate in drinking water for 2.5 years or in mice exposed to 4.1 mg vanadium/kg/day as vanadyl sulfate in the diet for 2 years (Schroeder and Balassa 1967).

Body Weight Effects. No significant alterations in body weight were observed in adults exposed to 0.12 mg vanadium/kg/day as vanadyl sulfate administered via capsules for 12 weeks (Fawcett et al. 1997). Numerous studies have reported significant decreases in body weight gain in rats or mice exposed to vanadium compounds. In general, intermediate-duration exposure to <10 mg vanadium/kg/day did not result in >10% decreases in body weight gain (Adachi et al. 2000a; Dai et al. 1995; Sanchez et al. 1998;

Ścibior 2005; Zaporwska et al. 1993). At higher concentrations, a considerable amount of variability in the magnitude of decreases in body weight gain was observed. Decreases of 12–15% were observed in rats or mice exposed to 10.69, 13, 20.93, 22.06, or 33 mg vanadium/kg/day as vanadyl sulfate, ammonium metavanadate, or sodium metavanadate in drinking water (Llobet et al. 1993; Ścibior et al. 2006; Yao et al. 1997; Zaporowski and Wasilewski 1989, 1990). However, decreases of ≥37% were observed in rats exposed to 12.99 or 19.73 mg vanadium/kg/day as ammonium vanadate in drinking water (Zaporowski and Wasilewski 1991, 1992a, 1992b); these decreases in body weight gain were accompanied by marked decreases in food intake and water consumption. A severe decrease in body weight gain (54%) and weight loss were observed in rats exposed to 30 or 55 mg vanadium/kg/day, respectively, as vanadium pentoxide for 75 days (Mountain et al. 1953). In contrast, no alterations in body weight gain were observed in rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water (Bursztyn and Mekler 1993) or administered via gavage at 31 mg vanadium/kg/day as vanadyl sulfate (Akgün-Dar et al. 2007; Jain et al. 2007). Significant decreases in maternal weight gain have been observed in rats exposed to 6 mg vanadium/kg/day as sodium metavanadate (Elfant and Keen 1997) and mice administered 7.5 mg vanadium/kg/day as vanadyl sulfate (Paternain et al. 1990). Following chronic exposure, a 20% decrease in body weight gain was observed in rats exposed to vanadyl sulfate in drinking water for 1 year (Dai et al. 1994a). No alterations in body weight gain were observed in mice exposed to 4.1 or 0.54 mg vanadium/kg/day as vanadyl sulfate (Schroeder and Balassa 1967; Schroeder and Mitchener 1975) or rats exposed to 0.7 mg vanadium/kg/day as vanadyl sulfate (Schroeder et al. 1970).

It is likely that the decreases in body weight in a number of these studies are secondary to decreases in water consumption (possibly due to palatability). Decreases in food intake and body weight gain have been observed in rats placed on a water restricted diet (Crampton and Lloyd 1954); young rats were particularly sensitive to the effect (2-month-old rats were used in the Zaporowski and Wasilewski studies). Thus, LOAELs for decreases in body weight gain in drinking water studies reporting decreases in water consumption (possibly due to palatability) are not presented in Table 3-3 or Figure 3-2; similarly, LOAELs were not listed for studies that did not report whether there was an effect on drinking water consumption.

Metabolic Effects. No studies were located regarding metabolic effects in healthy humans after oral exposure to vanadium. No significant alterations in blood glucose or insulin levels were observed in rats exposed to 22 mg vanadium/kg/day as sodium metavanadate in drinking water for 4 weeks (Bursztyn and Mekler 1993), rats administered 31 mg vanadium/kg/day as vanadyl sulfate for 60 days (Akgün-Dar et al.

2007), or rats exposed to 19 mg vanadium/kg/day as vanadyl sulfate in drinking water for 1 year (Dai et al. 1994a). Additionally, no alterations in the response to an oral glucose tolerance test were observed in rats exposed to 13 mg vanadium/kg/day as vanadyl sulfate in drinking water for 7.4 weeks (Yao et al. 1997).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to vanadium. Minimal information on immunological effects in animals was located. Mice exposed to 0.13, 1.3, or 6.5 mg vanadium/kg/day as sodium orthovanadate in the drinking water for 6 weeks showed a dose-related, but nonsignificant, decrease in the antibody-forming cells in the spleen when challenged with sheep erythrocytes (Sharma et al. 1981). The number of plaques formed was 46, 69, and 78%, respectively, lower than the response in the controls; the investigators noted that statistical significance was not achieved due to the large variation in the control group. Decreases in B-cell levels and IgG and IgM levels were observed in rats exposed to 2.1 mg vanadium/kg/day as sodium metavanadate in the diet for 10 weeks (Adachi et al. 2000a). Mild spleen hypertrophy and hyperplasia were seen in rats exposed to sodium metavanadate in the drinking water for 3 months (Domingo et al. 1985); the investigators noted that the effects were more evident at the highest dose (3.5 mg vanadium/kg/day), but incidence data were not reported. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to vanadium. Data on the neurotoxicity of vanadium are limited to two studies in rats. In one study, decreases in travelling distance and horizontal movement in an open field test and poorer avoidance performance and higher latency period in an active avoidance test were observed in rats administered 1.72 mg vanadium/kg/day as sodium metavanadate for 8 weeks (Sanchez et al. 1998). In the second study, no alterations in travelling distance or vertical movements were observed in an open field test in rats administered 6.84 mg vanadium/kg/day as sodium metavanadate for 8 weeks (Sanchez et al. 1999). A decrease in the number of avoidance responses to conditioned stimuli and increases in the latency period were also observed in these rats. These LOAEL values are recorded in Table 3-3 and Figure 3-2.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to vanadium. Decreases in fertility have been observed in female rats mated to unexposed males (Ganguli et al. 1994b; Morgan and El-Tawil 2003) and in male rats or mice mated with unexposed females (Jain et al. 2007; Llobet et al. 1993; Morgan and El-Tawil 2003). The lowest LOAEL values for decreased fertility are 12 and 10 mg vanadium/kg/day for females and males, respectively (Morgan and El-Tawil 2003). No alterations in fertility were observed in male and female rats administered 8.4 mg vanadium/kg/day as sodium metavanadate (Domingo et al. 1986). Decreases in sperm count and motility have also been observed in rats administered 31 mg vanadium/kg/day as vanadyl sulfate for 60 days (Jain et al. 2007). This NOAEL value and reliable LOAEL values are recorded in Table 3-3 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 vanadium. A variety of fetal malformations/anomalies have been observed in animals following gestational exposure to vanadium. Exposure on gestation days 6–14 or 6–15 resulted in increases in facial hemorrhages (Paternain et al. 1987), hematomas in facial, neck, and dorsal areas (Paternain et al. 1990), and delayed ossification (Paternain et al. 1990; Sanchez et al. 1991); the rat and mouse dams were administered 7.5–8.3 mg vanadium/kg/day as vanadyl sulfate, sodium metavanadate, or sodium orthovanadate. One study also reported increases in early resorptions and decreases in fetal growth in the offspring of mice administered 7.5 mg vanadium/kg/day as vanadyl sulfate (Paternain et al. 1990); marked decreases in maternal body weight were also observed at this dose level. Vanadium exposure throughout gestation and lactation resulted in decreases in pup body weight and length at ≥2.1 mg vanadium/kg/day (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003). Increases in stillbirths and decreases in pup survival were observed at 6 mg vanadium/kg/day (Elfant and Keen 1987); this dose level was associated with decreases in maternal food intake and body weight. Increases in gross, skeletal, and visceral anomalies were observed in the offspring of rats exposed to 12 mg vanadium/kg/day as ammonium metavanadate (Morgan and El-Tawil 2003); similar effects were observed in unexposed dams mated with males exposed to 10 mg vanadium/kg/day (Morgan and El-Tawil 2003). In rats exposed to 10 mg vanadium/kg/day as vanadyl sulfate in drinking water during gestation and lactation and exposed until postnatal day 100, significant decreases in survival were observed (Poggioli et al. 2001). This study also found significant decreases in the number of rearings in an open field test and no alterations in locomotor activity or working memory. A two-generation, one-dose study in rats showed altered lung collagen metabolism in fetuses of adults with lifetime exposure (Kowalska 1988). The toxicological significance

of this finding is also not known. Reliable LOAEL values from these studies are recorded in Table 3-3 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located that specifically studied cancer in humans or animals after oral exposure to vanadium. However, some studies designed to test other end points noted no increase in tumor frequency in rats and mice chronically exposed to 0.5–4.1 mg vanadium/kg as vanadyl sulfate in drinking water (Schroeder and Balassa 1967; Schroeder and Mitchener 1975; Schroeder et al. 1970). Although results of these oral studies were negative for carcinogenicity, they were inadequate for evaluating carcinogenic effects because insufficient numbers of animals were used, it was not determined whether or not a maximum tolerated dose was achieved, a complete histological examination was not performed, and only one exposure dose per study was evaluated.

3.2.3 Dermal Exposure

No studies were located regarding the following health effects in humans or animals after dermal exposure to vanadium:

3.2.3.1 Death

3.2.3.2 Systemic Effects

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

The *in vitro* and *in vivo* data on the genotoxicity of vanadium compounds are summarized in Tables 3-4 and 3-5, respectively. In workers exposed to vanadium pentoxide, no alterations in the occurrence of sister chromatid exchange (Ivancsits et al. 2002) or deoxyribonucleic acid (DNA) strand breaks (Ehrlich et al. 2008; Ivancsits et al. 2002) were observed; however, an increase in micronuclei formation was observed in lymphocytes (Ehrlich et al. 2008). Similarly, increases in the micronuclei formation were observed in mouse bone marrow cells following oral exposure to vanadyl sulfate (Ciranni et al. 1995;

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Bacillus subtilis	Recombination repair	No data	+ + +	Kada et al. 1980	V_2O_5 $VOCl_2$ NH_4VO_3
B. subtilis	Recombination repair	No data	+ + +	Kanematsu et al. 1980	V_2O_5 $VOCl_2$ NH_4VO_3
Escherichia coli	Gene mutation	No data	– –	Kanematsu et al. 1980	V_2O_5 NH_4VO_3
Salmonella typhimurium	Gene mutation	No data	– –	Kanematsu et al. 1980	V_2O_5 NH_4VO
S. typhimurium	Gene mutation	–	–	NTP 2002	V_2O_5
Saccharomyces cerevisiae	Induction of diploid spores	No data	+	Sora et al. 1986	$VOSO_4$
S. cerevisiae	Reverse point mutation	+	+	Bronzetti et al. 1990	NH_4VO_3
S. cerevisiae	Mitotic gene conversion	+	+	Bronzetti et al. 1990	NH_4VO_3
Mouse erythroleukemia cells	DNA repair	No data	+	Foresti et al. 2001	$NaVO_3$
Mouse 3T3 and 3T6 cells	DNA synthesis	No data	+	Smith 1983	Na_3VO_4 $VOSO_4$
Chinese hamster ovary cells	DNA protein crosslinks	No data	+	Cohen et al. 1992	NH_4VO_3
Hamster V79 fetal lung fibroblasts	*hprt* mutation frequency	No data	+	Cohen et al. 1992	NH_4VO_3
Chinese hamster V79 cells	*hprt* mutation frequency	No data	+	Klein et al. 1994	NH_4VO_3
Chinese hamster V79 cells	*gpt* mutation frequency	No data	–	Klein et al. 1994	NH_4VO_3
Chinese hamster V79 cells	*hprt* mutation frequency	No data	–	Zhong et al. 1994	V_2O_5
Syrian hamster ovary cells	Micronuclei formation	No data	–	Gibson et al. 1997	V_2O_5
Chinese hamster V79 cells	Micronuclei formation	No data	+	Zhong et al. 1994	V_2O_5
Chinese hamster ovary cells	Sister chromatid exchange	+ + +	+ + +	Owusu-Yaw et al. 1990	$VOSO_4$ V_2O_3 NH_4VO_3
Chinese hamster V79 cells	Sister chromatid exchange	No data	–	Zhong et al. 1994	V_2O_5

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Zhong et al. 1994	V_2O_5
Chinese hamster ovary cells	Chromosomal aberrations	+ + +	+ + +	Owusu-Yaw et al. 1990	$VOSO_4$ V_2O_3 NH_4VO_3
Human tumor cells	Colony formation	No data	+	Hanauske et al. 1987	<0.1 pM V
Human tumor cells	Colony formation	No data	–	Hanauske et al. 1987	>0.1 pM V
Human leukocytes	DNA strand break	No data	+	Birnboim 1988	Na_3VO_4
Human fibroblasts	DNA strand break	No data	+	Ivancsits et al. 2002	V_2O_5
Human erythrocytes, lymphocytes	DNA strand break	No data	–	Ivancsits et al. 2002	V_2O_5
Human nasal epithelial cells	DNA strand break	No data	–	Kleinsasser et al. 2003	V_2O_5
Human lymphocytes	DNA strand break	No data	+	Kleinsasser et al. 2003	V_2O_5
Human lymphocytes	DNA strand break	No data	+	Wozniak and Blasiak 2004	$VOSO_4$
Human cervical cancer cells (HeLa)	DNA strand break	No data	+	Wozniak and Blasiak 2004	$VOSO_4$
Human lymphocytes	DNA strand break	No data	±	Rojas et al. 1996	V_2O_5
Human leukocytes	DNA strand break	No data	+	Rojas et al. 1996	V_2O_5
Human lymphocytes	Chromosomal aberrations	No data	+ + + +	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$
Human lymphocytes	Structural chromosomal aberrations	No data	–	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Numerical chromosomal aberrations	No data	+	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Sister chromatid exchange	No data	–	Roldán and Altamirano 1990	V_2O_5
Human lymphocytes	Sister chromatid exchange	No data	– – – –	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$

Table 3-4. Genotoxicity of Vanadium and Compounds *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Human lymphocytes	Micronuclei formation	No data	+ +	Migliore et al. 1995	Na_3VO_4, $VOSO_4$
Human lymphocytes	Micronuclei formation	No data	+ + + +	Migliore et al. 1993	NH_4VO_3, $NaVO_3$, Na_3VO_4, $VOSO_4$

— = negative result; + = positive result; ± = weakly positive; DNA = deoxyribonucleic acid; hprt = hypoxanthine phosphoribosyltransferase; $NaVO_3$= sodium metavanadate; Na_3VO_4 = sodium orthovanadate; NH_4VO_3 = ammonium metavanadate; V_2O_5 = vanadium pentoxide; V_2O_3 = vanadium trioxide; $VOSO_4$ = vanadyl sulfate; $VOCl_2$ = vanadyl dichloride

Table 3-5. Genotoxicity of Vanadium and Compounds *In Vivo*

Species (test system)	End point	Exposure Route	Result	Reference	Form
Human leukocytes	Sister chromatid exchange	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	Sister chromatid exchange	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	Micronuclei formation	Inhalation (occupational)	+	Ehrlich et al. 2008	V_2O_5
Human leukocytes	DNA strand breaks	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	DNA strand breaks	Inhalation (occupational)	–	Ivancsits et al. 2002	V_2O_5
Human lymphocytes	DNA strand breaks	Inhalation (occupational)	–	Ehrlich et al. 2008	V_2O_5
CD-1 mouse bone marrow	Micronuclei formation	Drinking water	–	Villani et al. 2007	$VOSO_4$
CD-1 mouse blood reticulocytes	Micronuclei formation	Drinking water	±	Villani et al. 2007	$VOSO_4$
CD-1 mouse bone marrow	Micronuclei formation	Gavage	+ + +	Ciranni et al. 1995	$VOSO_4$ Na_3VO_4 NH_4VO_3
B6C3F1 mouse erythrocytes	Micronuclei formation	Inhalation	–	NTP 2002	V_2O_5
CD-1 mouse bone marrow	Chromosome aberrations	Gavage	+ + +	Ciranni et al. 1995	$VOSO_4$ Na_3VO_4 NH_4VO_3
CD-1 mouse bone marrow	DNA damage	Drinking water	–	Villani et al. 2007	$VOSO_4$
CD-1 mouse testis cells	DNA damage	Drinking water	–	Villani et al. 2007	$VOSO_4$

– = negative result; + = positive result; ± = weakly positive; DNA = deoxyribonucleic acid; V_2O_5 = vanadium pentoxide; $VOSO_4$ = vanadyl sulfate; Na_3VO_4 = sodium orthovanadate; NH_4VO_3 = ammonium metavanadate

Villani et al. 2007), sodium orthovanadate (Ciranni et al. 1995), or ammonium metavanadate (Ciranni et al. 1995); however no increases in micronuclei formation were observed in mouse erythrocytes following intermediate duration inhalation exposure to vanadium pentoxide (NTP 2002). Increases in chromosomal aberrations were also observed in mouse bone marrow following a single gavage exposure to vanadyl sulfate, sodium orthovanadate, or ammonium metavanadate (Ciranni et al. 1995). As with the vanadium workers, DNA damage was not observed in mouse bone marrow or testis cells following intermediate duration exposure to vanadyl sulfate in drinking water.

Conflicting results have been found for genotoxicity tests in prokaryote assays. Impaired recombination repair were found in *Bacillus subtilis* following exposure to vanadium pentoxide, vanadyl dichloride, or ammonium metavanadate (Kada et al. 1980; Kanematsu et al. 1980). No alterations in gene mutation frequency were found in *Escherichia coli* or *Salmonella typhimurium* for vanadium pentoxide (Kanematsu et al. 1980; NTP 2002) or ammonium metavanadate (Kanematsu et al. 1980). In nonmammalian eukaryotes, increases in reverse point mutations and mitotic gene conversion were found in *Saccharomyces cerevisiae* (Bronzetti et al. 1990). In general, alterations in DNA repair, synthesis, formation of cross links or strand breaks, and gene mutation frequency were observed in mammalian cells for vanadium pentoxide, ammonium metavanadate, vanadyl sulfate, sodium orthovanadate (Birnboim 1988; Cohen et al. 1992; Foresti et al. 2001; Ivancsits et al. 2002; Klein et al. 1994; Kleinsasser et al. 2003; Rojas et al. 1996; Smith 1983; Wozniak and Blasiak 2004; Zhong et al. 1994). *In vitro* human data suggest cell-specific differences in the ability of vanadium compounds to induce DNA strand breaks. DNA strand breaks were found in fibroblasts and lymphocytes (Ivancsits et al. 2002; Kleinsasser et al. 2003; Wozniak and Blasiak 2004) but not in erythrocytes or nasal epithelial cells (Ivancsits et al. 2002; Kleinsasser et al. 2003). Increases in the occurrence of chromosomal aberrations were observed in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994), Chinese hamster ovary cells exposed to vanadyl sulfate, vanadium trioxide, or ammonium metavanadate (Owusu-Yaw et al. 1990), and human lymphocytes exposed to ammonium metavanadate, sodium metavanadate, sodium orthovanadate, vanadium pentoxide, or vanadyl sulfate (Migliore et al. 1993; Roldán and Altamirano 1990). An increase in sister chromatid exchange was found in Chinese hamster ovary cells exposed to vanadyl sulfate, vanadium trioxide, or ammonium metavanadate (Owusu-Yaw et al. 1990), but not in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994) or human lymphocytes exposed to vanadium pentoxide, ammonium metavanadate, sodium metavanadate, sodium orthovanadate, or vanadyl sulfate (Migliore et al. 1993; Roldán and Altamirano 1990). Increases in micronuclei formation were also found in Chinese hamster V79 cells exposed to vanadium pentoxide (Zhong et al. 1994) and in human lymphocytes exposed to sodium orthovanadate, vanadyl sulfate, ammonium

metavanadate, or sodium metavanadate (Migliore et al. 1993, 1995), but not in Syrian hamster ovary cells exposed to vanadium pentoxide (Gibson et al. 1997). Thus, the available data provide evidence that vanadium compounds are genotoxic, both clastogenic effects and DNA damage have been observed in *in vitro* and *in vivo* studies.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Several occupational studies indicate that absorption can occur in humans following inhalation exposure. An increase in urinary vanadium levels was found in workers exposed to <1 ppm of vanadium (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983). The vanadium concentration in serum was also reported to be higher than the nonoccupationally exposed controls following exposure to vanadium pentoxide dust (Kiviluoto et al. 1981b).

Indirect evidence of absorption after inhalation of vanadium in animals is indicated in studies involving inhalation exposure or intratracheal administration. In rats and mice exposed to 0.28–2.2 mg vanadium/m^3 as vanadium pentoxide for 14 days or 2 years (6 hours/day, 5 days/week), marginal increases in blood vanadium levels were observed, suggesting that vanadium pentoxide was poorly absorbed or rapidly cleared from the blood (NTP 2002); in the 2-year studies, the increase in blood vanadium levels were somewhat concentration-related. Intratracheal studies suggest that soluble vanadium compounds are readily absorbed through the lungs. Initial pulmonary clearance is rapid in rats. There was rapid 100% absorption of vanadium in rats receiving radiolabeled vanadyl chloride (Conklin et al. 1982). The greatest absorption of a radioactive dose, ^{48}V, was found to occur 5 minutes after administration (Roshchin et al. 1980). Most of the vanadium, 80 and 85% of the tetravalent (V4+) and pentavalent (V5+) forms of vanadium, respectively, cleared from the lungs 3 hours after intratracheal exposure (Edel and Sabbioni 1988). After 24 hours, >50% of vanadyl oxychloride was cleared from the lungs of male rats (Oberg et al. 1978), and at 3 days, 90% of vanadium pentoxide was eliminated from the lungs of female rats (Conklin et al. 1982). In another study 50% was cleared in 18 minutes, and the rest within a few days (Rhoads and Sanders 1985).

3.4.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption in humans after oral exposure to vanadium.

The absorption of vanadium through the gastrointestinal tract of animals is low. Less than 0.1% of an intragastric dose was detectable in the blood of rats at 15 minutes postexposure, and less than 1% at 1 hour (Roshchin et al. 1980). Similarly, only 2.6% of an orally administered radiolabeled dose of vanadium pentoxide was absorbed 3 days after exposure in rats (Conklin et al. 1982). In contrast, 16.5% of vanadium was absorbed in rats exposed to sodium metavanadate in the diet for 7 days (Adachi et al. 2000b). Vanadium was reported in tissues and urine within hours after a single (Edel and Sabbioni 1988) and repeated oral exposure in rats (Bogden et al. 1982; Parker and Sharma 1978), suggesting that it is rapidly absorbed. Young rats that consumed vanadium in the drinking water and feed were found to have higher tissue vanadium levels 21 days after birth than they did 115 days after birth (Edel et al. 1984). The data suggest that there is a higher absorption of vanadium in these young animals due to a greater nonselective permeability of the undeveloped gastrointestinal barrier.

3.4.1.3 Dermal Exposure

No specific studies were located regarding absorption in humans or animals after dermal exposure to vanadium, although absorption by this route is generally considered to be very low (WHO 1988). Absorption through the skin is thought to be quite minimal due to its low lipid/water solubility.

3.4.2 Distribution

Vanadium has been detected in the lungs (in 52% of the cases) and intestines (in 16% of the cases) of humans with no known occupational exposure, collected from autopsy data (Schroeder et al. 1963). In the gastrointestinal tract, it was primarily found in the ileum (37%), cecum (45.1%), sigmoid colon (15.9%), and rectum (26.2%). The heart, aorta, brain, kidney, muscle, ovary, and testes were found to have no detectable vanadium concentrations. Bone was not tested.

3.4.2.1 Inhalation Exposure

There are limited data on the distribution of vanadium in workers; serum vanadium levels in workers were highest within a day after exposure followed by a rapid decline in levels upon cessation of exposure

(Gylseth et al. 1979; Kiviluoto et al. 1981b). Analytical studies have shown low levels of vanadium in human kidneys and liver, with even less in brain, heart, and milk. Higher levels were detected in hair, bone, and teeth (Byrne and Kosta 1978). Inhalation exposure and intratracheal administration studies in laboratory animals have examined the distribution of vanadium. In rats chronically exposed to 0.56 or 1.1 mg vanadium/m^3 as vanadium pentoxide (6 hours/day, 5 days/week), vanadium lung burdens peaked after 173 days of exposure and declined for the remainder of the study (day 542); lung burden levels never reached steady state (NTP 2002). In contrast, lung burdens appeared to reach steady state by exposure day 173 in rats exposed to 0.28 mg vanadium/m^3 (NTP 2002). Similarly, lung burdens did not reach steady state in mice exposed to 1.1 or 2.2 mg vanadium/m^3 as vanadium pentoxide, 6 hours/day, 5 days/week for 542 days (NTP 2002). Rather, lung burdens peaked near day 54 and declined through day 535. Steady state was achieved in mice exposed to 0.56 mg vanadium/m^3 during the first 26 days of exposure. These data suggest that vanadium is cleared more rapidly from the lungs of mice compared to rats.

Vanadium is rapidly distributed in tissues of rats after acute intratracheal administration. Within 15 minutes after exposure to 0.36 mg/kg vanadium oxychloride, radiolabeled vanadium was detectable in all organs except the brain. The highest concentration was in the lungs, followed by the heart and kidney. The other organs had low levels. Maximum concentrations were reached in most tissues between 4 and 24 hours (Oberg et al. 1978). Vanadium is found to have a two-phase lung clearance after a single acute exposure (Oberg et al. 1978; Rhoads and Sanders 1985). The initial phase is rapid with a large percentage of the absorbed dose distributed to most organs and blood 24 hours postexposure, followed by a slower clearance phase. Vanadium is transported mainly in the plasma. It is found in appreciable amounts in the blood initially and only at trace levels 2 days after exposure (Roshchin et al. 1980). The pentavalent and tetravalent forms of vanadium compounds were found to have similar distribution patterns (Edel and Sabbioni 1988). Three hours after intratracheal exposure to the pentavalent or tetravalent form, 15–17% of the absorbed dose was found in the lung, 2.8% in the liver, and 2% in the kidney (Edel and Sabbioni 1988). Although levels in the kidney are high after exposure, the bone had greater retention of vanadium.

Skeletal levels of vanadium peaked 1–3 days postexposure (Conklin et al. 1982; Rhoads and Sanders 1985; Roshchin et al. 1980) and have been reported to persist after 63 days (Oberg et al. 1978).

3.4.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to vanadium.

Acute studies with rats showed the highest vanadium concentration to be located in the skeleton. Male rats had approximately 0.05% of the administered ^{48}V in bones, 0.01% in the liver, and <0.01% in the kidney, blood, testis, or spleen after 24 hours (Edel and Sabbioni 1988). Similar findings were noted by other authors who found that the bone had the greatest concentration of radiolabeled vanadium, followed by the kidney (Roshchin et al. 1980). Conklin et al. (1982) reported that after 3 days, 25% of the absorbed vanadium pentoxide was detectable in the skeleton and blood of female rats. In female rats exposed to sodium metavanadate in the diet for 7 days, the highest concentrations of vanadium were found in bone, followed by the spleen and kidney (Adachi et al. 2000b); the lowest concentration was found in the brain. As summarized in Table 3-6, vanadium elimination half-times in various tissues were 3.57–15.95 or 3.18–13.50 days following a 1-week exposure to 8.2 mg vanadium/kg/day as sodium metavanadate or vanadyl sulfate, respectively, administered in a liquid diet (Hamel and Duckworth 1995). Although the elimination half-times were longer in rats administered sodium metavanadate compared to vanadyl sulfate, no statistical comparisons were made.

Oral exposure for an intermediate duration produced the highest accumulation of vanadium in the kidney. Adult rats exposed to 5 or 50 ppm vanadium in the drinking water for 3 months had the highest vanadium levels in the kidney, followed by bone, liver, and muscle (Parker and Sharma 1978). The retention in bone may have been due to phosphate displacement. All tissue levels plateaued at the third week of exposure. A possible explanation for the initially higher levels in the kidney during intermediate-duration exposure is the daily excretion of vanadium in the urine. When the treatment is stopped, levels decrease in the kidney. At the cessation of treatment, vanadium mobilized rapidly from the liver and slowly from the bones. Other tissue levels decreased rapidly after oral exposure was discontinued. Thus, retention of vanadium was much longer in the bones (Edel et al. 1984; Parker and Sharma 1978).

In rats exposed to approximately 100 mg/L vanadium in drinking water as vanadyl sulfate or ammonium metavanadate for 12 weeks, significant increases, as compared to controls, in bone, kidney, and liver vanadium levels were observed; no alterations in vanadium muscle levels were found (Thompson et al. 2002). The highest concentration of vanadium was found in the bone, followed by the kidney and liver. Tissue vanadium concentrations were significantly higher in rats exposed to ammonium metavanadate as compared to animals exposed to vanadyl sulfate.

Table 3-6. Vanadium Elimination Half-Times in Various Organs in Rats Exposed to 8.2 mg Vanadium/kg/day for 1 Week

	Half-time (days)	
Organ	Sodium metavanadate	Vanadyl sulfate
Liver	3.57	3.18
Kidney	3.92	3.27
Fat	4.06	5.04
Lung	5.52	4.45
Muscle	6.11	4.49
Heart	7.03	5.05
Spleen	9.13	5.15
Brain	11.17	9.17
Testes	15.95	13.50

Source: Hamel and Duckworth 1995

3.4.2.3 Dermal Exposure

No studies were located regarding distribution in humans and animals after dermal exposure to vanadium.

3.4.2.4 Other Routes of Exposure

After intraperitoneal administration to rats, vanadium is distributed to all organs. After 24 hours, the highest concentrations were found in the bones and kidney, although initial levels were highest in the kidney (Roshchin et al. 1980; Sharma et al. 1980). This is similar to the distribution seen following inhalation and oral exposure.

3.4.3 Metabolism

Vanadium is an element, and as such, is not metabolized. In the oxygenated blood, it circulates as a polyvanadate (isopolyanions containing pentavalent vanadium) but in tissues, it is retained mainly as the vanadyl cation (cationic form of tetravalent vanadium). Depending on the availability of reducing equivalents (such as reduced glutathione-SH, NADPH, NADH) and oxygen, vanadium may be reduced, reoxidized, and/or undergo redox cycling (Byczkowski and Kulkarni 1998).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Occupational studies showed that urinary vanadium levels significantly increased in exposed workers (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962). Male and female workers exposed to 0.1–0.19 mg/m^3 vanadium in a manufacturing company, had significantly higher urinary levels (20.6 μg/L) than the nonoccupationally exposed control subjects (2.7 μg/L) (NIOSH 1983). The correlation between ambient vanadium levels and urinary levels of vanadium is difficult to determine from these epidemiological studies (Kiviluoto et al. 1981b). In most instances, no other excretion routes were monitored. Analytical studies have shown very low levels in human milk (Byrne and Kosta 1978). Evidence from animal studies supports the occupational findings. Vanadium administered intratracheally to rats was reported to be excreted predominantly in the urine (Oberg et al. 1978) at levels twice that found in the feces (Rhoads and Sanders 1985). Three days after exposure to vanadium pentoxide, 40% of the ^{48}V dose was excreted, mostly in the urine while 30% remained in the skeleton (5 days after exposure) (Conklin et al. 1982).

In female rats exposed to 0.56 or 1.1 mg vanadium/m^3 as vanadium pentoxide for 16 days (6 hours/day, 5 days/week), lung clearance half-times during an 8-day recovery period were 4.42 and 4.96 days, respectively (NTP 2002). In mice similarly exposed to 1.1 or 2.2 mg vanadium/m^3, lung clearance half-times were 2.55 and 2.40 days, respectively (NTP 2002). In contrast to the 16-day exposure data, the lung clearance half-times in female rats exposed to 0.28, 0.56, or 1.1 mg vanadium/m^3 for 2 years (6 hours/day, 5 days/week) were 37.3, 58.6, and 61.4 days, respectively (NTP 2002). In mice, the half-times were 6.26, 10.7, and 13.9 days at 0.56, 1.1, and 2.2 mg vanadium/m^3 exposure levels (NTP 2002). These data suggest that vanadium is more rapidly cleared from the lungs following a short exposure period compared to longer periods.

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to vanadium.

Since vanadium is poorly absorbed in the gastrointestinal tract, a large percentage of vanadium is excreted unabsorbed in the feces in rats following oral exposure. More than 80% of the administered dose of ammonium metavanadate or sodium metavanadate accumulated in the feces after 6 or 7 days (Adachi et al. 2000b; Patterson et al. 1986). After 2 weeks of exposure, 59.1±18.8% of sodium metavanadate was found in the feces (Bogden et al. 1982). However, the principal route of excretion of absorbed vanadium is through the kidney in animals. Approximately 0.9% of ingested vanadium was excreted in the urine of rats exposed to sodium metavanadate in the diet for 7 days (Adachi et al. 2000b). An elimination half-time of 11.7 days was estimated in rats exposed to vanadyl sulfate in drinking water for 3 weeks (Ramanadham et al. 1991).

3.4.4.3 Dermal Exposure

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

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 and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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) are 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.

If PBPK models for vanadium exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models for vanadium were located.

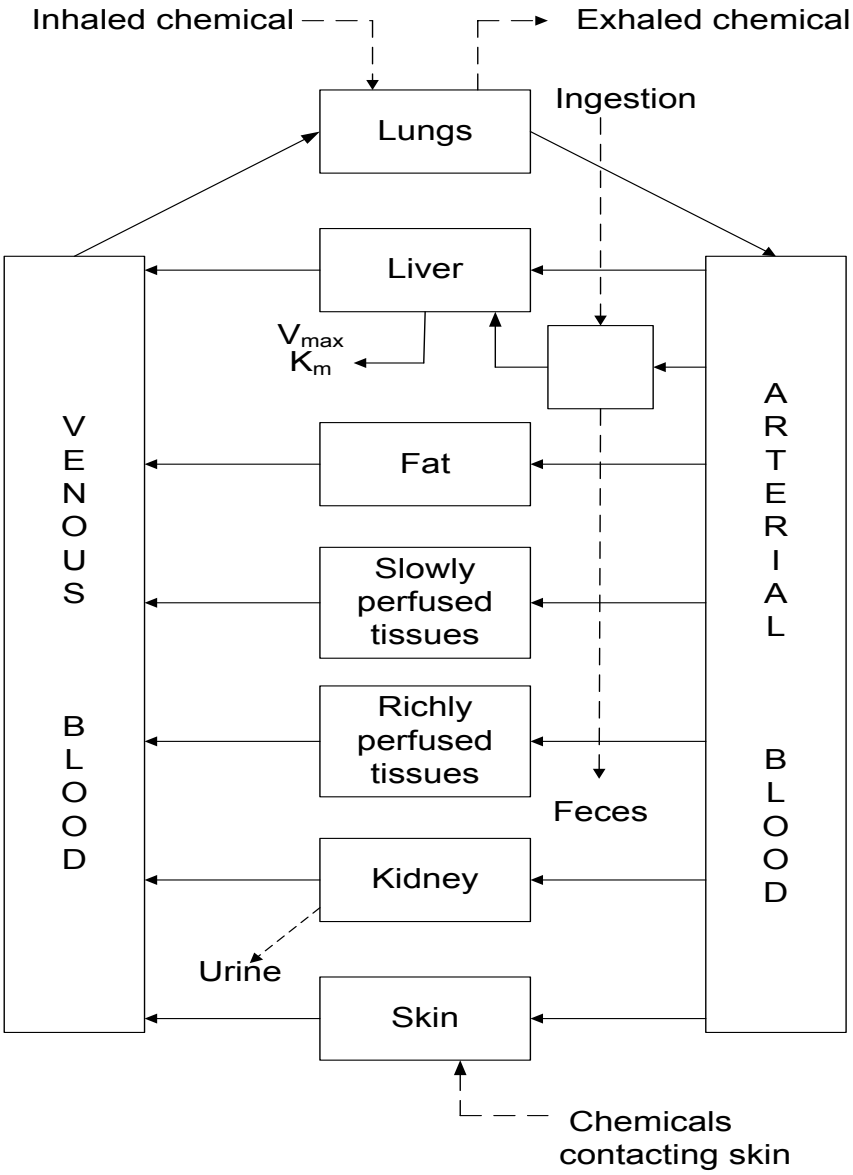
3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

In the body, there is an interconversion of two oxidation states of vanadium, the tetravalent form, vanadyl (V^{+4}), and the pentavalent form, vanadate (V^{+5}). Vanadium can reversibly bind to transferrin protein in the blood and then be taken up into erythrocytes. Vanadate is considered more toxic than vanadyl because vanadate is reactive with a number of enzymes and is a potent inhibitor of the Na+K+-ATPase of plasma membranes (Harris et al. 1984; Patterson et al. 1986). There is a slower uptake of vanadyl into erythrocytes compared to the vanadate form. Five minutes after an intravenous administration of radiolabeled vanadate or vanadyl in dogs, 30% of the vanadate dose and 12% of the vanadyl dose is found in erythrocytes (Harris et al. 1984). It is suggested that this difference in uptake is due to the time required for the vanadyl form to be oxidized to vanadate. When V^{+4} or V^{+5} is administered intravenously, a balance is reached in which vanadium moves in and out of the cells at a rate that is comparable to the rate of vanadium removal from the blood (Harris et al. 1984). Initially, vanadyl leaves the blood more rapidly than vanadate, possibly due to the slower uptake of vanadyl into cells (Harris et al. 1984). Five hours after administration, blood clearance is essentially identical for the two forms. A decrease in glutathione-SH, NADPH, and NADH occurs within an hour after intraperitoneal injection of sodium vanadate in mice (Bruech et al. 1984). It is believed that the redox cycling of vanadium V^{+5}/V^{+4}, depending on the local availability of oxygen in tissues, depletes reducing equivalents that are necessary for activity of cytochrome P-450.

Vanadium in the plasma can exist in a bound or unbound form (Bruech et al. 1984). Vanadium as vanadyl (Patterson et al. 1986) or vanadate (Harris and Carrano 1984) reversibly binds to human serum transferrin at two metal-binding sites on the protein. With intravenous administration of vanadate or vanadyl, there is a short lag time for vanadate binding to transferrin, but at 30 hours, the association is

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



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.

Source: adapted from Krishnan and Andersen 1994

identical for the two vanadium forms (Harris et al. 1984). The vanadium-transferrin binding is most likely to occur with the vanadyl form as this complex is more stable (Harris et al. 1984). The transferrin-bound vanadium is cleared from the blood at a slower rate than unbound vanadium in rats, which explains a biphasic clearance pattern (Sabbioni and Marafante 1978). The metabolic pathway appears to be independent of route of exposure (Edel and Sabbioni 1988).

3.5.2 Mechanisms of Toxicity

In vitro studies (as reviewed by Barceloux 1999; Etcheverry and Cortizo 1998; Harland and Harden-Williams 1994; Léonard and Gerber 1994; Mukherjee et al. 2004) have shown that vanadium acts as a phosphate analog and, as such, interferes with various ATPases, phosphatases, and phosphate-transfer enzymes. Vanadium has been shown to inhibit Na+K+ATPase, Ca2+ATPase, H+K+ATPase, K+ATPase, Ca+Mg+ATPase, dynein ATPase, actomyosin ATPase, acid and alkaline phosphatases, glucose-6-phosphatase, ribonuclease, phosphodiesterase, and phosphotryosyl-phosphatase. It has also been shown to stimulate tyrosine kinase phosphorylase, NADPH oxidase, and adenylate cyclase. Additionally, vanadium has been shown to have insulin-mimetic properties, particularly the ability to stimulate glucose uptake and oxidation and glycogen synthesis, and the ability to induce cell proliferation. The effect of vanadium on various enzymes may be responsible for the diverse effects observed in animals exposed to vanadium. However, little information is available regarding the mechanism of vanadium toxicity *in vivo*.

3.5.3 Animal-to-Human Extrapolations

There are little data available to evaluate potential toxicokinetic differences between humans and laboratory animals. Similar effects have been reported in humans and animals following inhalation or oral exposure to vanadium; however, this conclusion is based on the limited human toxicity data. In absence of data to the contrary, rats or mice appear to be valid models for extrapolation to 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 Thomas and Colborn (1992), was also used in 1996 when Congress mandated the 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), and in 1998, the EDSTAC 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 1997b). 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).

No *in vivo* or *in vitro* studies were located regarding endocrine disruption in humans and/or animals after exposure to vanadium.

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 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 vanadium in children. One study examined the influence of age on the renal toxicity of vanadium in male rats administered 10 mg/kg/day sodium orthovanadate via intraperitoneal injection for 8 days. Similar morphological effects were observed in the kidneys of 22-day-old rats and 62-day-old rats; however, the effects were more severe in the older rats (de la Torre et al. 1999). The difference in lesion severity is likely due to the significantly lower renal vanadium concentration in the young rats.

Edel et al. (1984) examined age-related changes in the distribution of vanadium in rats exposed to background levels of vanadium. At 21 days of age, the highest concentrations of vanadium (ng vanadium/g wet weight) were found in the kidney, heart, lung, brain, and liver. By 115 days of age, the highest concentration was in the femur; levels in the heart, lung, brain, spleen, and muscle were approximately 3–4 times lower. The concentrations of vanadium in the kidney, liver, and lungs significantly decreased with increasing age of the rat. The investigators suggested several mechanisms that may be responsible for the age-related changes in vanadium tissue concentration, including higher gastrointestinal absorption of vanadium in young rats, which may be due to increased bioavailability of vanadium in breast milk compared to the diet, or a higher vanadium retention capacity in undeveloped tissue due to a greater affinity or lower elimination rate.

As discussed in Section 3.2, a number of developmental effects including decreases in growth, increases in malformation and anomalies, and death have been observed in developmental toxicity studies (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Paternain et al. 1990); however most of these effects occurred at doses associated with significant maternal toxicity.

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).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is

available at http://www.cdc.gov/exposurereport/. The biomonitoring data for vanadium from this report is discussed in Section 6.5. 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, 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 vanadium 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 vanadium 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 Vanadium

Several biomarkers of exposure have been identified for vanadium but none of them can be used to quantitatively determine exposure levels. Elevated levels of vanadium have been found in the serum

(Gylseth et al. 1979; Kiviluoto et al. 1981b) and urine (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962) of exposed workers. However, relationships between exposure levels and serum or urine vanadium levels have not been established. Some vanadium workers develop a characteristic green tongue, as a result of direct accumulation of the vanadium dusts on the tongue (Lewis 1959). One report from the 1950s states that vanadium exposure was associated with decreased cystine content in the fingernails of vanadium workers (Mountain et al. 1955). However, alterations in cystine levels can also be associated with dietary changes and with other disease states, so this is not specific for vanadium exposure. No other commonly measured cellular changes have been identified with vanadium exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Vanadium

The primary effects of inhalation exposure to vanadium dusts are coughing, wheezing, and other respiratory difficulties. These effects, however, are not specific to vanadium and can be found following inhalation of many types of dusts.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Vanadium in the drinking water of mice had no influence on tumor induction by the known carcinogen 1,2-dimethylhydrazine given by subcutaneous injection (Kingsnorth et al. 1986), but dietary vanadium did decrease mammary tumors in mice caused by 1-methyl-1-nitrosourea administered concurrently (Thompson et al. 1984). The latter effect may have been due to interaction with DNA.

The combination of manganese and vanadium or of nickel and vanadium administered to pregnant mice caused some alterations in behavioral development of the pups as compared to either element administered alone (Hoshishima et al. 1983). Oral administration of vanadium in rats interfered with copper metabolism, probably by inhibiting the intestinal absorption of copper (Witkowska et al. 1988).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to vanadium than will most persons exposed to the same level of vanadium 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 vanadium, or compromised function of organs

affected by vanadium. Populations who are at greater risk due to their unusually high exposure to vanadium are discussed in Section 6.7, Populations with Potentially High Exposures.

No unusually susceptible populations have been identified, but persons with pre-existing respiratory disorders such as asthma or chronic obstructive pulmonary disease (COPD) may be expected to have increased adverse effects from breathing vanadium dusts. Due to the insulin-mimetic effects of vanadium, individuals with hypoglycemia may be unusually susceptible to exposure to high levels of vanadium.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to vanadium. 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 vanadium. 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 vanadium:

Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 1033.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 406-407.

3.11.1 Reducing Peak Absorption Following Exposure

There is no known treatment to decrease absorption after inhaling vanadium and/or its compounds. Following oral exposure, dilution with water or milk is one way to decrease overall absorption (Stutz and Janusz 1988). To decrease gastrointestinal absorption, especially for organic vanadium compounds, it has been suggested that activated charcoal be ingested. If vanadium gets onto the skin, washing the contaminated area with soapy water has been advised. For ocular exposure, it is suggested that the eyes be flushed with large amounts of saline or water (Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Several studies have evaluated the effectiveness of chelating agents in reducing vanadium body burden. Significant increases in urinary excretion of vanadium were observed in rodents treated with ascorbic acid

(Domingo et al. 1990), tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) (Domingo et al. 1990; Gomez et al. 1991), deferoxamine mesylate (Gomez et al. 1988, 1991), or 2-mercaptosuccinic (Domingo et al. 1990) following intramuscular injection of vanadyl sulfate (Domingo et al. 1990) or 6-week oral exposure to sodium metavanadate or vanadyl sulfate (Gomez et al. 1991). Administration of EDTA, 2-mercaptosuccinic or tiron also significantly reduced kidney vanadium levels (Domingo et al. 1990) and tiron reduced spleen and kidney vanadium levels (Gomez et al. 1991). Administration of calcium disodium EDTA resulted in increases in urinary excretion of vanadium in calves exposed to high levels of dietary vanadium (Gummow et al. 2006); however, no difference in vanadium excretion was observed after vanadium exposure was terminated. Other studies have examined the potential of chelating agents to reduce toxicity. Humans or animals with vanadium poisoning have not been helped by the chelating agent dimercaprol (BAL), which is often effective in lessening the toxicity of other metals (Lusky et al. 1949). Intraperitoneal injections of ascorbic acid and of ethylene diamine tetraacetate (EDTA) reduced vanadium-induced morbidity in mice and rats (Jones and Basinger 1983; Mitchell and Floyd 1954). Administration of tiron 0, 24, 48, or 72 hours after pregnant mice received a 25 mg/kg sodium metavanadate intraperitoneal injection on gestation day 12 resulted in significant reductions in vanadium-induced abortions, early deliveries, fetal deaths, and incidence of reduced ossification (Domingo et al. 1993a). Administration of tiron after a 6-week exposure to sodium metavanadate reverted the vanadium-induced impairment in performance on neurobehavioral tests (Sanchez et al. 1999). Co-exposure to calcium disodium EDTA did not significantly alter the toxicity of ingested vanadium in calves (Gummow et al. 2006).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are limited data on treatments which interfere with the mechanism of action for vanadium toxicity. Moderate to severe morphological alterations (average severity score of 3.0) were observed in the kidneys 25 days after rats were administered 1 mg vanadium/kg/day as ammonium metavanadate via subcutaneous injection (Al-Bayati et al. 2002). Administration of the antifibrotic agent, pirfenidone, for 41 days after exposure termination resulted in a decrease in the severity of the kidney lesions; the lesions were scored as very mild with a severity score of 1.42. Although the mechanism associated with the reduction in toxicity was not determined, it is possible that the pirfenidone-induced reduction in collagen-deposition in the kidney may have contributed to the diminished toxicity. Chandra et al. (2007a) demonstrated a reduction in testes toxicity in rats administered 0.4 mg vanadium/kg/day as sodium metavanadate via intraperitoneal injection for 26 days and 50 or 100 mg/kg vitamin E acetate simultaneously in the diet compared to rats administered vanadium only. The likely mechanism is that

vitamin E interrupts the chain reactions of lipid peroxidation and scavenges ROS generated during the univalent reduction of molecular oxygen and normal activity of oxidative enzymes; thus its prevents the detrimental effect of vanadium on testis by inhibiting the oxidative stress.

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 vanadium 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 vanadium.

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 Vanadium

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to vanadium are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of vanadium. 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.

Data are available from humans regarding acute, intermediate, and chronic inhalation exposure to vanadium pentoxide and on immunologic and neurologic effects, primarily from case studies of factory

Figure 3-4. Existing Information on Health Effects of Vanadium and Compounds

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

Human

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

Animal

● Existing Studies

workers. Data regarding acute effects are available from volunteers who ingested ammonium vanadyl tartrate in capsules for intermediate periods. No human dermal data were located.

Data are available regarding the effects of inhalation of vanadium pentoxide in rats, mice, and monkeys following acute, intermediate, and chronic exposures. Data are available in humans orally exposed to vanadyl sulfate or ammonium metavanadate. Data are available following acute, intermediate, and chronic oral exposures in animals, including information on death (from ammonium metavanadate, sodium metavanadate, or vanadyl sulfate), systemic toxicity (from vanadyl sulfate, sodium metavanadate, sodium orthovanadate, or ammonium metavanadate), immunological (from sodium orthovanadate), neurological (from vanadium pentoxide), developmental (from vandyl sulfate, sodium orthovanadate, ammonium metavanadate, or sodium metavanadate), and reproductive effects (from sodium metavanadate, ammonium metavanadate, or vanadyl sulfate). No animal dermal data were located.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information on the acute toxicity of inhaled vanadium in humans is limited to the finding of symptoms of respiratory irritation (persistent coughing) in a small number of subjects exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). Several animal studies confirm that the respiratory tract is the most sensitive target of vanadium toxicity (Knecht et al. 1985, 1992; NTP 2002). These studies only examined the respiratory tract; however, longer duration studies have confirmed the respiratory tract as the most sensitive target following inhalation exposure. At lower concentrations, the observed effects included lung inflammation and alveolar and bronchiolar epithelial hyperplasia in rats and mice exposed to vanadium pentoxide for 6 or 13 days (NTP 2002); the severity of the lung effects increased with increasing vanadium concentrations. Impaired lung function was reported in monkeys exposed to fairly low concentrations of vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992). The animal data were sufficient to derive an acute-duration inhalation MRL for vanadium based on lung inflammation in rats (NTP 2002).

There are limited data on human toxicity following ingestion of vanadium; gastrointestinal effects (diarrhea, cramps, nausea, vomiting) have been reported in patients given vanadium supplement as part of a diabetes treatment plan (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). However, these studies are limited by the small number of subjects and the lack of control groups. A small number of studies in laboratory animals have examined the acute toxicity of vanadium following oral exposure. At the lowest doses tested, marked developmental toxicity (decreases in fetal growth, increases in resorptions

and gross, visceral, and skeletal malformations and anomalies) was observed in rat and mouse offspring (Paternain et al. 1987, 1990; Sanchez et al. 1991). In adult rats, hematological effects (including increases in reticulocyte levels and polychromatophilic erythroblasts in bone marrow) were observed at higher doses than the developmental effects (Zaporowska and Wasilewski 1989). The database was considered inadequate for derivation of an acute-duration oral MRL due to the limitations in the human studies and the serious effects observed at the lowest animal dose tested. At the lowest adverse effect level, a 46% decrease in weight gain (considered a serious health effect) was observed in the rat dams (Paternain et al. 1990); it is ATSDR policy to not use serious LOAELs as the basis of an MRL. Additional studies which examine a variety of end points are needed to identify the most sensitive effect following acute oral exposure. These additional studies might provide a suitable basis for an acute-duration oral MRL.

No dermal exposure studies were identified in humans or animals. Studies are needed to establish the potential toxicity of vanadium compounds applied to the skin.

Intermediate-Duration Exposure. No human studies examined the toxicity of vanadium following intermediate-duration inhalation exposure. Animal data come from 16-day and 13-week exposure studies in rats and mice (NTP 2002). These studies clearly identify the respiratory tract as the most sensitive target of toxicity. At low concentrations of vanadium pentoxide, alveolar and bronchiolar epithelial hyperplasia were observed in both species. At higher concentrations, nasal effects were also observed. Although the NTP (2002) study is a high quality study which identified NOAEL and LOAEL values for a sensitive end point, an intermediate-duration inhalation MRL was not derived because the NOAEL value was the same as the LOAEL for lung inflammation in rats exposed to vanadium pentoxide for 13 days (NTP 2002). An explanation for the inconsistent findings is not apparent from the available data. An additional study designed to examine respiratory effects after various exposure durations may provide insight into the inconsistent findings of the NTP study and may be useful for derivation of an MRL.

Data on the toxicity of vanadium following intermediate-duration oral exposure come from two human studies and a number of animal studies. The human studies examined a number of potential end points in subjects exposed to relatively low doses of vanadium for 6–12 weeks; no adverse effects were observed (Dimond et al. 1963; Fawcett et al. 1997). Animal studies have identified several sensitive effects including hematological alterations (decreased erythrocyte levels and increased reticulocyte levels) (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993), increased blood pressure (Boscolo et al. 1994; Carmagnani et al. 1991, 1992), alterations in

neurobehavioral performance tests (Sanchez et al. 1998), and developmental toxicity (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001). However, the findings are inconsistent and a cause of the conflicting results has not been identified. Additional animal studies examining hematological, blood pressure, and neurological end points are needed to support the findings of the animal studies. An intermediate-duration oral MRL based on the NOAEL identified in one of the human studies (Fawcett et al. 1997) was derived.

No dermal exposure studies were identified in humans or animals. Studies utilizing several vanadium compounds would be useful for assessing the potential dermal toxicity of vanadium.

Chronic-Duration Exposure and Cancer. Sufficient information is available in occupationally exposed humans to identify the respiratory system as a target organ following chronic inhalation exposure (Lewis 1959; NIOSH 1983; Sjöberg 1956; Vintinner et al. 1955; Wyers 1946). Two-year rat and mouse studies (NTP 2002) confirm the identification of the respiratory tract as the most sensitive target of inhaled vanadium pentoxide. At the lowest concentrations tested, histological alterations in the lungs (alveolar and bronchiolar epithelial hyperplasia), larynx (degeneration and hyperplasia of epiglottis epithelium), and nasal cavity (goblet cell hyperplasia) were observed. The NTP (2002) rat study was used as the basis of a chronic-duration inhalation MRL for vanadium.

No studies examining the chronic oral toxicity of vanadium in humans were identified. Several studies have examined chronic oral toxicity in rats and mice (Dai and McNeill 1994; Dai et al. 1994a, 1994b; Schroeder and Balassa 1967; Schroeder et al. 1970); however, the doses tested did not result in adverse effects, with the exception of a decrease in body weight gain, and the most sensitive targets of vanadium toxicity following chronic exposure have not been identified. Additional studies examining a variety of end points, including potential hematological and cardiovascular effects (sensitive targets following intermediate-duration exposure), are needed to identify sensitive targets and establish dose-response relationships.

Data are not available to determine target organs in humans from chronic dermal exposure. Dermal exposure studies which could be used to identify targets of toxicity and dose-response relationships are needed.

No studies were located regarding the carcinogenicity in humans after inhalation, oral, or dermal exposure to vanadium. Significant increases in the incidence of lung tumors (alveolar/bronchiolar adenoma and/or

carcinoma) were observed in mice exposed to airborne vanadium pentoxide for 2 years (NTP 2002). Suggestive evidence of lung carcinogenicity was also observed in male rats chronically exposed to vanadium pentoxide (NTP 2002). Although several oral studies did not find increases in tumor frequency in rats or mice exposed to vanadyl sulfate in drinking water (Schroeder and Balassa 1967; Schroeder and Mitchener 1975; Schroeder et al. 1970), these studies were considered inadequate for carcinogenicity assessment due to the small number of animals tested, low doses (maximum tolerated dose was not achieved), incomplete histological examination, and the use of one exposure dose per study. No studies examined the potential carcinogenicity of vanadium following dermal exposure. Additional studies are needed to evaluate the potential carcinogenicity of vanadium following oral and dermal exposure.

Genotoxicity. *In vivo* genotoxicity assays have been conducted in vanadium pentoxide workers (Ehrlich et al. 2008; Ivancsits et al. 2002), in mice exposed to airborne vanadium pentoxide (NTP 2002), in mice exposed to vanadyl sulfate in drinking water (Villani et al. 2007), and in mice administered a gavage dose of vanadyl sulfate, ammonium metavanadate, or sodium orthovanadate (Ciranni et al. 1995). Most of the *in vitro* genotoxicity assays have been conducted in mammalian systems, although there are also mutagenicity assays in cultured bacteria (Kada et al. 1980; Kanematsu et al. 1980; NTP 2002) and yeast (Bronzetti et al. 1990; Sora et al. 1986). In mammalian systems, mutagenicity (Cohen et al. 1992), DNA damage (Birnboim 1988; Foresti et al. 2001; Ivancsits et al. 2002; Kleinsasser et al. 2003; Rojas et al. 1996; Smith 1983; Wozniak and Blasiak 2004), and clastogenicity (Gibson et al. 1997; Migliore et al. 1993, 1995; Owusu-Yaw et al. 1990; Roldán and Altamirano 1990; Zhong et al. 1994) have been observed. In general these studies provide evidence that vanadium compounds damage DNA and induce clastogenic alterations. However, there are a number of inconsistencies in the results and additional studies are needed.

Reproductive Toxicity. No studies were located regarding the reproductive effects in humans after inhalation, oral, or dermal exposure to vanadium. Following inhalation exposure, alterations in estrous cycle were observed in female rats exposed to vanadium pentoxide for 3 months (NTP 2002); no alterations in sperm characteristics were observed. Studies examining reproductive function are needed to evaluate whether the alterations observed in female rats would result in impaired fertility. Decreases in male and/or female fertility were observed in rats and mice orally exposed to vanadium (Ganguli et al. 1994b; Jain et al. 2007; Llobet et al. 1993; Morgan and El-Tawil 2003). Dermal exposure studies are needed to evaluate whether the reproductive system is also a target of toxicity for this route.

Developmental Toxicity. The potential developmental toxicity of vanadium has not been assessed in humans. Oral exposure studies in animals provide evidence that developmental toxicity is a sensitive end point. The observed effects include decreases in fetal/pup growth, increased mortality, and increases in gross, skeletal, and visceral malformations and anomalies (Domingo et al. 1986; Elfant and Keen 1987; Morgan and El-Tawil 2003; Paternain et al. 1987, 1990; Poggioli et al. 2001). Most of these effects occurred at doses associated with decreases in maternal food intake and body weight. Additional studies utilizing doses not associated with maternal toxicity would be useful in determining whether the observed effects are secondary to maternal toxicity or whether the developing organism is a primary target. No studies were located regarding the developmental effects in animals after inhalation or dermal exposure to vanadium. Studies are needed to determine whether developmental toxicity would also be a sensitive target following inhalation or dermal exposure.

Immunotoxicity. Data regarding the immunotoxicity of vanadium in humans are limited to a study of vanadium workers which did not find signs of allergic reactions on the skin or in the respiratory tract (Sjöberg 1950). No alterations in immune response to bacteria and/or viruses were observed in mice exposed to airborne vanadium pentoxide for 16 days (NTP 2002); an altered response was observed in rats. An altered response to sheep red blood cells in mice exposed to sodium orthovanadate in drinking water for 6 weeks (Sharma et al. 1981) and decreases in B-cell, IgG, and IgM levels in rats exposed to sodium metavanadate in the diet for 10 weeks (Adachi et al. 2000a) were observed. No dermal exposure studies examining immunological end points were identified. Although the animal data provide some suggestive evidence of immunotoxicity, additional inhalation and oral exposure studies testing a full immunology battery are needed to establish the potential of vanadium to induce immunotoxicity.

Neurotoxicity. Some workers exposed to vanadium dust complained of dizziness, depression, headache, or tremors of the fingers and arms (Levy et al. 1984; Vintinner et al. 1955); however, these effects may not have been specifically due to vanadium exposure. Neurotoxicity was not evaluated in humans following oral or dermal exposure. In animals, alterations in performance on neurobehavioral tests were observed in rats orally exposed to sodium metavanadate (Sanchez et al. 1998, 1999). No histological alterations in the nervous system were observed in rats or mice exposed to airborne vanadium pentoxide (NTP 2002). Neurotoxicity potential was not assessed in animals following dermal exposure. Additional studies performing a complete neurological battery of tests are needed to fully evaluate the potential of vanadium to induce neurotoxicity, particularly since the Sanchez et al. (1998) study provides suggestive evidence that this may be a sensitive target following oral exposure.

Epidemiological and Human Dosimetry Studies. Studies of health effects on people who have inhaled vanadium in the workplace clearly show that the target organ is the respiratory system (Domingo et al. 1985; Levy et al. 1984; Lewis 1959; Musk and Tees 1982; NIOSH 1983; Sjöberg 1950, 1956; Thomas and Stiebris 1956; Vintinner et al. 1955; Wyers 1946; Zenz and Berg 1967; Zenz et al. 1962). The dose-response relationship is not known, because exposure levels are not well quantified. Further information on exposure levels associated with respiratory effects would be useful. However, people living near hazardous waste sites are unlikely to come in contact with amounts of vanadium dusts large enough to cause adverse health effects. Further epidemiological studies may be useful in revealing adverse health effects in people living near boiler ash dumps. Additional information on potentially susceptible populations, such as those people with asthma or other respiratory problems, would be useful. There are limited data regarding the oral toxicity of vanadium in humans. Studies in diabetics have shown that bolus administration can result in symptoms of gastrointestinal irritation (Boden et al. 1996; Cusi et al. 2001; Goldfine et al. 1995). Two studies in healthy individuals (Dimond et al. 1963; Fawcett et al. 1997) examined a wide variety of potential targets of vanadium toxicity. However, both studies used a small number of subjects and additional studies are needed to evaluate the long-term toxicity of vanadium in humans, particularly since vanadium is present in a number of nutritional supplements and there is a potential for human exposure. An intermediate-duration oral study (Fawcett et al. 1997) which found no adverse effects in subjects administered vanadyl sulfate via capsules was used as the basis of an MRL.

Biomarkers of Exposure and Effect.

Exposure. Biomarkers specific for exposure to vanadium include the presence of vanadium in the urine (Gylseth et al. 1979; Kiviluoto et al. 1981b; Lewis 1959; NIOSH 1983; Zenz et al. 1962) and serum (Gylseth et al. 1979) and a green discoloration of the tongue (Lewis 1959), the latter resulting from the direct accumulation of vanadium pentoxide. Further studies would be helpful in correlating urinary or serum vanadium levels with exposure levels. Vanadium can also be measured in the hair (Stokinger et al. 1953), and studies could be performed to determine if a correlation exists between levels of vanadium in hair and exposure levels. In the 1950s, decreased cystine content of the hair or fingernails was described as a possible biomarker of exposure (Mountain et al. 1955). However, this is not specific for vanadium since other factors, such as diet or disease, can also affect cystine content.

Effect. There are no specific biomarkers of effects. It is possible that further biochemical studies might show specific effects. For example, it is possible that specific effects may be seen on lung cells, which can be examined by lavage.

Absorption, Distribution, Metabolism, and Excretion. Data are available from human and animal studies regarding the kinetics of vanadium following inhalation and oral exposure. Specific data from dermal exposure are lacking; although significant absorption of vanadium by this route in humans is unlikely (WHO 1988), data are needed to confirm this hypothesis. No animal studies were located that evaluated absorption efficiency following inhalation exposure, although NTP (2002) reported marginal, but concentration-related, increases in blood vanadium in rats exposed to vanadium pentoxide for 14 days or 2 years. Additionally, information is available from intratracheal exposures (Conklin et al. 1982; Edel and Sabbioni 1988; Oberg et al. 1978; Rhoads and Sanders 1985). Oral exposure studies suggest that approximately 3–17% of ingested vanadium is absorbed and that absorption efficiency may vary among vanadium compounds (Adachi et al. 2000b; Conklin et al. 1982). Intratracheal administration and oral exposure suggest similar patterns of distribution and excretion (Adachi et al. 2000b; Conklin et al. 1982; Ramanadham et al. 1991; Rhoads and Sanders 1985) for the two routes of exposure. Additional studies are needed to provide information on the toxicokinetic properties of vanadium following inhalation and dermal exposure. Additionally, there are limited data comparing the absorption and distribution of various vanadium compounds; inhalation, oral, and dermal exposure studies are needed to evaluate whether there are compound-specific differences.

Comparative Toxicokinetics. Animal data (Conklin et al. 1982; Oberg et al. 1978; Rhoads and Sanders 1985; Roshchin et al. 1980) and limited human (Dimond et al. 1963; Gylseth et al. 1979; Schroeder et al. 1963) data are available on the kinetics of vanadium. There is little reason to believe that vanadium toxicokinetics would differ between animals and humans. The data indicate that the kinetics are similar in both. However, as with any particulate substance, extrapolations on inhalation absorption rates from animals to humans would be difficult. Studies are available in humans, rats, mice, and dogs.

Methods for Reducing Toxic Effects. No vanadium-specific information on reducing the absorption of vanadium following inhalation, oral, or dermal exposure were identified; such information would be useful in the treatment of persons who may have been exposed to vanadium and/or its compounds near hazardous waste sites. Several animal studies have explored the use of chelating agents for reducing the vanadium body burden. Administration of ascorbic acid, tiron, deferoxamine mesylate, or 2-mercaptosuccinic have been shown to increase urinary excretion of vanadium or reduce kidney levels

(Domingo et al. 1990; Gomez et al. 1988, 1991), and EDTA and tiron have been shown to reduce toxicity (Domingo et al. 1993a; Jones and Basinger 1983; Mitchell and Floyd 1954; Sanchez et al. 1999), presumably by reducing the body burden. There is some evidence that pirfenidone (an antifibrotic agent) (Al-Bayati et al. 2002) and vitamin E (Chandra et al. 2007a) may interfere with the mechanism of vanadium toxicity. Additional data are needed, particularly studies examining methods for reducing the toxicity of inhaled vanadium.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are limited data on the susceptibility of children to vanadium toxicity. No human or animal studies examined possible age-related differences in toxicity following inhalation, oral, or dermal exposure. An intraperitoneal study found decreases in the severity of renal lesions in young rats (22 days of age) compared to older rats (62 days of age) (de la Torre et al. 1999). Additional studies are needed to evaluate if there are age-related differences in vanadium toxicity or toxicokinetic properties.

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

3.12.3 Ongoing Studies

No ongoing studies examining the toxicity or toxicokinetics of vanadium were identified.

This page is intentionally blank.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Vanadium is a naturally occurring element that appears in group 5(B5) of the periodic table (Lide 2008). Vanadium is widely distributed in the earth's crust at an average concentration of 100 ppm (approximately 100 mg/kg), similar to that of zinc and nickel (Byerrum 1991). Vanadium is the 22nd most abundant element in the earth's crust (Baroch 2006). Vanadium is found in about 65 different minerals; carnotite, roscoelite, vanadinite, and patronite are important sources of this metal along with bravoite and davidite (Baroch 2006, Lide 2008). It is also found in phosphate rock and certain ores and is present in some crude oils as organic complexes (Lide 2008). Table 4-1 lists common synonyms and other pertinent identification information for vanadium and representative vanadium compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Vanadium is a gray metal with a body-centered cubic crystal system. It is a member of the first transition series. Because of its high melting point, it is referred to as a refractory metal (Baroch 2006). When highly pure, it is a bright white metal that is soft and ductile. It has good structural strength and a low-fission neutron cross section. Vanadium has good corrosion resistance to alkalis, sulfuric and hydrochloric acid, and salt water; however, the metal oxidizes readily above 660 °C (Lide 2008). The chemistry of vanadium compounds is related to the oxidation state of the vanadium (Woolery 2005). Vanadium has oxidation states of +2, +3, +4, and +5. When heated in air at different temperatures, it oxidizes to a brownish black trioxide, a blue black tetraoxide, or a reddish orange pentoxide. It reacts with chlorine at fairly low temperatures (180 °C) forming vanadium tetrachloride and with carbon and nitrogen at high temperatures forming VC and VN, respectively. The pure metal in massive form is relatively inert toward oxygen, nitrogen, and hydrogen at room temperature (HSDB 2009). Vanadium pentoxide is an industrially important vanadium compound (Lide 2008). Table 4-2 lists important physical and chemical properties of vanadium and vanadium compounds.

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

Characteristic	Vanadium	Vanadium pentoxide	Vanadyl sulfate
Synonym(s)	Vanadium, elemental	Vanadium oxide; vanadium(V) oxide; vanadic anhydride; divanadium pentoxide	Vanadic sulfate; vanadium oxide sulfate
Registered trade name(s)			
Chemical formula	V	V_2O_5	$VOSO_4$
Identification numbers:			
CAS registry	7440-62-2	1314-62-1	27774-13-6
EINECS	231-171-1	215-239-8	248-652-7
RTECS[b]	YW1355000	YW2450000	YW1925000
EPA hazardous waste	No data	P120	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	UN2862	UN2931
HSDB	1022	1024	1026
NCI	No data	No data	No data

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

Characteristic	Sodium metavanadate	Sodium orthovanadate	Ammonium metavanadate
Synonym(s)	Sodium vanadate(V); vanadic acid, monosodium	Sodium o-vanadate; sodium pervanadate; sodium vanadium oxide; vanadic(II) acid, trisodium salt	Ammonium vanadate(V); ammonium monovanadate; ammonium vanadium oxide; ammonium vanadium trioxide; vanadic acid, ammonium salt
Registered trade name(s)			
Chemical formula	$NaVO_3$	Na_3VO_4	NH_4VO_3
Identification numbers:			
CAS registry	13718-26-8	13721-39-6	7803-55-6
EINECS	237-272-7	237-287-9	232-261-3
RTECS[b]	YW1050000	YW1120000	YW0875000
EPA hazardous waste	No data	No data	P119
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	UN2859
HSDB	No data	No data	6310
NCI	No data	No data	No data

[a]All information obtained from ChemIDPlus 2009 and HSDB 2009, except where noted.
[b]RTECS 2009

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = 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; 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

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

Property	Vanadium	Vanadium pentoxide	Vanadyl sulfate dihydrate
Molecular weight	50.9415	181.88	199.035[c]
Color	Light gray or white lustrous powder, fused hard lumps or body-centered cubic crystals. Pure vanadium is bright white, soft and ductile.	Yellow to rust-brown orthorhombic crystals. Yellow-orange powder or dark-gray flakes dispersed in air. Yellow to red crystalline powder.	Blue crystalline powder[c]
Physical state	Solid[b]	Solid[b]	Solid
Melting point	1,910 °C	690 °C	
Boiling point	3,407 °C	1,750 °C (decomposes)	
Density at 18.7 °C	6.11	3.357	No data
Odor	No data	Odorless	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Insoluble	1 g dissolves in approximately 125 mL water	Soluble in water[c]
Other solvents	Soluble in nitric, hydrofluoric, and concentrated sulfuric acids; attacked by alkali, forming water soluble vanadates	Soluble in concentrated acids, alkalies; insoluble in alcohol	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	2.34×10^{-2} mm Hg at 1,916 °C (extrapolated)	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

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

Property	Sodium metavanadate	Sodium orthovanadate	Ammonium metavanadate
Molecular weight	121.830[c]	183.909[c]	116.98
Color	Colorless, monoclinic, prismatic crystals or pale-green crystalline powder[b]	Colorless, hexagonal prisms[b]	White or slightly yellow, crystalline powder
Physical state	Solid	Solid	Solid
Melting point	630°C[b]	850–866 °C[b]	200 °C
Boiling point	No data	No data	No data
Density	No data	No data	2.326 g/cm^3
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	21 g/100 g water at 25 °C[c]	Soluble in water[c]	Slightly soluble in cold water
Other Solvents	No data	Insoluble in ethanol[c]	Insoluble in alcohol, ether, ammonium chloride
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log 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	No data
Flashpoint	No data	No data	No data
Flammability limits	Noncombustible[b]	No data	Nonflammable[b]
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

[a]All information obtained from HSDB 2009, except where noted.
[b]Lewis 2007
[c]Lide 2008
[d]Vanadyl sulfate pentahydrate - Ethereal blue solid; readily soluble in water

This page is intentionally blank.

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

5.1 PRODUCTION

TRI information is available in the TRI database on facilities that manufacture or process vanadium (except when contained in an alloy) and vanadium compounds for Release Year 2007, in accordance with Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (TRI07 2009).

Seven U.S. firms produced ferrovanadium, vanadium pentoxide, vanadium metal, and vanadium-bearing chemicals or specialty alloys by processing materials such as petroleum residues, spent catalysts, utility ash, and vanadium-bearing pig iron slag (USGS 2009a).

Vanadium occurs in uranium-bearing minerals of Colorado, in the copper, lead, and zinc vanadates of Africa, and with certain phosphatic shales and phosphate rocks in the western United States. Commercial production from petroleum ash holds promise as an important source of vanadium. It is a constituent of titaniferous magnetites that are widely distributed in Russia, South Africa, Finland, People's Republic of China, eastern and western United Sates, and Australia. The vanadium deposits from sulfide and vanadate ores in the Peruvian Andes have been depleted. Most reserves are in deposits where vanadium would be a by-product or co-product with other minerals, including phosphate, titanium, iron, and petroleum (Baroch 2006). High-purity ductile vanadium can be obtained by reduction of vanadium chloride with magnesium or with magnesium-sodium mixtures. Much of the vanadium metal now being produced is made by calcium reduction of V_2O_5 in a pressure vessel (Lide 2008).

World mine production reported for 2008 (in metric tons) was: China, 20,000; Russia, 16,000; South Africa, 23,000; and other countries, 1,000, or about 60,000 metric tons for the world (USGS 2009a).

Table 5-1 lists the facilities in each state that manufacture or process vanadium (except when contained in an alloy), the intended use, and the range of maximum amounts of this material that are stored on site. Table 5-2 lists the facilities in each state that manufacture or process vanadium compounds, the intended use, and the range of maximum amounts of this material that are stored on site. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI07 2009). Only certain types of facilities were required to report (EPA 2005b). Therefore, this is not an exhaustive list.

Current U.S. manufacturers of vanadium and selected vanadium compounds are given in Table 5-3.

Table 5-1. Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	7	100	49,999,999	1, 2, 3, 5, 7, 12, 13, 14
AR	4	0	99,999	1, 5, 13, 14
AZ	5	10,000	9,999,999	1, 2, 3, 4, 5, 6, 12, 13, 14
CA	12	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
CT	2	10,000	999,999	1, 4, 5, 9, 12
FL	8	0	999,999	1, 4, 5, 9, 10, 12, 13, 14
GA	1	1,000,000	9,999,999	1, 11, 13
ID	3	100,000	999,999	1, 3, 5, 12
IL	9	0	999,999	1, 5, 7, 12, 13
IN	3	0	999,999	8, 10, 14
KS	4	100	999,999	1, 5, 11, 12, 14
KY	6	0	99,999	1, 5, 7, 8, 11, 12
LA	7	0	999,999	1, 2, 3, 6, 7, 10, 12, 13, 14
MD	3	0	99,999	1, 5
MI	2	1,000	99,999	2, 5, 7, 8, 11, 14
MO	1	1,000	9,999	12
MS	3	10,000	999,999	2, 3, 8, 10
NC	1	1,000	9,999	8
ND	1	100,000	999,999	1, 5, 12
NE	3	10,000	99,999	1, 3, 4, 5, 9, 12, 13
NJ	1	10,000	99,999	2, 13
NM	2	10,000	9,999,999	12
NY	3	100	999,999	1, 5, 6
OH	14	0	9,999,999	1, 3, 4, 5, 7, 8, 11, 12, 13, 14
OK	2	10,000	99,999	1, 5, 11, 14
PA	8	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 12
PR	1	0	0	0
SC	10	0	999,999	1, 3, 4, 5, 6, 9, 12, 13
TN	4	100	9,999	1, 2, 3, 5, 9, 13, 14
TX	24	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	3	0	99,999	1, 2, 5, 12, 13, 14
WI	1	1,000	9,999	7, 8

Table 5-1. Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
WV	2	1,000	99,999	10, 12
WY	2	10,000	99,999	10, 12

[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

Source: TRI07 2009 (Data are from 2007)

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	25	0	999,999	1, 3, 4, 5, 7, 8, 9, 12, 13, 14
AR	16	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	19	1,000	99,999,999	1, 3, 4, 5, 6, 9, 10, 12, 13, 14
CA	28	0	49,999,999	1, 2, 3, 4, 5, 6, 9, 10, 11, 12, 13, 14
CO	21	100	999,999	1, 4, 5, 9, 12, 13, 14
CT	5	100	9,999	1, 4, 5, 9, 12, 13
DE	10	0	999,999	1, 2, 5, 9, 10, 12, 13
FL	51	0	9,999,999	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14
GA	27	0	49,999,999	1, 3, 4, 5, 7, 9, 10, 12, 13, 14
HI	1	100	999	1, 5
IA	14	0	999,999	1, 3, 4, 5, 9, 12, 13, 14
ID	11	0	49,999,999	1, 2, 3, 5, 6, 10, 14
IL	45	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 14
IN	52	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
KS	19	0	999,999	1, 3, 4, 5, 9, 10, 12, 13, 14
KY	23	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
LA	50	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	10	1,000	99,999	1, 2, 5, 9, 11, 12, 13, 14
MD	16	0	999,999	1, 4, 5, 6, 7, 9, 12, 13, 14
ME	7	0	99,999	1, 5, 12, 13
MI	37	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
MN	10	100	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14
MO	21	0	999,999	1, 3, 5, 9, 10, 12, 13, 14
MS	14	0	9,999,999	1, 2, 3, 4, 5, 8, 9, 10, 13, 14
MT	5	100	999,999	1, 5, 9, 12, 14
NC	32	0	9,999,999	1, 2, 3, 4, 5, 7, 9, 12, 13, 14
ND	6	10,000	999,999	1, 5, 9, 12, 13, 14
NE	9	10,000	999,999	1, 3, 4, 5, 9, 12, 13
NH	7	0	999,999	1, 5, 9
NJ	20	100	999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14
NM	8	1,000	999,999	1, 3, 4, 5, 9, 12, 13, 14
NV	22	0	499,999,999	1, 2, 3, 5, 6, 9, 10, 12, 13, 14
NY	21	0	999,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
OH	46	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	14	1,000	99,999	1, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14
OR	3	1,000	99,999	1, 3, 4, 5, 9, 14
PA	59	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Vanadium 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	8	0	99,999	1, 2, 5, 10, 13
SC	18	0	9,999,999	1, 3, 4, 5, 7, 8, 9, 12, 13, 14
SD	2	10,000	99,999	1, 5, 9, 13, 14
TN	25	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
TX	69	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
UT	26	100	49,999,999	1, 2, 3, 4, 5, 7, 9, 10, 11, 12, 13, 14
VA	21	0	999,999	1, 3, 4, 5, 8, 9, 10, 12, 13, 14
VI	1	100,000	999,999	10, 14
WA	3	10,000	999,999	1, 3, 4, 5, 9, 12, 13
WI	17	0	999,999	1, 3, 4, 5, 9, 12, 13, 14
WV	26	0	999,999	1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 14

[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

Source: TRI07 2009 (Data are from 2007)

Table 5-3. Current U.S. Manufacturers of Vanadium and Selected Vanadium Compounds[a]

Company	Location
Vanadium	
International Specialty Alloys	New Castle, Pennsylvania
Vanadium pentoxide	
Denison Mines (USA) Corp.	Blanding, Utah
Gulf Chemical & Metallurgical Corp.	Freeport, Texas
Stratcor, Inc.	Hot Springs, Arizona
Vanadyl sulfate	
The Shepherd Chemical Co.	Cincinnati, Ohio
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Stratcor, Inc.	Hot Springs, Arizona
Sodium metavanadate	
Denison Mines (USA) Corp.	Blanding, Utah
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Sodium orthovanadate	
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Ammonium metavanadate	
Denison Mines (USA) Corp.	Blanding, Utah
Shieldalloy Metallurgical Corp.; Specialty Products Division	Cambridge, Ohio
Stratcor, Inc.	Hot Springs, Arizona

[a]Stanford Research Institute (SRI 2008), except where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.
[b]USGS 2009b

5.2 IMPORT/EXPORT

Import sources of ferrovanadium from 2004 to 2007 were 76% of the Czech Republic, 7% from Swaziland, 6% from Canada, 6% from the Republic of Korea and 5% from other sources. Vanadium pentoxide import sources in this same time period were 59% from South Africa, 20% from China, 18% from Russia, and 3% from other sources (USGS 2009a).

5.3 USE

Vanadium is used in producing rust-resistant, spring, and high-speed tool steels. It is an important carbide stabilizer in making steels. About 80% of the vanadium produced is used as ferrovanadium as a steel additive. Vanadium foil is used as a bonding agent in cladding titanium to steel. Vanadium pentoxide is used in ceramics and as a catalyst as well as in producing a superconductive magnet with a field of 175,000 gauss (Lide 2008). Metallurgical use as an alloying agent for iron and steel accounted for approximately 92% of domestic vanadium consumption in 2008 (USGS 2009a).

Vanadium, as elemental vanadium or vanadyl sulfate, also may be found in various commercial nutritional supplements and multivitamins (NLM 2009). Vanadyl sulfate and sodium metavanadate have been used in supplements for individuals with diabetes, as well by weight training athletes (Barceloux 1999; IOM 2001; Smith et al. 2008).

5.4 DISPOSAL

Waste material contaminated with vanadium should be disposed of in a manner not hazardous to employees. The disposal method must conform to applicable local, state, and federal regulations and must not constitute a hazard to the surrounding population or environment. Chemical precipitation has been investigated as a possible wastewater treatment technology for vanadium (EPA 1982).

Approximately 8.8×10^5 and 7.0×10^5 pounds of vanadium (except when contained in an alloy) and vanadium compounds, respectively, were reported for on-site disposal and other releases in 2007. On-site disposal or other releases include emissions to the air, discharges to bodies of water, disposal at the facility to land, and disposal in underground injection wells. Approximately 1.2×10^6 and 9.6×10^6 pounds of vanadium (except when contained in an alloy) and vanadium compounds, respectively, were reported for off-site disposal and other releases in 2007. An off-site disposal or other release is a discharge of a

toxic chemical to the environment that occurs as a result of a facility's transferring a waste containing a TRI chemical off-site for disposal or other release (TRI07 2009). The TRI data should be used with caution because only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list.

Some tool steel scrap was recycled mainly for its vanadium content, and vanadium was recycled from spent chemical process catalysts; however, these two sources together accounted for only a small percentage (USGS 2009a).

6. POTENTIAL FOR HUMAN EXPOSURE

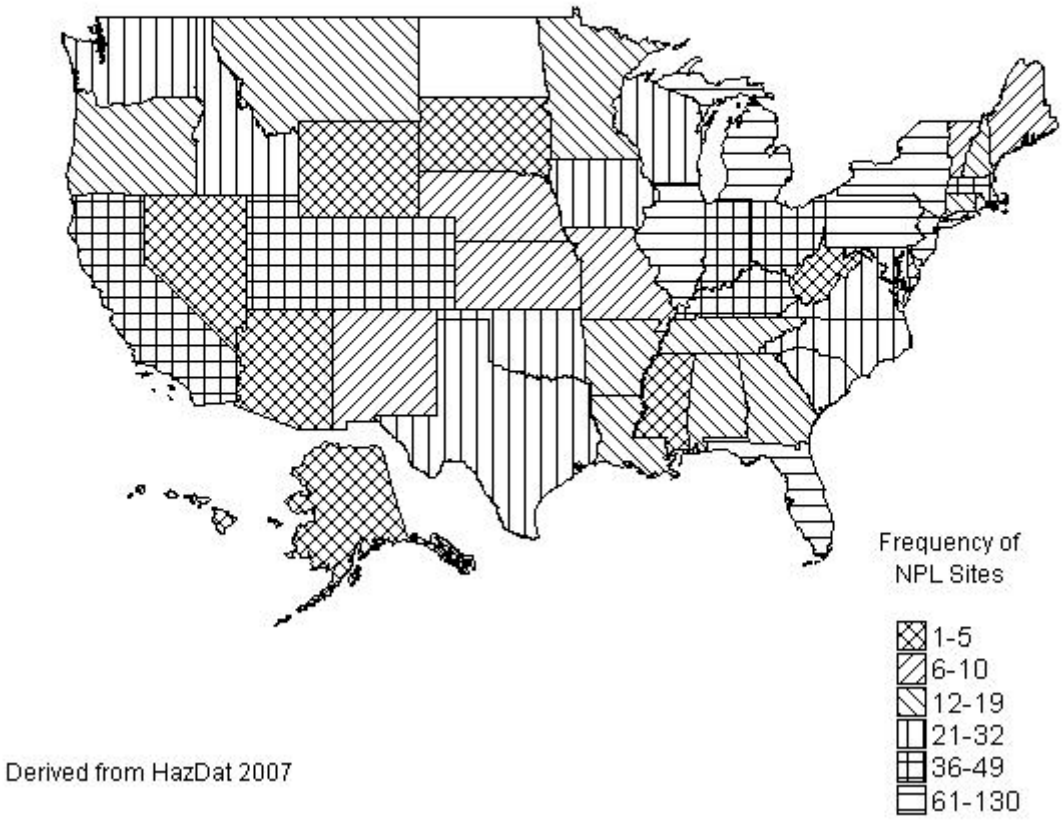
6.1 OVERVIEW

Vanadium has been identified in at least 319 of the 1,699 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2007). However, the number of sites evaluated for vanadium is not known. The frequency of these sites can be seen in Figure 6-1. All of these sites are located within the United States.

Vanadium is widely distributed in the earth's crust at an average concentration of 100 ppm (approximately 100 mg/kg), similar to that of zinc and nickel (Byerrum 1991). Vanadium is the 22nd most abundant element in the earth's crust (Baroch 2006). There are about 65 different vanadium-containing minerals; carnotite, roscoelite, vanadinite, and patronite are important sources of this metal along with bravoite and davidite (Baroch 2006; Lide 2008). It is also found in phosphate rock and certain ores and is present in some crude oils as organic complexes (Lide 2008).

Vanadium is released naturally to the atmosphere by the formation of continental dust, marine aerosols, and volcanic emissions. Vanadium is a constituent of nearly all coal and petroleum crude oils. Eastern U.S. coal has an average vanadium content of approximately 30 ppm, while coal from western states has average content of 15 ppm, and coal from the interior portion of the United States contains an average vanadium concentration of 34 ppm (Byerrum et al. 1974). The average vanadium content of bituminous and anthracite coal is 30 and 125 ppm, respectively (Byerrum et al. 1974). The most important anthropogenic sources of vanadium include the combustion of fossil fuels, particularly residual fuel oils, which constitute the single largest overall release of vanadium to the atmosphere. While the levels of vanadium in residual fuel oil vary by source, levels of 1–1,400 ppm have been reported (Byerrum et al. 1974). Natural gas and distillate fuel oils contain very low or undetectable levels (<0.05 ppm) of vanadium and are not considered a significant source of vanadium to the environment, except in the case of large accidental spills. The natural release of vanadium to water and soils occurs primarily as a result of weathering of rocks and soil erosion. This process usually involves the conversion of the less-soluble trivalent form to the more soluble pentavalent form. Deposition of atmospheric vanadium is also an important source both near and far from industrial plants burning residual fuel oils rich in vanadium. Other anthropogenic sources include leachates from mining tailings, vanadium-enriched slag heaps, municipal sewage sludge, and certain fertilizers. Natural releases to water and soil are far greater overall than anthropogenic releases to the atmosphere.

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



Ambient atmospheric levels of vanadium are generally low (parts per trillion range) in rural and remote areas and greater in urban locations; however, vanadium levels in both rural and urban locations in the eastern United States tend to be significantly higher than in other areas throughout the country, particularly during winter months. A high density of oil fired power plants that consume vanadium-rich residual fuel oil stretching from southern New York to North Carolina are likely to be the greatest potential source of the high vanadium levels observed in the eastern United States (Polissar et al. 2001). In 2007, the Department of Energy reported that nearly 80% of the residual fuel oil consumed for power generation was purchased in the East Coast districts (DOE 2008).

The general population is exposed to background levels of vanadium primarily through ingestion of food. Vanadium in food is mainly ingested as VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2-} (vanadate) (Sepe et al. 2003). Vanadium, as elemental vanadium or vanadyl sulfate, is also found in some dietary supplements and multivitamins; consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed those from food. Workers in industries processing or using vanadium compounds are commonly exposed to higher than background levels of vanadium as vanadium oxides via the inhalation pathway. Exposure to vanadium oxides through inhalation may also be of importance in urban areas, particularly in the northeastern United States where large amounts of residual fuel oil are burned. Other populations possibly exposed to higher-than-background levels, include those ingesting foodstuffs contaminated by vanadium-enriched soil, fertilizers, or sludge. Populations in the vicinity of vanadium-containing hazardous waste sites may also be exposed to higher than background levels. Individuals exposed to cigarette smoke may also be exposed to higher-than-background levels of vanadium.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities

primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005b).

6.2.1 Air

Estimated releases of 8.1×10^4 pounds (~37 metric tons) of vanadium (except when contained in an alloy) to the atmosphere from 49 domestic manufacturing and processing facilities in 2007, accounted for about 3.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). Estimated releases of 6.0×10^5 pounds (~270 metric tons) of vanadium compounds to the atmosphere from 520 domestic manufacturing and processing facilities in 2007, accounted for about 1.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). These releases are summarized in Tables 6-1 and 6-2.

Natural sources of atmospheric vanadium include continental dust, marine aerosol, and volcanic emissions (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980; Zoller et al. 1973). The quantities entering the atmosphere from each of these sources are uncertain; however, continental dust is believed to account for the largest portion of naturally emitted atmospheric vanadium followed by marine aerosols. Contributions from volcanic emissions are believed to be negligible when compared with the other two sources (Zoller et al. 1973).

Combustion of heavy fuels, especially in oil-fired power plants, refineries, and industrial boilers, and coal are the major source of anthropogenic emissions of vanadium into the atmosphere (Mamane and Pirrone 1998; Sepe et al. 2003). Global anthropogenic atmospheric emission of vanadium as been estimated to be 2.1×10^5 metric tons (MT)/year, 3 times higher than vanadium releases due to natural sources. However, other estimates indicated that anthropogenic releases of particulate-bound vanadium (9×10^4 MT/year) were more similar to releases due natural sources, such as continental or volcanic dusts, which have releases of 7×10^4 and 1×10^4 MT/year, respectively) (Mamane and Pirrone 1998).

Fuel oils may contain vanadium in concentrations ranging from 1 to 1,400 ppm, depending on their origin (Byerrum et al. 1974). During the combustion of residual oils organovanadium compounds found in fuel oils are oxidized and transformed into various compounds (e.g., vanadium pentoxide, vanadium tetroxide, vanadium trioxide, and vanadium dioxide). These compounds are emitted as fly ash into the atmosphere (Mamane and Pirrone 1998).

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	17,181	0	0	3,436	0	20,617	0	20,617
AR	2	6	0	0	0	1,739	6	1,739	1,745
AZ	2	77	0	0	187,092	0	187,167	2	187,169
CA	4	252	310	0	127,011	5	76,332	51,246	127,578
ID	1	38	0	0	244,713	0	244,751	0	244,751
IL	1	0	0	0	3,068	0	0	3,068	3,068
KS	3	5,709	0	0	102,300	608,717	11,009	705,717	716,726
KY	1	14	0	0	0	0	14	0	14
LA	2	140	5,152	0	56,388	0	5,292	56,388	61,680
MO	1	0	0	0	0	20	0	20	20
MS	1	0	0	0	131,300	0	0	131,300	131,300
ND	1	48,088	0	0	86,381	0	90,782	43,687	134,469
NE	1	140	0	0	13,000	0	13,140	0	13,140
NY	1	0	0	0	949	64,880	0	65,828	65,828
OH	6	1,614	1,674	2	138,507	26,328	48,265	119,860	168,125
PA	3	3,279	0	0	5	35,104	3,284	35,104	38,388
PR	1	0	0	0	0	0	0	0	0
SC	1	1,000	1,972	0	107	0	3,079	0	3,079
TN	1	10	0	0	1,512	274	10	1,786	1,796
TX	12	3,212	19,799	0	17,938	5	25,004	15,950	40,954
VA	1	83	15	0	4,108	4	98	4,112	4,210
WV	1	0	0	0	52,255	0	52,255	0	52,255

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium (Except When Contained in an Alloy)[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	1	201	0	0	100,057	0	100,258	0	100,258
Total	49	81,043	28,922	2	1,270,126	737,076	881,362	1,235,808	2,117,170

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI07 2009 (Data are from 2007)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	21	14,224	9,379	0	1,694,971	27	1,711,492	7,109	1,718,601
AR	8	16,188	169,170	0	1,709,832	1,858	1,895,125	1,923	1,897,048
AZ	7	1,099	0	0	244,363	0	245,462	0	245,462
CA	13	187	1,052	0	86,238	15	994	86,498	87,492
CO	10	1,375	119	0	303,890	7,052	163,631	148,805	312,436
CT	2	0	0	0	20,009	0	0	20,009	20,009
DE	4	1,743	17,501	0	428,513	179,436	56,244	570,949	627,193
FL	21	54,752	1,481	33,315	4,958,132	28,031	1,785,451	3,290,260	5,075,711
GA	15	27,261	20,059	0	1,873,231	0	1,881,251	39,300	1,920,551
IA	7	1,571	5	0	173,500	12,644	168,976	18,744	187,720
ID	2	3,819	1,405	0	616,407	1,620	621,632	1,620	623,252
IL	22	28,755	10,927	0	418,991	321	341,886	117,108	458,994
IN	29	19,920	12,250	0	3,311,659	18,648	2,693,285	669,192	3,362,477
KS	8	11,820	1	0	259,993	0	271,382	432	271,814
KY	23	20,580	21,751	0	3,198,893	124,137	3,054,104	311,257	3,365,361
LA	24	147,927	55,994	0	332,235	6,722	436,791	106,087	542,878
MA	4	4,938	2,491	0	64,314	0	38,274	33,469	71,743
MD	8	5,704	1,597	0	159,347	260,048	56,863	369,833	426,697
ME	2	1,500	4,662	0	21,274	0	27,436	0	27,436
MI	17	6,036	7,869	0	832,882	2,358	622,845	226,300	849,145
MN	5	2,070	863	0	392,039	3,182	277,956	120,198	398,154
MO	11	6,124	25	0	262,566	0	268,310	405	268,715
MS	8	1,037	67,469	1,261,497	2,701,215	0	4,030,172	1,046	4,031,218
MT	2	2,832	10	0	215,880	12,930	218,722	12,930	231,652
NC	20	15,186	8,878	0	1,373,808	15,355	1,350,201	63,027	1,413,228
ND	3	1,115	0	0	143,171	679	136,742	8,223	144,965
NE	3	2,615	0	0	78,511	0	81,126	0	81,126
NH	3	1,075	0	0	10,380	0	2,975	8,480	11,455
NJ	7	1,638	16,250	0	5,018	6,300	17,638	11,568	29,206
NM	5	1,971	830	0	490,597	0	493,398	0	493,398
NV	5	17	0	0	2,201,622	0	2,201,639	0	2,201,639
NY	9	20,512	3,276	0	585,147	247,051	551,640	304,346	855,986
OH	26	106,896	1,139	1,810	2,159,259	162,350	1,793,794	637,660	2,431,454
OK	10	2,842	11	0	126,270	0	77,723	51,400	129,123

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Vanadium Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OR	1	305	0	0	9,900	0	10,205	0	10,205
PA	29	13,634	1,127	0	1,499,090	550	936,936	577,465	1,514,401
PR	1	0	0	0	0	0	0	0	0
SC	16	4,754	4,227	0	276,695	322	263,725	22,274	285,999
SD	1	104	0	0	17,100	0	13,104	4,100	17,204
TN	15	3,931	30,351	0	1,508,290	0	1,268,104	274,468	1,542,572
TX	33	25,734	6,258	11,292	1,652,925	120,018	1,642,602	173,625	1,816,227
UT	9	1,021	1,000	0	284,148	28,151	285,391	28,929	314,320
VA	16	4,059	5,687	0	693,368	38,974	632,757	109,331	742,088
VI	1	37	8,387	0	24,878	0	11,990	21,312	33,302
WA	1	387	182	0	96,659	0	97,228	0	97,228
WI	14	4,914	868	0	577,355	131,721	106,054	608,803	714,857
WV	15	4,775	991	0	2,085,660	38,000	1,681,804	447,622	2,129,425
WY	4	1,913	0	0	244,462	0	176,966	69,409	246,375
Total	520	600,897	495,542	1,307,914	40,424,686	1,448,501	34,702,024	9,575,516	44,277,540

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI07 2009 (Data are from 2007)

Vanadium has not been identified in air collected at current or former NPL hazardous waste sites where vanadium was detected in some environmental media (HazDat 2007).

6.2.2 Water

Estimated releases of 2.9×10^4 pounds (~13 metric tons) of vanadium (except when contained in an alloy) to surface water from 49 domestic manufacturing and processing facilities in 2007, accounted for about 1.4% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). Estimated releases of 5.0×10^5 pounds (~230 metric tons) of vanadium compounds to surface water from 520 domestic manufacturing and processing facilities in 2007, accounted for about 1.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). These releases are summarized in Tables 6-1 and 6-2.

Natural sources of vanadium release to water include wet and dry deposition, soil erosion, and leaching from rocks and soils. The largest amount of vanadium release occurs naturally through water erosion of land surfaces. It has been estimated that approximately 32,300 tons of vanadium are dissolved and transported to the oceans by water, and an additional 308,650 tons are thought to be transported in the form of particulate and suspended sediment (Van Zinderen Bakker and Jaworski 1980).

Anthropogenic releases to water and sediments are far smaller than natural sources (Van Zinderen Bakker and Jaworski 1980). Such sources of vanadium in water may include leaching from the residue of ores and clays, vanadium-enriched slags, urban sewage sludge, and certain fertilizers, all of which are subjected to rain and groundwater drainage, as well as leachate from ash ponds and coal preparation wastes (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980). Leaching may potentially occur from landfills and from the airborne particulate matter that is deposited in areas with high residual fuel oil combustion, although neither of these release sources is documented.

Vanadium has been identified in groundwater and surface water at 224 and 129 sites, respectively, of the 319 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2007).

6.2.3 Soil

Estimated releases of 1.3 million pounds (~580 metric tons) of vanadium (except when contained in an alloy) to soils from 49 domestic manufacturing and processing facilities in 2007, accounted for about 60%

of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). An additional 2 pounds (~0.9 kilograms) of vanadium were released via underground injection (TRI07 2009). Estimated releases of 40 million pounds (~1.8×10^4 metric tons) of vanadium compounds to soils from 520 domestic manufacturing and processing facilities in 2007, accounted for about 91% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). An estimated 1.3 million pounds (~590 metric tons) of vanadium compounds were released via underground injection from 520 domestic manufacturing and processing facilities in 2007, accounted for about 3.0% of the estimated total environmental releases from facilities required to report to the TRI (TRI07 2009). These releases are summarized in Tables 6-1 and 6-2.

Natural releases of vanadium to soil result from weathering of rock-bearing vanadium minerals, precipitation of vanadium particulate from the atmosphere, deposition of suspended particulate from water, and plant and animal wastes. The largest amount of vanadium released to soil occurs through the natural weathering of geological formations (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980).

Anthropogenic releases of vanadium to soil are less widespread than natural releases and occur on a smaller scale. These include the use of certain fertilizers containing materials with a high vanadium content such as rock phosphate (10–1,000 mg/kg vanadium), superphosphate (50–2,000 mg/kg vanadium), and basic slag (1,000–5,000 mg/kg vanadium) (Van Zinderen Bakker and Jaworski 1980) as well as disposal of industrial wastes such as slag heaps and mine tailings. Additional release to the environment may also result from the disposal of vanadium-containing wastes in landfills, although this has not been specifically documented, and from wet and dry deposition of airborne particulate, particularly in areas with high levels of residual fuel oil combustion (Byerrum et al. 1974).

Vanadium has been identified in soil at 172 sites and in sediment at 44 sites collected from 319 NPL hazardous waste sites, where vanadium was detected in some environmental media (HazDat 2007).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The global biogeochemical cycling of vanadium is characterized by releases to the atmosphere, water, and land by natural and anthropogenic sources, long-range transportation of particles in both air and water, wet and dry deposition, adsorption, and complexing. Vanadium generally enters the atmosphere as an

aerosol. From natural sources, vanadium is probably in the form of mineral particles; it has been suggested that these may frequently be in the less-soluble trivalent form (Byerrum et al. 1974; Zoller et al. 1973). From human-made sources, almost all of the vanadium released to the atmosphere is in the form of simple or complex vanadium oxides (Byerrum et al. 1974).

The size distribution of vanadium-bearing particles in the atmosphere is substantially altered during long-range transportation (Zoller et al. 1973). Natural sources of vanadium, as well as man-made sources such as ore-processing dust, tend to release large particles that are more likely to settle near the source. Smaller particles, such as those emitted from oil-fueled power plants, have a longer residence time in the atmosphere and are more likely to be transported farther away from the site of release (Zoller et al. 1973). Vanadium transported within the atmosphere is eventually transferred to soil and water on the earth's surface by wet and dry deposition and dissolution in sea water (Duce and Hoffman 1976; Van Zinderen Bakker and Jaworski 1980). Eventually, in the course of biogeochemical movement between soil and water, these particulates are adsorbed to hydroxides or associated with organic compounds and are deposited on the sea bed (WHO 1988).

Deposition rates ranging from 20.5 to 84.9 $\mu g/cm^2$/day of vanadium were reported in urban dust collected between March and September 2002 from six locations Adapazarí, Turkey (Dundar 2006). Vanadium is considered a marker of air pollution emitted from residual oil and coal combustion (Mamane and Pirrone 1998).

The transport and partitioning of vanadium in water and soil is influenced by pH, redox potential, and the presence of particulate. In fresh water, vanadium generally exists in solution as the vanadyl ion (V^{4+}) under reducing conditions and the vanadate ion (V^{5+}) under oxidizing conditions, or as an integral part of, or adsorbed onto, particulate matter (Wehrli and Stumm 1989). The chemical formulas of the vanadyl species most commonly reported in fresh water are VO^{2+} and $VO(OH)^{+}$, and the vanadate species are $H_2VO_4^{-}$ and HVO_4^{2-} (Wehrli and Stumm 1989). The partitioning of vanadium between water and sediment is strongly influenced by the presence of particulate in the water. Both vanadate and vanadyl species are known to bind strongly to mineral or biogenic surfaces by adsorption or complexing (Wehrli and Stumm 1989). Thus, vanadium is transported in water in one of two ways: solution or suspension. It has been estimated that only 13% is transported in solution, while the remaining 87% is in suspension (WHO 1988).

Upon entering the ocean, vanadium in suspension or adsorbed and/or absorbed onto particulate is deposited upon the sea bed (WHO 1988). The fate of the remaining dissolved vanadium is more complex. Only about 0.001% of vanadium entering the oceans is estimated to persist in soluble form (Byerrum et al. 1974). Adsorption/absorption and biochemical processes are thought to contribute to the extraction of vanadium from sea water (WHO 1988). Adsorption to organic matter as well as to manganese oxide and ferric hydroxide, demonstrated by the high particle-water partition coefficient of 5.7×10^5 L/kg for the adsorption of manganese oxide in sea water, results in the precipitation of the dissolved vanadium (Wehrli and Stumm 1989; WHO 1988). Biochemical processes are also of importance in the partitioning from sea water to sediment (WHO 1988). Some marine organisms, in particular the ascidians (sea squirts), bioconcentrate vanadium very efficiently, attaining body concentrations approximately 10,000 times greater than the ambient sea water (Byerrum et al. 1974). Upon the death of the organism, the body burden adds to the accumulation of vanadium in silt (WHO 1988). The extent to which either bioconcentration or adsorption dominates is uncertain (WHO 1988).

In general, marine plants and invertebrates contain higher levels of vanadium than terrestrial plants and animals. In the terrestrial environment, bioconcentration is more commonly observed amongst the lower plant phyla than in the higher, seed-producing phyla. The vanadium levels in terrestrial plants are dependent upon the amount of water-soluble vanadium available in the soil, pH, and growing conditions. It has been found that the uptake of vanadium into the above-ground parts of many plants is low, although root concentrations have shown some correlation with levels in the soil (Byerrum et al. 1974). Certain legumes, such as *Astralagus preussi*, have been shown to be vanadium accumulators. Vanadium is believed to replace molybdenum as a specific catalyst in nitrogen fixation (Cannon 1963), and the root nodules of these plants may contain vanadium levels three times greater than those of the surrounding soil (Byerrum et al. 1974). Of the few plants known to actively accumulate vanadium, *Amanita muscaria*, a poisonous mushroom, has been demonstrated to contain levels up to 112 ppm (dry weight). Vanadium appears to be present in all terrestrial animals, but, in vertebrates, tissue concentrations are often so low that detection is difficult. The highest levels of vanadium in terrestrial mammals are generally found in the liver and skeletal tissues (Van Zinderen Bakker and Jaworski 1980; WHO 1988). No data are available regarding biomagnification of vanadium within the food chain, but human studies suggest that it is unlikely; most of the 1–2% vanadium that appears to be absorbed by humans following ingestion is rapidly excreted in the urine with no evidence of long-term accumulation (Fox 1987).

The form of vanadium present in the soil is determined largely by the parent rock. Ferric hydroxides and solid bitumens (organic) constitute the main carriers of vanadium in the sedimentation process. Iron acts

as a carrier for trivalent vanadium due to the high affinity between trivalent vanadium and trivalent iron, and is responsible for its diffusion through molten rocks where it becomes trapped during crystallization. The mobility of vanadium in soils is affected by the pH of the soil. Relative to other metals, vanadium is fairly mobile in neutral or alkaline soils, but its mobility decreases in acidic soils (Van Zinderen Bakker and Jaworski 1980). Similarly, under oxidizing, unsaturated conditions, some mobility is observed, but under reducing, saturated conditions, vanadium is immobile (Van Zinderen Bakker and Jaworski 1980). In a 30-month field study to examine the movement of metal ions through a profile of an acidic loamy sand soil from the Upper Coastal Plain (South Carolina), <3% of the applied vanadium, as dissolved salt (vanadyl sulfate), was found to move below the surface 7.5 cm region (Martin and Kaplan 1998). Buchter et al. (1989) reported log K_d values for various metal ions in 11 soils from 7 states in the U.S. (Louisiana, South Carolina, Hawaii, Iowa, New Hampshire, New Mexico, and Florida). Log K_d values for vanadium (applied as ammonium vanadate) ranged from 1.035 in Calciorthid soil from New Mexico (pH 8.5, 0.44% total organic carbon [TOC], 70.0% sand, 19.3% silt, 10.7% clay) to 3.347 in Kula soil from Hawaii (pH 5.9, 6.62% TOC, 73.7% sand, 25.4% silt, 0.9% clay).

6.3.2 Transformation and Degradation

As an element, vanadium cannot be degraded in the environment, but may undergo various precipitation or ligand exchange reactions. Vanadium in compounds may undergo oxidation-reduction reactions under various environmental conditions. Vanadium can be complexed by various ligands present in the environment (e.g., fulvic and humic acids). Despite forming complexes with organic matter, it is generally not incorporated into organic compounds. Thus, transformation occurs primarily between various inorganic compounds during its movement through the environment, and biotransformation is not considered to be an important environmental fate process. Vanadium can exist in many different oxidation states, ranging from -2 to +5; however, under environmental conditions, vanadium can exist in the +3, +4, or +5 oxidation states, with the +5 oxidation state being the most prevalent under most environmental conditions (Crans et al. 1998).

6.3.2.1 Air

Vanadium-containing particulates emitted to the atmosphere from anthropogenic sources are frequently simple or complex oxides (Byerrum et al. 1974) or may be associated with sulfates (Zoller et al. 1973). Generally, lower oxides formed during combustion of coal and residual fuel oils, such as vanadium trioxide, undergo further oxidation to the pentoxide form, often before leaving the stacks (EPA 1985a). The average residence time for vanadium in the atmosphere is unknown as the particle size varies

considerably. An estimated residence time of about 1 day has been proposed for the settling of fly ash vanadium pentoxide when associated with hydrogen sulfate (EPA 1985a).

6.3.2.2 Water

Vanadium entering water by leaching from vanadium-containing rocks is rapidly oxidized from less-soluble vanadium(III) to more-soluble vanadium(V), which is the most common oxidation state of vanadium found in surface waters (Byerrum et al. 1974; Crans et al. 1998). In water, vanadium can undergo hydrolytic reactions, forming oligomeric anionic species. The equilibrium of vanadium(V) in solution is sensitive to vanadium concentration, pH, ionic strength, and oxidation-reduction potential (Crans et al. 1998). The species of vanadium most likely to be found in sea water are $(H_2V_4O_{13})^{4-}$, HVO_4^{2-}, and VO^{3-} (Van Zinderen Bakker and Jaworski 1980). Vanadium(III) is only found in very reducing environments or is complexed to organic ligands (Crans et al. 1998). Vanadium is continuously precipitated from sea water by ferric hydroxides and organic matter (WHO 1988) and forms sediments on the seabed.

6.3.2.3 Sediment and Soil

There are about 65 different vanadium-containing minerals (Baroch 2006; Lide 2008). The main vanadium-containing minerals include carnotite, cuprodescloizite, descloizite, mottramite, patronite, roscoelite, and vanadinite (Crans et al. 1998). Vanadium exists in its +3 to +5 oxidation states in these minerals. Vanadium(V) is more soluble and is easily leached from soils into water. The vanadium oxides, carnotite, cuprodescloizite, descloizite, mottramite, and vanadinite, are mostly vanadium(V) minerals and comprise most of the vanadium-containing minerals. Roscoelite contains vanadium(III), and the exact chemical composition of patronite is not known (Crans et al. 1998). Weathering of rocks and minerals during soil formation may extract vanadium in the form of a complex anion that may remain in the soil or enter the hydrosphere. Vanadium remains in the soil after being precipitated from the weathering solution. This can be brought about by precipitation with polyvalent cations such as divalent calcium and divalent copper, by binding with organic complexing agents, adsorbing onto anion exchangers such as clay particles in the soil, and coprecipitating and adsorbing to hydrous ferric oxide in the soil (Van Zinderen Bakker and Jaworski 1980). In the presence of humic acids, mobile metavanadate anions can be converted to the immobile vanadyl cations resulting in local accumulation of vanadium (Van Zinderen Bakker and Jaworski 1980).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to vanadium depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of vanadium in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on vanadium levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring vanadium in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Levels of vanadium measured in ambient air vary widely between rural and urban locations, time of season, and geographical location. In general, urban locations often tend to have greater atmospheric levels of vanadium as compared to rural sites since there is a larger density of combustion sources capable of emitting particulate matter containing vanadium to the environment. Sweet et al. (1993) reported average vanadium concentrations of 3.0 and 3.0 ng/m^3 (fine particles, <2.5 μm) and 3.7 and 3.0 ng/m^3 (coarse particles, 2.5–10 μm) in samples of inhalable particulate matter collected over a 3-year sampling period in southeast Chicago and East St. Louis Illinois, respectively. Average vanadium concentrations in fine and coarse particulate matter collected from a rural site in Bondville, Illinois were 0.8 and 1.2 ng/m^3, respectively (Sweet et al. 1993). Aerosol sampling ($PM_{2.5}$ fraction) was conducted from 1988 to 1995 at a rural location in Underhill, Vermont (Polissar et al. 2001). A geometric mean concentration of 0.82 ng/m^3 was reported for vanadium, with seasonal maxima occurring during the winter and spring months and minimum concentrations observed during the summer months. A factor analysis method applied to the data determined that the most likely sources of the vanadium were oil fired power plants predominantly located in eastern Virginia, Pennsylvania, southern New York, New Jersey, Maryland, and Delaware (Polissar et al. 2001). Measurements obtained at five different rural sites in northwestern Canada were found have average vanadium concentrations of 0.72 ng/m^3 (range 0.21–1.9 ng/m^3) (Zoller et al. 1973). Between the years 1965 and 1969, average ambient vanadium concentrations in rural air in the United States ranged from <1 to 40 ng/m^3 (Byerrum et al. 1974), although some rural areas may have levels as high as 64 ng/m^3 due to localized burning of fuel oils with a high vanadium content (WHO 1988). Vanadium concentrations in air samples collected from a rural forest in Denmark that received heavy deposition from European cities were 11.5 and 4.4 ng/m^3 in samples from 1979 to 1980 and 2002 to 2005, respectively (Hovmand et al. 2008).

Northeastern locations in the United States typically have higher atmospheric levels of vanadium as compared to other regions of the country. U.S. cities were divided into two groups based on the levels of vanadium present in the atmosphere and geographic location (Zoller et al. 1973). The first group of cities is widely distributed throughout the United States and is characterized by ambient air vanadium concentrations that range from 3 to 22 ng/m^3, with an average concentration of 11 ng/m^3 (approximately 20 times that of remote areas). Cities in the second group, primarily located in the northeastern United States, had vanadium concentrations in air that ranged from 150 to 1,400 ng/m^3 with an average of 620 ng/m^3 (Zoller et al. 1973). The variation is attributed to the use of large quantities of residual fuel oil for the generation of heat and electricity, particularly during winter months

Atmospheric levels of vanadium at remote sites tend to be lower since both natural and anthropogenic emissions are typically negligible. Vanadium concentrations measured over the South Pole ranged from 0.001 to 0.002 ng/m^3 (WHO 1988) and are frequently 2 orders of magnitude smaller than those over the ocean at middle latitudes (WHO 1988). For example, vanadium concentrations in air measurements taken at nine rural sites located in the Eastern Pacific averaged 0.1 ng/m^3 (range 0.02–0.8 ng/m^3). Atmospheric aerosols were collected from Mt. Everest in May–June, 2005; vanadium concentrations ranged from 0.9 to 3.8 ng/m^3, with a mean of 1.4 ng/m^3 (Cong et al. 2008). Vanadium concentrations at other remote locations of 0.044 and 0.0039 ng/m^3 were reported for Greenland, 1988–1989 and Terra Nova Bay, Antarctica, 2000–2001, respectively (Cong et al. 2008; Mosher et al. 1993).

Vanadium was detected in exhaust aerosol collected from the Elbtunnel, a major highway tunnel in Hamburg, Germany, at an average concentration of 14.8 ng/m^3 (range: 7.6–36.9 ng/m^3) (Dannecker et al. 1990). Fine atmospheric particulate $PM_{2.5}$ (particles with diameters of <2.5 μm) were collected from November 2000 to September 2001 in Guaynabo, Puerto Rico, an urban industrialized area, and in Fajardo, Puerto Rico, a less polluted reference site (Figueroa et al. 2006). Vanadium concentrations in the $PM_{2.5}$ were 40 and 1.4 ng/m^3 for Guaynabo and Fajardo, respectively. Mean urban vanadium concentrations in winter and summer air (fine and course particulate combined) collected from the Birmingham University campus, Edgbaston, United Kingdom in January-February 1992 and July-August 1992 were 11.2 and 3.5 ng/m^3, respectively. Vanadium concentrations were higher in the fine particle fraction, 7.6 and 2.3 ng/m^3 (winter and summer), as compared to the coarse particle samples, 3.6 and 1.2 ng/m^3 (winter and summer) (Harrison et al. 1996). Mean vanadium concentrations in air samples from a central Copenhagen street (January–March 1992 and February–March 1993) and a city park (January–March 1992) were reported to be 12 and 10 ng/m^3, respectively (Nielsen 1996). Smith et al. (1996) reported mean vanadium concentrations in air samples collected from a city site, a rural site, and

an industrial site in Lahore, Pakistan in 1992–1993 of 127, 161, and 253 ng/m^3, respectively. Mean vanadium concentrations in air samples of 10, 180, and 110 ng/m^3 were reported in Karachi, Pakistan; Calcutta, India; and Bombay, India, respectively (Smith et al. 1996). Schroeder et al. (1987) reported concentration ranges of vanadium associated with particulate matter in the atmosphere: 0.001–14 ng/m^3 (remote areas); 2.7–97 ng/m^3 (rural); 10–130 ng/m^3 (urban Canada); 0.4–1,460 ng/m^3 (urban United States); 11–73 ng/m^3 (urban Europe); and 1.7–180 ng/m^3 (urban other).

Vanadium and nickel were measured in air particulate samples collected during and after the Kuwait oil fires (from March 1991 to July 1992) at Dhahran, Saudi Arabia (Sadiq and Mian 1994). Vanadium concentrations ranged from not detected to 1,165.8 ng/m^3 in the inhalable (PM_{10}, <10 μm) and from not detected to 160.26 ng/m^3 in the total suspended particulate. The minimum vanadium concentration was found in samples collected in December 1991 and gradually increased through May 1992.

Air sampling in homes in two New York counties in the winter of 1986 measured various contaminants in the indoor air (Koutrakis et al. 1992). Mean vanadium concentrations in indoor air of non-source homes (no kerosene heaters, wood stoves, or cigarette smokers), wood-burning homes, kerosene heater homes, and smoking homes were 5, 4, 6, and 6 ng/m^3, respectively. Miguel et al. (1995) reported vanadium concentrations in samples of indoor air from non-industrial office workplaces and restaurants in the cities of Sao Paulo and Rio de Janeiro, Brazil in the summer of 1993 ranging from less than the detection limit to 0.360 μg/m^3. Kinney et al. (2002) reported mean winter and summer vanadium concentrations of 9.49 and 4.17 ng/m^3 in indoor air (particle-associated) in 38 homes sampled in 1999 in the West Central Harlem section of New York City. A mean vanadium concentration of 0.8 ng/m^3 was reported inside patrol cars of ten nonsmoking North Carolina State Highway Patrol troopers during 25 work days (3 pm to midnight shift) during August–October of 2001 (Riediker et al. 2003).

6.4.2 Water

Levels of vanadium in fresh water illustrate geographic variations produced by differences in effluents and leachates, from both anthropogenic and natural sources, entering the water table. Vanadium concentrations in water can range from approximately 0.2 to >100 μg/L depending on geographical location (Sepe et al. 2003). Vanadium was detected in 3,387 of 3,625 surface water samples recorded in the STORET database for 2007–2008 at concentrations ranging from 0.04 to 104 μg/L in samples where vanadium was detected (EPA 2009a). Measurements of vanadium in such natural fresh waters as the Animas, Colorado, Green, Sacramento, San Joaquin, and San Juan Rivers, as well as some fresh water

supplies in Wyoming, range from 0.3 to 200 μg/L (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980). The presence of naturally occurring uranium ores resulted in rivers in the Colorado Plateau containing vanadium concentrations of up to 70 μg/L, and in Wyoming, vanadium concentrations in water were found to range from 30 to 220 μg/L (Byerrum et al. 1974).

Taylor et al. (2001) reported vanadium concentrations of <0.05 μg/L in water collected in June and September 1994 from the Alamosa River, Colorado and 6.2 μg/L in water collected in September 1992 from Big Arsenic Spring, New Mexico. Saleh and Wilson (1999) reported various metal concentrations in surface water from the Houston Ship Channel, Texas; vanadium concentrations ranged from 4.062 to 115.600 μg/L in samples from Buffalo Bayou and the Washburn Tunnel, respectively. Coal mining activity in the west-central region of Indiana has resulted in a number of sites where surface waters are contaminated with acidic mine drainage. Surface water samples collected from 12 locations in west-central Indiana that have been contaminated with acidic mine drainage were reported to contain vanadium at concentrations ranging from 0.17 to 0.66 mg/L (Allen et al. 1996). Kennish (1998) reported vanadium concentrations ranging from 1.0 to 38 nmol/L (0.05–1.9 μg/L) in waters from U.S. estuaries and 32 nmol/L (1.6 μg/L) in U.S. coastal marine waters.

Levels in sea water are considerably lower than those in fresh water because much of the vanadium is precipitated (Byerrum et al. 1974; Van Zinderen Bakker and Jaworski 1980). Vanadium concentrations measured usually average 1–3 μg/L (Sepe et al. 2003; Van Zinderen Bakker and Jaworski 1980), although levels as high as 29 μg/L have been reported (Byerrum et al. 1974). The total content of vanadium in sea water has been estimated to be 7.5×10^{12} kg (7.5×10^{9} metric tons) (Byerrum et al. 1974). Mean vanadium concentrations ranging from 2.08 to 2.60 μg/L were reported in seawater samples collected along the Saudi coast of the Arabian Gulf (Sadiq et al. 1992b).

Fiorentino et al. (2007) measured vanadium concentrations in groundwater collected from the southwest of the Province of Buenos Aires, Argentina; all samples contained vanadium, and concentrations ranged from 0.05 to 2.47 mg/L. Groundwater samples collected from 104 monitoring wells from shallow aquifers beneath an industrial city in the Eastern Province of Saudi Arabia contained vanadium concentrations that ranged from 0.04 to 55.69 μg/L, with a mean concentration of 7.46 μg/L (Sadiq and Alam 1997).

Vanadium is on the EPA Drinking Water Contaminant Candidate List (CCL). The contaminants on this list are known or anticipated to occur in public water systems; however, they are currently not regulated

by existing national primary drinking water regulation. Research in ongoing to determine whether regulations are needed (EPA 2008b).

Mean vanadium concentrations in tap water collected from homes participating a dietary study in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) for the National Human Exposure Assessment Survey (NHEXAS) were 1.2 and 1.0 μg/L, respectively, in samples collected after running the water at high velocity for 3 minutes (flushed tap water) and after there had been no usage of any tap water or toilet in the home for the previous 4 hours (standing tap water) (Thomas et al. 1999).

As part of the National Water-Quality Assessment Program of the U.S. Geological Survey (USGS), water samples were collected during 1991–2004 from domestic wells (private wells used for household drinking water) for analysis of drinking-water contaminants. Vanadium was detected in 452 of 662 samples, with a median concentration of 1.29 μg/L (USGS 2009c).

Lagerkvist et al. (1986) summarized older reports from the 1960s and 1970s regarding vanadium concentrations in drinking water. One report stated that 91% of drinking water samples analyzed from U.S. sources had vanadium concentrations below 10 μg/L, with an average concentration of 4.3 μg/L. In another report, the typical vanadium concentrations in drinking water were about 1 μg/L.

6.4.3 Sediment and Soil

Vanadium is widely distributed in the earth's crust at an average concentration of 100 ppm (approximately 100 mg/kg) (Byerrum 1991). The level of vanadium measured in soil is closely related to the parent rock type (Van Zinderen Bakker and Jaworski 1980; Waters 1977). A range of 3–310 mg/kg has been observed, with tundra podsols and clays exhibiting the highest concentration, 100 and 300 mg/kg, respectively (Byerrum et al. 1974). The average vanadium content of soils in the United States is 200 mg/kg (Byerrum et al. 1974) and seems to be most abundant in the western United States, especially the Colorado Plateau (Cannon 1963; Grayson 1983).

Gallagher et al. (2008) measured various metal concentrations in soils collected during the summer of 2005 from a site in Jersey City, New Jersey on the west bank of Upper New York Bay. This land was originally an intertidal mud flat and a salt marsh that was filled during 1860–1919 with material consisting of mostly debris from construction projects and refuse from New York City. It was used as a railroad yard until 1967. The site was then transferred to the New Jersey Division of Parks and Forestry

in 1970. Vanadium concentrations in soil collected from this site ranged from below the detection limit (<0.01 μg/g) to 317 μg/g, with a median value of 56.4 μg/g (Gallagher et al. 2008). Metal concentrations were measured in two alluvial soils from the lower Mississippi River Delta. Median vanadium concentrations of 3.2 and 3.8 μg/g were reported in freshly deposited alluvium soil from Bonnet Carré Spillway and in urban soil samples from New Orleans, respectively (Mielke at el. 2000).

Various trace elements were measured in 13 surface soils collected from southwestern Saskatchewan, Canada (Mermut et al. 1996). Fertilizers and pesticides are the two major anthropogenic sources of trace elements in the Canadian Prairies. Vanadium concentrations ranged from 31.75 mg/kg in Hatton soil (0–13 cm, pH 6.2, 1.32% organic content [OC], 6% clay) to 180.06 mg/kg in Sceptre soil (90–105 cm, pH 8.0, 0.85% OC, 73% clay). Clay soils were found to contain more vanadium that other soils (Mermut et al. 1996). Vanadium concentrations in 16 soil samples collected in May 2000 in the vicinity of a cement plant in Catalonia, Spain ranged from 5.6 to 12.4 mg/kg dry weight. These values were generally lower than vanadium levels found in urban areas (Schuhmacher et al. 2002). The geometric mean vanadium concentrations in 112 samples street dust and 40 samples of urban soil collected in Aviles, Northern Spain were 28.1 (range 25.0–34.0) and 34.1 (22.0–67.0) μg/g, respectively (Ordóñez et al. 2003).

Metal contamination was determined in soil samples collected from 10 locations in the Hafr Al Batin Area (Saudi Arabia) near the Saudi/Kuwaiti border following the Gulf War (1990–1991) (Sadiq et al. 1992a). Oil burning in Kuwait, atmospheric fallout of particulates form the use of explosives in the Gulf War, and other war-related ground activities created air pollution problems in the countries neighboring Kuwait. Vanadium concentrations in soil ranged from 2 mg/kg collected at the most distant sampling site from the Kuwaiti border (15–25 cm depth) to 59 mg/kg collected from a sampling site near the border (0–5 cm depth). Vanadium concentrations in soil samples were found to decrease with increasing distance from the border (Sadiq et al. 1992a). Various metal concentrations were determined in 25 surface soil samples from Surat, India, an industrial area. Vanadium concentrations ranged from 141.9 to 380.6 mg/kg with a mean 284.8 mg/kg (Krishna and Govil 2007).

Mean vanadium concentration of 44 and 82 mg/kg were reported in the sediments of Lake Huron and Lake Superior. Vanadium was detected in sediment samples from the Georgian Bay and North Channel (Lake Huron) at mean concentrations of 67 and 66 mg/kg, respectively (International Joint Commission 1978). Heit et al. (1984) reported vanadium concentrations in Rocky Mountain Lake sediments of 27.3 and 15 mg/kg dry weight in Lake Husted surface (0–2 cm) and subsurface sediments, respectively, and 35 and 32.8 mg/kg dry weight in Lake Louise surface and subsurface sediments, respectively.

Vanadium concentrations of 55 and 43 mg/kg dry weight were reported in surface sediments from Lake Haiyaha and The Loch, two other Rocky Mountain lakes. Total vanadium concentrations of 136 and 222 mg/kg dry weight were reported in sediment samples from the Texas City channel and Ashtabula River, Ohio (Engler 1979).

Four sediment cores collected January 1996 from Central Park Lake New York City, New York were analyzed for various metals including vanadium; average vanadium concentrations ranged from 87 μg/g at a depth of 44–47 cm to 665 μg/g at a depth of 12–14 cm (Chillrud et al. 1999). In 1966, approximately 35% of the residual fuel oil used in New York City was from Venezuela. Vanadium is enriched in the sulfur-rich petroleum from Venezuela. Comparison of the approximate year of deposition to vanadium concentration in the sediment for Central Park Lake showed that vanadium levels in sediments from Central Park Lake were found to decrease after restrictions on sulfur content of fuel oils used in New York City were introduced starting in 1966. The average vanadium concentration peaks at 665 μg/g in sediments from 12 to 14 cm depth, which correlates with approximately with the mid 1960s (Chillrud et al. 1999). Trace metal concentrations were measured in sediment cores collected in February 1992 from the Gulf of Mexico; the average vanadium concentration was 47.78 μg/g and ranged from 15.6 to 117.5 μg/g (Macias-Zamora et al. 1999). Metal concentrations were measured in sediment collected during early and late autumn of 1993 and 1994 from 16 locations in Lake Erie, the Niagara River, and Lake Ontario; vanadium concentrations ranged from 6.0 to 31.1 μg/kg dry weight in these sediment samples (Lowe and Day 2002).

Vanadium concentrations in surface sediments collected during 1988–1991 from the Great Astrolabe Lagoon, Fiji ranged from 2 to 726 mg/kg dry weight. This lagoon, which encompasses a number of small volcanic islands, is considered to be a pristine marine environment with minimal human impact in this study (Morrison et al. 1997).

A diesel oil spill occurred in April 2002 from a pipeline on the Pacific side of Mexico, in Salina Cruz into the San Pedro stream, Xadani estuary, and the Superior Lagoon mouth (Salazar-Coria et al. 2007). Vanadium concentrations in sediment collected after the spill during the dry and rainy seasons were 110.5 and 123.0 mg/kg dry weight at the San Pedro site, 95.4 and 148.9 mg/kg dry weight at the Piedra Estuary, 113.3 and 107.7 mg/kg dry weight at the Xadani estuary, and <5.0 mg/kg dry weight at Superior Lagoon, respectively. Vanadium concentrations in a reference site, upstream from the spill were below the limit of detection, <5.0 mg/kg dry weight.

Chemical contamination was measured in sediment from the Shuaiba Industrial Area (SIA), a coastal area in Kuwait that receives industrial effluent (Beg et al. 2001). The SIA contains a petrochemical company, three refineries, two power desalination plants, a melamine company, an industrial gas corporation, a paper products company, and other smaller industrial plants, as well as a large harbor. Vanadium concentrations were reported to range from 9.8 to 146.0 mg/kg dry weight in sediment from Shuaiba coastal area (Beg et al. 2001).

6.4.4 Other Environmental Media

The majority of foods have naturally occurring low concentrations of vanadium, many of them ≤1 ng/g (Byrne and Kosta 1978). Food items containing the highest levels of vanadium include ground parsley (1,800 ng/g dry weight), freeze-dried spinach (533–840 ng/g), wild mushrooms (50–2,000 ng/g dry weight), and oysters (455 ng/g wet weight) (Byrne and Kosta 1978). Intermediate levels are found in food types such as certain cereals (ranging from 0.7 ng/g in maize to 30 ng/g in Macedonian rice), fish (ranging from 3.5 ng/g in mackerel to 28 ng/g in freeze-dried tuna), and liver (ranging from 7.3 ng/g in beef to 38 ng/g in chicken) (Byrne and Kosta 1978). In general, seafoods have been found to be higher in vanadium than terrestrial animal tissues (WHO 1988). Vanadium concentrations in cow milk ranging from about 0.2 to 10 μg/kg also have been reported in older reports from the late 1970s and early 1960s, respectively (Lagerkvist et al. 1986). Pennington and Jones (1987) surveyed 234 foods from a 1984 collection of the FDA's Total Diet Study for various trace elements including vanadium. Sixty-four percent of the Total Diet Foods had vanadium concentrations of <0.5 μg/100 g and 88% had vanadium concentrations of <2 μg/100 g. Foods with the highest vanadium concentrations included breakfast cereals, canned fruit juices, fish sticks, several vegetables, sweeteners, wine, and beer. The data from this survey are summarized in Table 6-3.

Vanadium, as elemental vanadium or vanadyl sulfate, also may be found in various commercial nutritional supplements and multivitamins; vanadium concentration can range from 0.0004 to 12.5 mg in these supplements depending on the serving size recommended by the manufacturer (NLM 2009). Vanadium has been used in supplements for individuals with diabetes; intakes of 30–150 mg/day for vanadyl sulfate (9–47 mg V/day) and 125 mg/day for sodium metavanadate (52 mg V/day) have been reported (IOM 2001; Smith et al. 2008).

Table 6-3. Vanadium Levels in Food

Food item	Mean	Range
	(μg/100 g)	
Adult foods		
Milk, yogurt, and cheese	0.1	0–0.6
Meat, fish, and poultry	1.0	0–11.9
Eggs	0.3	0.2–0.4
Nuts	0.6	0.2–1.0
Legumes	0.1	0–0.3
Grains and grain products	2.3	0–14.7
Fruits and fruit juices	0.6	0–7.1
Vegetables	0.6	0–7.2
Mixed dishes and soups	0.6	0–2.0
Desserts	0.9	0–2.9
Sweeteners	2.3	0.4–4.7
Fats and sauces	0.3	0–0.6
Beverages	0.7	0–3.3
Infant foods		
Formulas	0.1	0–0.2
Meat and poultry	0.5	0–0.8
Cereals	1.6	1.2–2.0
Fruit and juices	1.6	0–13.4
Vegetables	0.4	0–1.1
Mixed dishes	0.2	0–0.6
Custard	0.2	No data

Source: Pennington and Jones 1987

Gummow et al. (2005) reported a study that looked at the commonly consumed tissues and milk concentrations of vanadium in cattle in South Africa that were extensively farmed over a 5-year period (1999–2004) in an area adjacent to a vanadium processing plant that was known to have higher-than-normal background levels of vanadium. The group of cattle included two groups, one group of 10 cattle that was farmed adjacent to the mine, with an average exposure of 1,229 mg V/day, and another group of 20 cattle that was farmed 2–3 km from the first group with an exposure about half that of the high exposure group (mean=532 mg V/day). Cattle in the trial were monitored over a 5-year period and six cohorts of animals were slaughtered over this period. Concentrations of vanadium in commonly consumed tissues (liver, kidney, fillet, and triceps) ranged from <0.05 to 11.51 mg/kg (wet-weight) in triceps and liver, respectively, over both groups. The median concentration of vanadium in milk was 0.23 mg/kg (range: <0.05–1.92 mg/kg) over both groups. Concentrations of vanadium in tissues from the group raised adjacent to the mine and those raised 2–3 km away were not differentiated in the presentation of the data.

Concentrations of various metals, including vanadium, were measured in samples of six fish species collected during 1997 and 1998 along the coast of the Adriatic Sea. Vanadium concentrations (µg/kg fresh weight) were 45.3–74.4 (anchovy), <4.0–4.8 (angler), <4.0 (hake), 6.7–29.8 (mackerel), 11.8–32.4 (red mullet), and <4.0–2.9 (sole) (Sepe et al. 2003).

Vanadium is found in almost all coals used in the United States, with levels ranging from extremely low to 10 g/kg (Byerrum et al. 1974; WHO 1988). Eastern U.S. coal has an average content of 30 ppm, western coal has an average content of 15 ppm, and coal from the interior contains an average of 34 ppm (Byerrum et al. 1974). The average vanadium content of bituminous and anthracite coal is 30 and 125 ppm, respectively (Byerrum et al. 1974).

Vanadium is usually the most abundant trace metal found in petroleum samples (Amorim et al. 2007). Vanadium concentrations in petroleum may be as high as 1,500 mg/kg, while some crude oils contain <0.1 mg/kg. Vanadium occurs predominantly as the vanadyl ion (VO^{2+}) in the form of organometallic complexes with porphyrins. Vanadyl porphyrins originated from the formation of crude oil; the vanadyl ion was substituted for magnesium ion (Mg^{2+}) in the chlorophylls of plants. Other vanadium complexes in petroleum include non-porphyrin and organic acid complexes (Hovmand et al. 2008). Mamane and Pirrone (1998) reported that residual fuel oils manufactured from U.S. crude oils contain 25–50 ppm of vanadium. Venezuelan, Middle Eastern, and North African residual oils have vanadium concentrations of 200–300, 10–20, and 50–90 ppm, respectively. Vanadium is highly enriched relative to other elements in

heavy fuel oils due to vanadium porphyrins. Because of this, vanadium is used as a marker for emissions from fuel oil combustion (Mamane and Pirrone 1998).

Vanadium concentrations ranging from 0.49 to 5.33 μg/g in were measured in 45 different brands of whole unsmoked cigarettes. Mean vanadium concentrations of 1.11, 0.67, 0.09, and 0.33 μg/cigarette in whole unsmoked cigarettes, ash, filter, and smoke of six different brands of cigarettes, respectively (Adachi et al. 1998a).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Food is the main source of vanadium intake for humans (Lagerkvist et al. 1986). Higher dietary intake levels are possible when food is grown in soil contaminated with greater than background levels of vanadium. Vanadium in food is mainly ingested as VO^{2+} (vanadyl, V^{4+}) or HVO_4^{2-} (vanadate) (Sepe et al. 2003). Byrne and Kučera (1991) reported a daily intake of vanadium of 10–20 μg. The dietary intake of vanadium estimated from the combined total intake of solids and liquids from a dietary study in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) for the NHEXAS was 0.34 μg/kg of body weight/day (Thomas et al. 1999). Pennington and Jones (1987) surveyed 234 foods from a 1984 collection of the FDA's Total Diet Study for various trace elements including vanadium. Based on this survey, estimated daily intakes of vanadium ranged from 6.2 μg/day for 60–65-year-old females to 18.3 μg/day for 25–30-year-old males. Table 6-4 summarizes the estimated daily intakes of vanadium for the various age groups in this study.

Various metal concentrations were determined in foods (meat, fish and seafood, pulses [lentil, bean], cereals, vegetables, fruits, tubers, whole milk, yogurt, eggs, and sugar) purchased from local markets, supermarkets, and grocery stores in zones of Tarragona County (Catalonia, Spain) near a hazardous waste incinerator, which has been operating since 1999 (Bocio et al. 2005). A dietary intake for vanadium of 28.9 μg/day was estimated for an average adult man (70 kg body weight) in Tarragona County (Catalonia, Spain). Fish and seafood (hake, sardine, and mussels) were the only foods that contributed to this value; vanadium was not detected in any other foods that were surveyed. The detection limit for vanadium in this study was 0.25 μg/g (Bocio et al. 2005). Sepe et al. (2003) reported an 11–34% contribution to the daily vanadium ingestion from fish collected during 1997 and 1998 along the coast of the Adriatic Sea for the population in this area.

Table 6-4. Estimated Daily Vanadium Intake

Age group	Intake (μg/day)
6–11 Months	6.7
2 Years	6.5
14–16 Years, female	7.1
14–16 Years, male	11.0
25–30 Years, female	8.1
25–30 Years, male	18.3
60–65 Years, female	6.2
60–65 Years, male	10.6

Source: Pennington and Jones 1987

Gummow et al. (2005) estimated dietary intakes of vanadium from the consumption of cattle in South Africa that were raised over a 5-year period (1999–2004) in an area adjacent to a vanadium processing plant that was known to have higher-than-normal background levels of vanadium. The median potential daily intakes of vanadium in the diet of humans consuming beef from these cattle were estimated to be 1.9, 1.8, 2.9, and 1.2 μg/kg body weight/day for consuming fillet, triceps, liver, and kidney, respectively. The median potential daily intake of vanadium from drinking milk of these cattle was estimated to be 4.6 μg/kg body weight/day (Gummow et al. 2005).

As compared to food, drinking water is a less important source of vanadium exposure for the general population. Thomas et al. (1999) reported mean vanadium concentrations of 1.2 and 1.0 μg/L in flushed tap water and standing tap water samples from Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin, respectively. Assuming a daily intake of 2 L of water (EPA 1988), a daily intake of approximately 2 μg of vanadium from tap water can be estimated.

Vanadium is present in many dietary supplements, including multivitamin and mineral supplement formulations, as well as products marketed for weight control, bodybuilding, and diabetes control (NTP 2008). The National Library of Medicine's (NLM's) Dietary Supplements Label Database lists >100 products containing vanadium (NLM 2009). Many of these products contain <10 μg of vanadium. Some of these products contain up to 12.5 mg of vanadium depending on the serving size recommended by the manufacturer. Three containing vanadyl sulfate are also listed on the NLM's Dietary Supplements Label Database, containing 0.01–1.66 mg of vanadyl sulfate (0.003–0.52 mg vanadium) depending on the serving size recommended by the manufacturer (NLM 2009). According to the Third National Health and Nutrition Examination Survey on supplement use of vanadium, the median intake of supplement vanadium by adults was approximately 9 μg/day (IOM 2001). Vanadium has been used in supplements for individuals with diabetes. Intakes of 30–150 mg/day for vanadyl sulfate (9–47 mg V/day) and 125 mg/day for sodium metavanadate (52 mg V/day) have been reported (IOM 2001; Smith et al. 2008). Vanadyl sulfate supplements have been used as well by weight training athletes at levels up to 60 mg/day (18.6 mg V/day) (Barceloux 1999). Consumption of some vanadium-containing supplements may result in intakes of vanadium that would exceed those from food and water.

The general population may also be exposed to airborne vanadium through inhalation, particularly in areas where use of residual fuel oils for energy production is high (Zoller et al. 1973). Assuming air concentrations of approximately 50 ng/m^3, Byrne and Kosta (1978) estimated a daily intake of 1 μg vanadium, assuming an average inhalation rate of 20 m^3/day. In addition, cigarette smoke can contribute

vanadium exposure. Koutrakis et al. (1992) estimated an emission rate for vanadium from cigarette smoke of 373 ng/cigarette; approximately 0.04 μg of vanadium is given off by in the smoke of one cigarette.

Lin et al. (2004) reported vanadium concentrations in the blood of 52 Taiwanese college students (19–42 years old). None of these students had occupational exposure to vanadium and five of the students (all male) were smokers. The average vanadium concentration in was 0.42 ng/mL in all students, with a range of 0.01–1.20 ng/mL. The average vanadium concentration in blood for the female students was 0.37 ng/L and the average concentration for nonsmoking male students was 0.44 ng/L; the average for the five smokers was 0.47 ng/mL. Concentrations of vanadium in human blood reported in the literature range from 0.032 to 0.095 ng/mL (Kučera et al. 1992; Lin et al. 2004; Sabbioni et al. 1996). The average vanadium concentration in blood of individuals that have occupational exposure is 33.2 (3.10–217) ng/mL (Lin et al. 2004). Sabbioni et al. (1996) surveyed the literature for reports on vanadium determination in human blood, serum, and urine and reported that vanadium concentrations in blood and/or serum ranged from 0.45–18.4 nmol/L (0.022–0.937 μg/L) and concentrations in urine ranged from 4.16–15.7 nmol/L (0.212–0.800 μg/L). Normal concentrations of vanadium in blood and serum were reported to be around 1 nmol/L (0.05 μg/L) and around 10 nmol/L (0.5 μg/L) for urine. Nixon et al. (2002) reported similar values for vanadium concentrations of 0.05 and 0.24 μg/L in serum and urine, respectively, in healthy individuals from a literature survey. Vanadium concentrations ranging from 30 to 160 μg/kg have been reported in hair (Fernandes et al. 2007; Kučera et al. 1992). No functional role for vanadium in higher animals or humans has been identified (IOM 2001).

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 Section 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).

Similar to adults, dietary intake of vanadium through the ingestion of food is the primary exposure route for children. This route of exposure is particularly relevant when the food is contaminated with soil because soil contains an average of about 10,000 times as much vanadium as is found in many biological materials (Byrne and Kosta 1978). Since young children tend to ingest soil and dust during daily activities, children may be exposed to vanadium through the ingestion of soil or dust. Cigarette smoke can contribute vanadium exposure of children. Approximately 0.04 μg of vanadium is given off by in the smoke of one cigarette (Koutrakis et al. 1992).

Blood and hair samples were collected from 23 children living in the vicinity of a metallurgical plant producing vanadium pentoxide (V_2O_5) approximately 20 km from Prague, Czechoslovakia (Kučera et al. 1992). These children may have been exposed to vanadium due to contamination of well water. A control group consisted of 17 children from a nonpolluted rural area about 30 km from Prague. Median vanadium concentrations in hair samples from the exposed and control groups did not differ significantly, and were 98 and 88 μg/kg, respectively. The median vanadium concentration in the blood of the exposed children and the children in the control group were 0.078 and 0.042 μg/L, respectively, and were considered significantly different (Kučera et al. 1992).

Concentrations of vanadium in human breast milk of 0.46, 0.27, 0.21, 0.11, 0.69, and 0.13 μg/g have been reported in samples from Nigeria, Zaire, Guatemala, Hungary, Philippines, and Sweden, respectively (Nriagu et al. 1992). Ikem et al. (2002) reported mean vanadium concentrations of 0.001, 0.002, and 0.003 μg/mL in milk-based liquid formulas from the United Kingdom, milk based powdered formulas from the United States, and soy-based powder formulas from the United States, respectively. Vanadium was not detected in milk-based powdered formulas from Nigeria and the United Kingdom. Daily intakes of vanadium for infants in the United States were estimated to be 0.05, 3.5, and 2.8 μg/day for milk-based powder formulas, soy-based powder formulas, and hypoallergenic powder formulas from the United States, respectively (Ikem et al. 2002).

Pennington and Jones (1987) reported concentrations in infant foods that ranged from 0.1 μg/100 g in formulas to 1.6 μg/100 g in cereals, fruits, and juices. Daily intakes of vanadium of 6.7, 6.5, 7.1, and 11.6 μg/day for children aged 6–11 months, 2 years, 14–16 years (female), and 14–16 years (male),

respectively, were estimated based on this food survey. A summary of these data are found in Tables 6-3 and 6-4.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations consuming foods grown in soils supplemented with fertilizers or sludge containing vanadium or in soils naturally high in vanadium content may be exposed to concentrations higher than background levels. This is due primarily to surface deposition.

Populations in areas with high levels of residual fuel oil consumption may also be exposed to above-background levels of vanadium, both from increased particulate deposition upon food crops and soil in the vicinity of power plants and higher ambient air levels (Zoller et al. 1973). Cities in the northeastern United States frequently fall into this category, where ambient air levels often range from 150 to 1,400 ng/m^3 (Zoller et al. 1973).

Personal exposure measurements were conducted on 18 boilermakers and 11 utility workers before and during a 3-week overhaul of a large oil-fired power plant (Liu et al. 2005). Utility workers included mechanics, welders, laborers, painters, precipitator operators, work crew supervisors, and laboratory workers. During the overhaul, boilermakers worked both inside and outside the boiler and were more likely to be exposed to ash. Utility workers worked outside the boiler in adjacent areas and had little direct contact with the ash. Time-weighted average exposures for the boilermakers and the utility workers were 1.20 and 1.10 μg/m^3, respectively, before the overhaul work and 8.9 and 1.4 μg/m^3, respectively, during the overhaul work (Liu et al. 2005).

Full-shift, personal breathing sampling was conducted on nine employees working in the finishing and cut-off areas (torch cutting, pneumatic hammer, water blast, and the five finishing workstations) of a titanium investment casting plant in Redmond, Oregon during July 7–10, 2003. Respirable vanadium pentoxide concentrations ranged from 0.0005 to 0.0089 mg/m^3, with the highest measurement of 0.123 mg/m^3 in the torch cutting area (NIOSH 2004).

Vanadium, as elemental vanadium or vanadyl sulfate, may be found in various commercial nutritional supplements and multivitamins; vanadium concentration can range from 0.0004 to 12.5 mg in these supplements depending on the serving size recommended by the manufacturer (NLM 2009). Vanadium supplements have be used and studied as supplements for diabetic individuals. Intakes of 30–150 mg/day

for vanadyl sulfate (9–47 mg V/day) and 125 mg/day for sodium metavanadate (52 mg V/day) have been reported (IOM 2001; Smith et al. 2008). Vanadyl sulfate supplements have been used as well by weight training athletes at levels up to 60 mg/day (18.6 mg V/day) (Barceloux 1999). Consumption of some vanadium containing supplements may result in intakes of vanadium that would exceed that from food and water.

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 vanadium is available. Where adequate information is not available, ATSDR, in conjunction with 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 vanadium.

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. The physical and chemical properties of vanadium and its compounds are reasonably well documented (see Tables 4-1 and 4-2). No data needs are indentified.

Production, Import/Export, Use, Release, and Disposal. 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 TRI, which contains this information for 2007, became available in March of 2009. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Companies involved in the vanadium production industry (see Table 5-3), uses of vanadium and various vanadium compounds (Lide 2008; USGS 2009a), and various sources of release are also available (see Table 6-1). There is little information available describing the amounts of vanadium consumed in each

use category or the quantities recycled and disposed of within the United States. Few details were found regarding the specific disposal methods used (HSDB 2009; USGS 2009a). Information in each of these areas would provide an indication of the potential for human exposure as a result of disposal practices.

Environmental Fate. The relative contributions of natural (Byerrum et al. 1974; Zoller et al. 1973) and anthropogenic sources (Byerrum et al. 1974; TRI07 2009) of vanadium to the different environmental media are available. Partitioning between the various media is described, in particular from soil to water and from water to sediment (Wehrli and Stumm 1989; WHO 1988), but specific coefficients are not available in many studies. Information on the transport of vanadium within each media is available (Duce and Hoffman 1976; Martin and Kaplan 1998; Wehrli and Stumm 1989; WHO 1988; Zoller et al. 1973).

Bioavailability from Environmental Media. Occupational studies on the uptake of vanadium via the inhalation route exist; however, data suggesting that this route is relevant with regard to hazardous waste sites are lacking. Dermal absorption data are limited; however, it is likely that absorption via this route is low since vanadium, like other metals, has low solubility in lipids (WHO 1988). The daily intakes of vanadium from air, food, and water are generally small (Bocio et al. 2005; Thomas et al. 1999; Zoller et al. 1973). Seafood or milk from cows raised in an area with vanadium contamination can be a more significant dietary contribution of vanadium (Gummow et al. 2005; Sepe et al. 2003). No data needs are identified.

Food Chain Bioaccumulation. The uptake of vanadium in aquatic plants and animals is reasonably well documented; levels of vanadium present in different species have been established (Byerrum et al. 1974; WHO 1988). Levels present in terrestrial plants (Byerrum et al. 1974; Cannon 1963) and animals (Van Zinderen Bakker and Jaworski 1980; WHO 1988) have been established for several species. Uptake of vanadium by terrestrial plants grown on sludge-amended, or vanadium-containing fertilized fields has been studied. Vanadium does not appear to concentrate in above-ground portions of terrestrial plants (Byerrum et al. 1974). No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of vanadium in contaminated media at hazardous waste sites are needed so that the information obtained on levels of vanadium in the environment can be used in combination with the known body burden of vanadium to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Estimates of human exposure to vanadium from food (Bocio et al. 2005; Byrne and Kosta 1978; Byrne and Kučera 1991; Gummow et al. 2005; Pennington and Jones 1987; Sepe et al. 2003; Thomas et al. 1999; WHO 1988), drinking water (USGS 2009c; Lagerkvist et al. 1986; Thomas et al. 1999), and air (Byrne and Kosta 1978) are limited. Current information on emission levels from the combustion of residual fuel oil would enable a more complete picture of populations potentially exposed to higher than background ambient air levels. A data need is identified regarding vanadium levels found in environmental media in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Limited information was located describing levels of vanadium present in human tissues for the general population (Byrne and Kosta 1978; Fernandes et al. 2007; Kučera et al. 1992; Lin et al. 2004; Nixon et al. 2002; Sabbioni et al. 1996). Little information is available on tissue levels found in populations near hazardous waste sites. A data need for vanadium levels in blood samples of the general population and those residing near hazardous waste sites is identified.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Measurements of the vanadium in blood and hair of children who have been exposed to vanadium, as well as unexposed children, are limited (Kučera et al. 1992). Additional information monitoring vanadium concentrations in children are needed. Specific data on the intake of vanadium from food eaten by children and from their diet are also limited (Ikem et al. 2002; Pennington and Jones 1987).

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for vanadium were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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

No long-term research studies on the environmental fate of vanadium were identified. No ongoing studies or long-term research concerning occupational or general population exposures to vanadium were identified (FEDRIP 2009).

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring vanadium, its metabolites, and other biomarkers of exposure and effect to vanadium. 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.

Vanadium can be determined as the total metal, as well as in its different oxidation states (species). The various oxidation states of vanadium can interconvert between the oxidation state depending on conditions such as, oxidation-reduction potential, pH, and salinity. In natural waters, dissolved vanadium exists as vanadium(IV) or vanadium(V) and these species have different toxic properties; therefore, determination of the vanadium species present in a sample can be more important than the total vanadium content of the sample in order to best evaluate human exposure (Pyrzyńska and Wierzbicki 2004).

Analytical techniques for the determination of species of vanadium include standard atomic spectroscopic techniques and separations methods coupled with sensitive detectors. Separation methods include capillary electrophoresis (CE) and liquid chromatography (LC). Atomic spectroscopic methods used for the determination of vanadium include atomic absorption spectroscopy (AAS) with flame and graphite tube atomizers, inductively coupled plasma optical emission spectrometry (ICP-OES), inductively coupled plasma mass spectrometry (ICP-MS), x-ray fluorescence spectrometry (XRF), and spectrophotometric methods (Chen and Owens 2008).

Sample preparation is one of the most important steps in the analysis of vanadium in biological and environmental samples. Direct analysis of vanadium species using atomic spectroscopic or separation techniques is generally not feasible due to the relatively low concentrations of vanadium found in samples as compared to other metals. In addition, the complexity of the matrices of biological and environmental samples can interfere with the determination of vanadium species, and it is often necessary to remove the matrices prior to vanadium analysis (Pyrzyńska and Wierzbicki 2004; Chen and Owens 2008).

The main methods for matrix removal are liquid-liquid extraction (LLE) and solid phase extraction (SPE). LLE is based on the distribution of the analyte between two immiscible solvents and involves the formation of an uncharged chemical species in the aqueous phase by chelation or ion-association of the vanadium ion, followed by extraction into an organic solvent. Example of complexing reagents (chelates) used to bind vanadium species include, vanadium(IV) with bis(salicylaldehyde) tetramethylethylene-diimine in a chloroform/water mixture, vanadium(V) with N-benzoyl-N-phenylhydroxylamine (BPHA) in a chloroform/water mixture, and vanadium(V) with 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulfopropy-lamino)-phenol (5-Br-PAPS) in a xylene/water mixture. Each of these LLE steps was followed by separation using liquid chromatography with UV detection. Other complexing agents that have been studied include dibenzo-18-crown-6 and N-phenyl-(1,2-methanofullerene)-formohydroxamic acid (PMFFA) (Chen and Owens 2008; Pyrzyńska and Wierzbicki 2004).

SPE is based on the transfer of metal ions from an aqueous phase to the active sites of a solid phase. Compared to LLE, SPE is simpler and more convenient to automate. It also uses less solvent and requires fewer manipulations. Several ion-exchange resins, functionalized cellulose sorbents, and chelating resins have been studied for the selective preconcentration and separation of vanadium species. Cellulose sorbent with phosphonic acid exchange groups gives excellent enrichment of vanadium(IV) and vanadium(V) and can be simultaneously eluted using an ethylenediamine tetraacetic acid (EDTA) solution. Other solid phases used to separate and preconcentrate vanadium species include Sephadex DEAE A-25 with Eriochrome Cyanide R complexation, C_{18} microcolumn or XAD-7 resin with complexation using 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol or dithizone or 8-hydroxyquinoline (8-HQ), and Chelex 100 (Chen and Owens 2008; Pyrzyńska and Wierzbicki 2004).

Vanadium concentrations in biological and environmental samples are typically very low, and vanadium analysis requires powerful analytical methods. Analytical methods with sufficient sensitivity include neutron activation analysis (NAA), electrothermal atomic absorption spectrometry (ETAAS), inductively coupled plasma atomic emission spectrometry (ICP-AES), ICP-MS, and some UV-vis spectrophotometric methods (Pyrzyńska and Wierzbicki 2004). ETAAS is routinely used for the determination of trace concentrations of vanadium. ICP-MS has better sensitivity than ETAAS; however, interference from the sample matrix can complicate the analysis. The species $^{16}O^{35}Cl^{+}$ and $^{34}S^{16}OH^{+}$ from the sample matrix can overlap with the most abundant isotope of vanadium at *m/z*=51 (Nixon et al. 2002; Pyrzyńska and Wierzbicki 2004).

Due to the low levels of vanadium that are typically found in biological and environmental samples, care must be exercised during sample handling in order to avoid contamination. Vanadium may be found in disposable steel needles, collection vials, storage containers, and chemicals and reagents (Kučera and Sabbioni 1998).

7.1 BIOLOGICAL MATERIALS

Methods for determination of vanadium in biological samples are summarized in Table 7-1.

NAA has been widely used to measure trace elements (including vanadium) in biological samples (Allen and Steinnes 1978; Lavi and Alfassi 1988; Martin and Chasteen 1988; Mousty et al. 1984). In NAA, the sample is bombarded with neutrons, and the element of interest is made radioactive. The amount of the element present in the sample is then determined by measurement of the radioactivity or radioactive decay products. When ^{51}V is bombarded with neutrons, it becomes ^{52}V (half-life 3.75 minutes and γ emission of 1.433 MeV). The resultant γ emission is detected with an efficient detector with high spectral resolution such as a well-type germanium detector combined with a multichannel analyzer. The concentration of vanadium is determined through its short-lived half-life of ^{52}V (Seiler 1995). Detection limits of low- to sub-ppb (µg/L) levels of vanadium in blood and urine samples have been obtained (Allen and Steinnes 1978; Lavi and Alfassi 1988; Mousty et al. 1984). The advantages of the NAA technique are its sensitivity and multi-elemental capability. The disadvantages of this technique include its high cost and the limited availability of nuclear facilities for NAA analysis (Seiler 1995).

Sabbioni et al. (1996) surveyed the literature for reports on vanadium determination in human blood, serum, and urine. Many analytical methods have been used to determine vanadium concentrations in blood, serum, and urine samples, including spectrography, colorimetry, catalytic reactions, XRF, particle induced x-ray emission (PIXE), ICP-AES, isotope dilution mass spectrometry (ID-MS), graphite furnace AAS (GF-AAS), and NAA. Only ID-MS, NAA, and GF-AAS can determine vanadium concentrations at levels of a few picograms (pg) of vanadium; GF-AAS and NAA are used most frequently (Kučera and Sabbioni 1998; Nixon et al. 2002; Sabbioni et al. 1996).

Nixon et al. (2002) reported the use of a Dynamic Reaction Cell™ ICP-MS (DRC-ICP-MS) for the analysis of vanadium in serum and urine. Generally, Zeeman graphite furnace atomic absorption spectrometry (ZGFAAS) and NAA are routinely used for the determination of vanadium in urine and serum. While ICP-MS as been routinely used to determine heavy metal concentrations in blood, serum,

Table 7-1. Analytical Methods for Determining Vanadium in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood/urine	Digest sample and evaporate; redissolve in acid; extract with MIBK; evaporate; redissolve in acid	NAA	~1 μg/L (blood); 2–4 μg/L (urine)	No data	Allen and Steinnes 1978
Urine	Wet ashing with HNO_3; chelation with cupferron; extraction into MIBK	GFAAS	1 μg/L	96–100%	Buchet et al. 1982
Serum/urine	Digestion in $H_2SO_4/HClO_4/HNO_3$ add $KMnO_4$, sulfamic acid, and HCl; extract with BTA in benzene	ETAAS	0.008 μg/L	90.3% (serum); 90.8% (urine)	Ishida et al. 1989
Serum	Coprecipitate sample with lead nitrate or bismuth nitrate; dry and irradiate	NAA	0.7 μg/L	No data	Lavi and Alfassi 1988
Blood	Microwave digestion with HNO_3	ICP-MS	0.0078 μg/L	No data	Lin et al. 2004
Serum/urine	Dilution with 1% HNO_3 and addition of internal standard	DRC-ICP-MS	0.028 μg/L	No data	Nixon et al. 2002
Hair	Washing and drying of hair samples, followed by cryogenic grinding; powdered hair samples prepared as slurries in mixtures of HNO_3 and a slurry stabilizer	ETAAS	0.28–0.34 μg/L	No data	Fernandes et al. 2007

BTA = N-benzoyl-N-(o-tolyl)hydroxylamine; DRC-ICP-MS = Dynamic Reaction Cell™ inductively coupled mass spectrometry; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis

and urine, and ICP-MS quantitation is at least an order of magnitude better than ZGFAAS for elements such as arsenic, lead, selenium, and cadmium, interference from $^{16}O^{35}Cl^{+}$, which is produced in the argon plasma of the instrument, has limited the use of ICP-MS for the determination of vanadium. In this study it was found that with proper dynamic reaction cell conditions, OCl^{+} interference can be eliminated. The detection limit for vanadium (0.028 μg/L) was also found to be superior to that of ZGFAAS (1.9 μg/L) (Nixon et al. 2002).

Fernandes et al. (2007) reported on a method to analyze hair samples using ETAAS. Samples were powdered using cryogenic grinding and hair slurries contained nitric acid, Triton X-100 (a nonionic surfactant), and water soluble tertiary amines. Limits of detection of 0.28 and 0.34 μg/L were reported using longitudinal heating and transversal heating graphite furnace atomizers, respectively.

7.2 ENVIRONMENTAL SAMPLES

Standard methods are available to measure vanadium concentrations in air, surfaces, water, soil, sediment, and plant and animal tissue (EPA 1983a, 1983b, 1983c, 1994a, 1994b, 1997a, 2003a; NIOSH 2003a, 2003b, 2003c, 2003d; OSHA 2002; USGS 1987, 1993, 1996, 1998, 2006, 2007). Atomic spectroscopic methods are generally used in these methods as well as ICP-MS and spectrophotometric methods. NIOSH Method 7504 (1994) and OSHA Method ID-185 (1991) can be used to measure vanadium oxides in air samples using XRF. Methods for determination of vanadium in environmental samples are summarized in Table 7-2.

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 vanadium is available. Where adequate information is not available, ATSDR, in conjunction with 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 vanadium.

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

Table 7-2. Analytical Methods for Determining Vanadium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Vanadium					
Air	Collect sample on MCE or PVC filter, followed by $HNO_3/HClO_4$ ashing	ICP-AES	0.028 μg/filter	98.3–103.2% (MCE) 102.5–108.3% (PVC)	NIOSH 2003a (Method 7300)
Air	Collect sample on MCE or PVC filter, followed by aqua regia ashing	ICP-AES	0.028 μg/filter	101.3–106.0% (MCE) 77.8–96.1% (PVC)	NIOSH 2003b (Method 7301)
Air	Collect sample on MCE filter, followed by hot block/HCl/HNO_3 digestion	ICP-AES	0.003 μg/mL	No data	NIOSH 2003c (Method 7303)
Wipes	Wipe surface; ash wipe with $HNO_3/HClO_4$	ICP-AES	0.01 μg/wipe	No data	NIOSH 2003d (Method 9102)
Air, wipe, or bulk	Digestion of filters with HNO_3/ H_2SO_4/H_2O_2	ICAP-AES	1.9 μg	No data	OSHA 2002 (Method ID-125G)
Water	Acid solubilization	ICP-MS	0.014 μg/L	97–109.2%	EPA 1997a (EPA Method 200.10)
Water	Sample is mixed with HNO_3/HCl and heated	AVICP-AES	0.2 μg/L	93%	EPA 2003 (EPA Method 200.5)
Water	Acidified with HNO_3	FAAS	200 μg/L	95–100%	EPA 1983a, 1983b (EPA Method 286.1)
Water	Acidified with HNO_3	GFAAS	4 μg/L	No data	EPA 1983a, 1983c (EPA Method 286.2)
Water	Filter and acidified samples	ICP-AES	6 μg/L	No data	USGS 1987 (USGS Method I-1472-87)
Water	Filter and acidified samples	ICP-MS	0.08 mg/L	64–105%	USGS 1998 (USGS Method I-2477-92)

Table 7-2. Analytical Methods for Determining Vanadium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Treatment with an ammonium persulfate phosphoric acid reagent and gallic acid solution	Colorimetric	1 μg/L	No data	USGS 1993 (USGS Method I-2880)
Water	Filter and acidified samples	ICP-OES	5 μg/L	98%	USGS 1998 (USGS Method I-4471-97)
Water (filtered)	Filtered (0.045 μm membrane); preserved with HNO_3	ICP-MS	0.05 μg/L	No data	USGS 2006 (USGS Method I-2020-05)
Water (unfiltered)	Preserved with HNO_3 followed by digestion	ICP-MS	0.05 μg/L	No data	USGS 2006 (USGS Method I-4020-05)
Water/waste water/solid wastes	Digestion with nitric and hydrochloric acid	ICP-AES	3 μg/L	84–104%	EPA 1994a (EPA Method 200.7)
Water/wastes	Digestion with nitric and hydrochloric acid	ICP-MS	2.5 μg/L	74.9–113.4%	EPA 1994b (EPA Method 200.8)
Water/waste water/solid wastes	Acid digestion	ICP-AES	5 μg/L	No data	EPA 2007 (EPA Method 6010 C)
Soil/sediment	Air-dried and sieved; digestion with HNO_3 using a closed-vessel microwave digestion procedure	ICP-MS	0.01 μg/L	No data	USGS 2006 (USGS Method I-5020-05)
Animal tissue	Acid digestion	ICP-MS	0.06 μg/g	101%	USGS 1996 (USGS Method B-9001-95 [ICP-MS])
Animal tissue	Acid digestion	ICP-AES	Not calculatable	96%	USGS 1996 (USGS Method B-9001-95 [ICP-AES])

Table 7-2. Analytical Methods for Determining Vanadium in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biota	Digestion with HNO_3 using a closed-vessel microwave digestion procedure	ICP-MS	0.01 μg/L	No data	USGS 2006 (USGS Method I-9020-05)
Vanadium oxides					
Air	Collect sample on PVC filter, dissolve filter in THF; redeposit on silver filter	XRD	4–28 μg (V_2O_5), 5–62 μg (V_2O_3), 7–50.3 μg (NH_4VO_3)	No data	NIOSH 1994 (Method 7504)
Vanadium pentoxide					
Air	Collect sample on PVC filter, dissolve filter in THF; suspension is produced with the collected dust, which is transferred to silver membrane	XRD	25 μg at 65 s	163.4–190.2% (respirable dust); 85.9–91.1% (fine-respirable dust)	OSHA 1991 (Method ID-185)

AVICP-AES = axially viewed inductively coupled plasma-atomic emission spectrometry; EPA = Environmental Protection Agency; FAAS = flame atomic absorption spectrometry; GFAAS : graphite furnace atomic absorption spectrometry; ICAP-AES = inductively coupled argon plasma-atomic emission spectroscopy; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively couples plasma-mass spectrometry; ICP-OES = inductively coupled plasma-optical emission spectroscopy; MCE = mixed cellulose ester; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PVC = polyvinyl chloride; THF = tetrahydrofuran; USGS = United States Geological Survey; XRD = X-ray diffraction

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. Sensitive and selective methods are available for the detection and quantitative measurement of vanadium after the sample matrix in which it is contained as been properly treated. Atomic spectroscopic methods used for the determination of vanadium include AAS with flame and graphite tube atomizers, ICP-OES, ICP-MS, XRF, and spectrophotometric methods (Chen and Owens 2008). No data needs are identified.

Exposure. Methods exist to determine vanadium levels in environmental samples and human tissues. While several biomarkers of exposure have been indentified, none of them can be used to quantitatively determine exposure levels (Rydzynski 2001). Kučera et al. (1998) reported that blood and urinary vanadium levels are considered the most reliable indicators of occupational exposure to vanadium. No data needs are identified.

Effect. No well-documented biomarkers of effect specific for vanadium have been report (Rydzynski 2001). The primary effects of exposure to vanadium dusts are coughing, wheezing, and other respiratory difficulties; however, these effects are not specific to vanadium and can be found following inhalation of many types of dusts (Rydzynski 2001). No data needs are identified.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining vanadium in water, air, and waste samples with adequate selectivity and sensitivity are well developed and undergoing constant improvement. No data needs are identified.

7.3.2 Ongoing Studies

No ongoing studies regarding methods for measuring vanadium in biological and environmental samples were located (FEDRIP 2009).

This page is intentionally blank.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration inhalation MRL of 0.0008 mg vanadium/m^3 based on a LOAEL of 0.56 mg vanadium/m^3 for lung inflammation in rats exposed to vanadium pentoxide 6 hours/day, 5 days/week for 13 days (NTP 2002). The MRL was derived by dividing the human equivalent concentration of the LOAEL (0.073 mg vanadium/m^3) by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human extrapolation with dosimetric adjustments, and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.0001 mg vanadium/m^3 based on a $BMCL_{10}$ of 0.04 mg vanadium/m^3 for degeneration of epiglottis respiratory epithelium of rats exposed to vanadium pentoxide 6 hours/day, 5 days/week for 2 years (NTP 2002). The MRL was derived by dividing the human equivalent concentration of the $BMCL_{10}$ (0.003 mg vanadium/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 an intermediate-duration oral MRL of 0.01 mg vanadium/kg/day based on a NOAEL of 0.12 mg vanadium/kg/day for hematological and blood pressure effects in humans exposed to vanadyl sulfate for 12 weeks (Fawcett et al. 1997) and an uncertainty factor of 10 for human variability.

IRIS (2009) has derived an oral reference dose (RfD) of 0.009 mg/kg/day for vanadium pentoxide based on a NOAEL of 0.89 mg/kg/day for decreased hair cysteine levels in rats exposed to vanadium pentoxide for 2.5 years (Stokinger et al. 1953) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 to protect against unusually susceptible individuals).

EPA has not derived an inhalation reference concentration (RfC) for vanadium and vanadium compounds.

OSHA has required employers of workers who are occupationally exposed to vanadium peroxide to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs) (OSHA 2009). The employer must use engineering and work practice

controls to reduce exposures to not exceed 0.5 mg/m^3 for vanadium peroxide as respirable dust (as V_2O_5) and 0.1 mg/m^3 as fume (as V_2O_5) at any time (OSHA 2009).

Vanadium pentoxide, vanadyl sulfate dehydrate, and ammonium metavanadate are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 1,000 pounds each (EPA 2009d). Vanadium pentoxide is also considered to be an extremely hazardous substance (EPA 2009e). The RQ represents the amount of a designated hazardous substance which, when released to the environment, must be reported to the appropriate authority.

The international and national regulations, advisories, and guidelines regarding vanadium and compounds in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Vanadium and Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2009
	Vanadium pentoxide	Group 2B[a]	
WHO	Air quality guidelines		WHO 2000
	Vanadium		
	TWA based on effects other than cancer or odor/annoyance using an averaging time of 24 hours	1 μg/m^3	
	Drinking water quality guidelines	No data	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[b]		ACGIH 2008
	Vanadium pentoxide (respirable fraction of dust or fume, as V_2O_5)	0.05 mg/m^3	
	TLV Basis	Irritation and lung	
AIHA	ERPG values	No	AIHA 2008
EPA	Second AEGL chemical priority list		EPA 2008a
	Vanadium and compounds	Yes[c]	
	Hazardous air pollutant	No	EPA 2009b 42 USC 7412
NIOSH	REL (15-minute ceiling)		NIOSH 2005
	Vanadium pentoxide[d]	0.05 mg/m^3	
	IDLH	35 mg/m^3	
	Target organ	Eyes, skin, and respiratory system	
OSHA	PEL (ceiling limit) for general industry		OSHA 2009 29 CFR 1910.1000, Table Z-1
	Vanadium pentoxide		
	Respirable dust (as V_2O_5)	0.5 mg/m^3	
	Fume (as V_2O_5)	0.1 mg/m^3	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2009h 40 CFR 116.4
	Vanadium pentoxide	Yes	
	Vanadyl sulfate dehydrate	Yes	
	Drinking water contaminant candidate list		EPA 1998b

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Vanadium and Compounds

Agency	Description	Information	Reference
	Vanadium	Yes	63 FR 10274
NATIONAL *(cont.)*			
EPA	Drinking water standards and health advisories	No	EPA 2006a
	National primary drinking water standards	No	EPA 2003b
	National recommended water quality criteria	No	EPA 2006b
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2009c 40 CFR 117.3
	Vanadium pentoxide	1,000 pounds	
	Vanadyl sulfate dehydrate	1,000 pounds	
c. Food			
FDA	EAFUS[e]	No	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification	A4[f]	ACGIH 2008
	Biological exposure indices (end of shift at end of workweek)		
	Vanadium in urine	50 μg/g creatinine	
EPA	Carcinogenicity classification	No	IRIS 2009
	RfC	No	
	RfD		
	Vanadium pentoxide	$9x10^{-3}$ mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and their reportable quantities		EPA 2009d 40 CFR 302.4
	Vanadium pentoxide[g]	1,000 pounds	
	Vanadyl sulfate dehydrate[h]	1,000 pounds	
	Ammonium metavanadate[i]	1,000 pounds	
	Effective date of toxic chemical release reporting		EPA 2009f 40 CFR 372.65
	Vanadium (except when contained in an alloy)	01/01/2000	
	Extremely hazardous substance and its threshold planning quantity		EPA 2009e 40 CFR 355, Appendix A
	Vanadium pentoxide	100/10,000 pounds	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Vanadium and Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
	TSCA chemical lists and reporting periods		EPA 2009g 40 CFR 712.30
	Vanadium, vanadium pentoxide, vanadyl sulfate dehydrate, sodium metavanadate, sodium orthovanadate, and ammonium metavanadate		
	Effective date	07/11/2003	
	Reporting date	09/09/2003	
DHHS	Carcinogenicity classification	No data	NTP 2005
IOM	Upper Tolerable Limit	1.8 mg/day	IOM 2001

[a]Group 2B: possibly carcinogenic to humans
[b]Vanadium peroxide is included in the 2008 Notice of Intended Changes in which the substance and its corresponding values and notations for which the withdrawal of the Documentation and adopted TLV are proposed.
[c]Vanadium and compounds are included on the list of 371 priority chemicals that are acutely toxic and represent the selection of chemicals for AEGL development by the NAC/AEGL committee during the next several years.
[d]The REL applies to all vanadium compounds except vanadium metal and vanadium carbide.
[e]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[f]A4: not classifiable as a human carcinogen
[g]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act and Section 3001 of the Resource Conservation and Recovery Act.
[h]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act.
[i]Designated CERCLA hazardous substance pursuant to Section 3001 of the Resource Conservation and Recovery Act.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; IOM = Institute of Medicien; NAC = National Advisory Council; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

This page is intentionally blank.

9. REFERENCES

Abbasi SA. 1981. Pollution due to vanadium and a new spot test for detection of traces of vanadium in water, plants, soils, and rocks. Int J Environ Stud 18:51-52.

Abbasi SA. 1987. Trace analysis of vanadium in environmental as its ternary complex with N-p methoxyphenyl-2-furylacrylohydroxamic acid and 3-(o-carboxyphenyl)-1-phenyltriazine-n-oxide. Anal Lett 20:1347-1361.

ACGIH. 2001. Vanadium pentoxide. In: Documentation of the threshold limit values and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*ACGIH. 2008. Vanadium pentoxide. In: Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*Adachi A, Asai K, Koyama Y, et al. 1998a. Vanadium content of cigarettes. Bull Environ Contam Toxicol 61(2):276-280.

Adachi A, Asai K, Koyama Y, et al. 1998b. Determination of vanadium in cigarettes by atomic absorption spectrophotometry. Anal Lett 31(10):1769-1776.

*+Adachi A, Asai K, Koyama Y, et al. 2000a. Subacute vanadium toxicity in rats. J Health Sci 46(6):503-508.

*Adachi A, Ogawa K, Tsushi Y, et al. 2000b. Balance, excretion and tissue distribution of vanadium in rats after short-term ingestion. J Health Sci 46(1):59-62.

*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27(4):532-537.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Fed Regist 54(174):37618-37634.

Agency for Toxic Substances and Disease Registry. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. Subcommittee on Biomarkers of Organ Damage and Dysfunction. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

---

*Cited in text
+Cited in supplemental document

Agency for Toxic Substances and Disease Registry. 2007. Health consultation: Assessment of cancer incidence from the Louisiana tumor registry from 1988-2004. Calcasieu Parish, Louisiana. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation. http://www.atsdr.cdc.gov/HAC/pha/CalcasieuCancer/CalcasieuCancerHC92707.pdf. May 14, 2009.

Agrawal YK. 1975. Extraction and spectrophotometric determination of vanadium (V) with n-phenyl 2-naphthohydroxamic acid. Anal Chem 47:940-942.

*AIHA. 2008. Emergency Response Planning Guidelines (ERPG). Fairfax, VA: American Industrial Hygiene Association. http://www.aiha.org/1documents/Committees/ERP-erpglevels.pdf. May 19, 2009.

Aiton JF, Cramb G. 1985. The effects of vanadate on rabbit ventricular muscle adenylate cyclase and sodium pump activities. Biochem Pharmacol 34:1543-1548.

Akera T, Temma K, Takeda K. 1983. Cardiac actions of vanadium. Fed Proc 42:2984-2988.

*+Akgün-Dar K, Bolkent S, Yanardag R, et al. 2007. Vanadyl sulfate protects against streptozotocin-induced morphological and biochemical changes in rat aorta. Cell Biochem Funct 25(6):603-609.

Al-Bayati MA, Raabe OG, Giri SN, et al. 1991. Distribution of vanadate in the rat following subcutaneous and oral routes of administration. J Am Coll Toxicol 10(2):233-242.

*Al-Bayati MA, Xie Y, Mohr FC, et al. 2002. Effect of pirfenidone against vanadate-induced kidney fibrosis in rats. Biochem Pharmacol 64(3):517-525.

Alexandrova R, Alexandrov I, Nikolova E. 2002. Effect of orally administered ammonium vanadate on the immune response of experimental animals. Dokl Bulg Acad Nauk 55(3):69-72.

Alimonti A, Petrucci F, Krachler M, et al. 2000. Reference values for chromium, nickel and vanadium in urine of youngsters from the urban area of Rome. J Environ Monit 2(4):351-354.

*Allen RO, Steinnes E. 1978. Determination of vanadium in biological materials by radiochemical neutron activation analysis. Anal Chem 50:1553-1555.

*Allen SK, Allen JM, Lucas S. 1996. Dissolved metal concentrations in surface waters from west-central Indiana contaminated with acidic mine drainage. Bull Environ Contam Toxicol 56:240-243.

Alliksaar T, Punning JM. 1998. The spatial distribution of characteristics fly-ash particles and trace metals in lake sediments and catchment mosses: Estonia. Water Air Soil Pollut 106(3-4):219-239.

Altamirano M, Ayala ME, Flores A, et al. 1991. Sex differences in the effects of vanadium pentoxide administration to prepubertal rats. Med Sci Res 19(23):825-826.

Altamirano MA, Betancourt M, Roldan E. 1993a. Effects of caffeine on sister chromatid exchanges in human lymphocytes treated with vanadium pentoxide. 24th Annual Scientific Meeting of the Environmental Mutagen Society, Norfolk, Virginia, USA, April 17-22, 1993. Environ Mol Mutagen 21(suppl 22):2.

Altamirano-Lozano M, Alvarez-Barrera L, Basurto-Alcantara F, et al. 1996. Reprotoxic and genotoxic studies of vanadium pentoxide in male mice. Teratog Carcinog Mutagen 16(1):7-17.

Altamirano-Lozano M, Alvarez-Barrera L, Roldan-Reyes E. 1993b. Cytogenic and teratogenic effects of vanadium pentoxide on mice. Med Sci Res 21(19):711-713.

Altamirano-Lozano M, Valverde M, Alvarez-Barrera L, et al. 1999. Genotoxic studies of vanadium pentoxide (V_2O_5) in male mice. II. Effects in several mouse tissues. Teratog Carcinog Mutagen 19(4):243-255.

*Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies of Experimental Biology.

Amiard JC, Journel R, Bacheley H. 2008. Influence of field and experimental exposure of mussels (*Mytilus* sp.) to nickel and vanadium on metallothionein concentration. Comp Biochem Physiol C Toxicol Pharmacol 147(3):378-385.

*Amorim FA, Welz B, Costa AC, et al. 2007. Determination of vanadium in petroleum and petroleum products using atomic spectrometric techniques. Talanta 72(2):349-359.

*Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, and replacement. New York, NY: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87(2):185-205.

Aragon AM, Altamirano-Lozano M. 2001. Sperm and testicular modifications induced by subchronic treatments with vanadium (IV) in CD-1 mice. Reprod Toxicol 15(2):145-151.

Aragon MA, Ayala ME, Fortoul TI, et al. 2005. Vanadium induced ultrastructural changes and apoptosis in male germ cells. Reprod Toxicol 20(1):127-134.

Arbouine MW, Smith NJ. 1991. Determination of vanadium in urine and its application to biological monitoring of occupationally exposed workers. Atom Spectrosc 12(2):54-58.

Attia SM, Badary OA, Hamada FM, et al. 2005. Orthovanadate increased the frequency of aneuploid mouse sperm without micronucleus induction in mouse bone marrow erythrocytes at the same dose level. Mutat Res 583(2):158-167.

Avila-Costa MR, Colin-Barenque L, Zepeda-Rodriguez A, et al. 2005. Ependymal epithelium disruption after vanadium pentoxide inhalation. A mice experimental model. Neurosci Lett 381(1-2):21-25.

Avila-Costa MR, Fortoul TI, Nino-Cabrera G, et al. 2006. Hippocampal cell alterations induced by the inhalation of vanadium pentoxide (V_2O_5) promote memory deterioration. Neurotoxicology 27(6):1007-1012.

Avila-Costa MR, Montiel Flores E, Colin-Barenque L, et al. 2004. Nigrostriatal modifications after vanadium inhalation: An immunocytochemical and cytological approach. Neurochem Res 29(7):1365-1369.

Azay J, Bres J, Krosniak M, et al. 2001. Vanadium pharmacokinetics and oral bioavailability upon single-dose administration of vanadyl sulfate to rats. Fundam Clin Pharmacol 15(5):313-324.

Barbante C, Boutron C, Moreau AL, et al. 2002. Seasonal variations in nickel and vanadium in Mont Blanc snow and ice dated from the 1960s and 1990s. J Environ Monit 4(6):960-966.

*Barceloux DG. 1999. Vanadium. J Toxicol Clin Toxicol 37(2):265-278.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

Barnes D, Bellin J, DeRosa C, et al. 1988. Reference dose (RfD): Description and use in health risk assessments. Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

*Baroch EF. 2006. Vanadium and vanadium alloys. In: Kirk-Othmer encyclopedia of chemical technology. John Wiley & Sons, Inc. http://mrw.interscience.wiley.com/emrw/9780471238966/kirk/article/vana.a01/current/pdf. May 12, 2009.

Barth A, Schaffer AW, Konnaris C, et al. 2002. Neurobehavioral effects of vanadium. J Toxicol Environ Health A 65(9):677-683.

*Beauge LA, Cavieres JJ, Glynn IM, et al. 1980. The effects of vanadate on the fluxes of sodium and potassium ions through the sodium pump. J Physiol 301:7-23.

*Beg MU, Al-Muzaini S, Saeed T, et al. 2001. Chemical contamination and toxicity of sediment from a coastal area receiving industrial effluents in Kuwait. Arch Environ Contam Toxicol 41:289-297.

*Berger GS, ed. 1994. Epidemiology of endometriosis. In: Endometriosis: Modern surgical management of endometriosis. New York, NY: Springer-Verlag, 3-7.

*Birnboim HC. 1988. A superoxide anion induced DNA strand-break metabolic pathway in human leukocytes: Effects of vanadate. Biochem Cell Biol 66:374-381.

*Bocio A, Nadal M, Domingo JL. 2005. Human exposure to metals through the diet in Tarragona, Spain: Temporal trend. Biol Trace Elem Res 104(3):193-201.

*+Boden G, Chen X, Ruiz J, et al. 1996. Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin-dependent diabetes mellitus. Metabolism 45(9):1130-1135.

*Bogden JD, Higashino H, Lavenhar MA, et al. 1982. Balance and tissue distribution of vanadium after short-term ingestion of vanadate. J Nutr 112:2279-2285.

Boice JD, Jr., Mumma MT, Blot WJ. 2007. Cancer and noncancer mortality in populations living near uranium and vanadium mining and milling operations in Montrose County, Colorado, 1950-2000. Radiat Res 167(6):711-726.

Bonner JC, Rice AB, Moomaw CR, et al. 2000. Airway fibrosis in rats induced by vanadium pentoxide. Am J Physiol Lung Cell Mol Physiol 278(1):L209-L216.

*+Boscolo P, Carmignani M, Volpe AR, et al. 1994. Renal toxicity and arterial hypertension in rats chronically exposed to vanadate. Occup Environ Med 51(7):500-503.

Brichard SM, Henquin JC. 1995. The role of vanadium in the management of diabetes. Trends Pharmacol Sci 16(8):265-270.

*Bronzetti G, Morichetti E, Della Croce C, et al. 1990. Vanadium: Genetical and biochemical investigations. Mutagenesis 5(3):293-295.

Brooks SM. 1986. Pulmonary reactions to miscellaneous mineral dusts, man-made mineral fibers, and miscellaneous pneumoconioses. Washington, DC: U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health, Division of Respiratory Disease Studies. Occupational respiratory diseases. DHHS (NIOSH) Publication No. 86-102.

Browning E. 1969. Toxicity of industrial metals. 2nd ed. New York, NY: Appleton-Century-Crofts, 340-343.

*Bruech M, Quintanilla ME, Legrum W, et al. 1984. Effects of vanadate on intracellular reduction equivalents in mouse liver and the fate of vanadium in plasma, erthrocytes, and liver. Toxicology 31:283-295.

*Buchet JP, Knepper E, Lauwerys R. 1982. Determination of vanadium in urine by electrothermal atomic absorption spectrometry. Anal Chim Acta 136:243-248.

*Buchter B, Davidoff B, Amacher MC, et al. 1989. Correlation of Freundlich Kd and n retention parameters with soils and elements. Soil Sci 148(5):370-378.

Bu-Olayan AH, Al-Yakoob S. 1998. Lead, nickel and vanadium in seafood: An exposure assessment for Kuwaiti consumers. Sci Total Environ 223(2-3):81-86.

Bu-Olayan AH, Subrahmanyam MN. 1998. Trace metal concentrations in the crab *Macrophthalmus depressus* and sediments on the Kuwait coast. Environ Monit Assess 53(2):297-304.

*+Bursztyn M, Mekler J. 1993. Acute hypertensive response to saline induced by vanadate, an insulinomimetic agent. J Hypertens 11(6):605-609.

Butte W, Heinzow B. 2002. Pollutants in house dust as indicators of indoor contamination. Rev Environ Contam Toxicol 175:1-46.

*Byczkowski JZ, Kulkarni AP. 1998. Oxidative stress and pro-oxidant biological effects of vanadium. In: Nriagu JO, ed. Vanadium in the environment. Part 2: Health effects. Vol. 31. New York, NY: John Wiley & Sons, 235-264.

*Byerrum RU. 1991. Vanadium. In: Merian E, ed. Metals and their compounds in the environment. Weinheim, Germany: VCH, 1289-1297.

*Byerrum RU, Eckardt RE, Hopkins LL, et al. 1974. Vanadium. Washington, DC: National Academy of Sciences, 19-45.

*Byrne AR, Kosta L. 1978. Vanadium in foods and in human body fluids and tissues. Sci Total Environ 10:17-30.

*Byrne AR, Kucera J. 1991. New data on levels of vanadium in man and his diet. In: Momcilovic B, ed. Trace elements in man and animals. Vol. 7. Copenhagen, Denmark: World Health Organisation (WHO), Regional Office for Europe, 25-18 to 25-20.

Cadene A, Gross R, Poucheret P, et al. 1996. Vanadyl sulphate differently influences insulin response to glucose in isolated pancreas of normal rats after in vivo or in vitro exposure. Eur J Pharmacol 318(1):145-151.

Cam MC, Pederson RA, Brownsey RW, et al. 1993. Long-term effectiveness of oral vanadyl sulphate in streptozotocin-diabetic rats. Diabetologia 36(3):218-224.

*Cannon HL. 1963. The biogeochemistry of vanadium. Soil Sci 98:196-204.

+Carlton BD, Beneke MB, Fisher GL. 1982. Assessment of the teratogenicity of ammonium vanadate using syrian golden hamsters. Environ Res 29:256-262.

*+Carmignani M, Boscolo P, Volpe AR, et al. 1991. Cardiovascular system and kidney as specific targets of chronic exposure to vanadate in the rat: Functional and morphological findings. Arch Toxicol Suppl 14:124-127.

*+Carmignani M, Volpe AR, Porcelli G, et al. 1992. Chronic exposure to vanadate as factor of arterial hypertension in the rat: Toxicodynamic mechanisms. Arch Toxicol Suppl 15:117-120.

Caroli S, Forte G, Iamiceli AL, et al. 1999. Determination of essential and potentially toxic trace elements in honey by inductively coupled plasma-based techniques. Talanta 50(2):327-336.

*Castranova V, Bowman L, Wright JR, et al. 1984. Toxicity of metallic ions in the lung: Effects on alveolar macrophages and alveolar type II cells. J Toxicol Environ Health 13:845-856.

Chandra AK, Ghosh R, Chatterjee A, et al. 2007a. Amelioration of vanadium-induced testicular toxicity and adrenocortical hyperactivity by vitamin E acetate in rats. Mol Cell Biochem 306(1-2):189-200.

Chandra AK, Ghosh R, Chatterjee A, et al. 2007b. Vanadium-induced testicular toxicity and its prevention by oral supplementation of zinc sulphate. Toxicol Mech Methods 17(4):175-187.

+Chanh PH. 1965. The comparative toxicity of sodium chromate, molybdate, tungstate and metavanadate. II. Experiments on mice and rats. Arch Int Pharmacodyn Ther 157(1):109-114.

*ChemIDplus. 2009. Vanadium and vanadium compounds. ChemIDplus. Bethesda, MD: U.S. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp. May 21, 2009.

*Chen ZL, Owens G. 2008. Trends in speciation analysis of vanadium in environmental samples and biological fluids - a review. Anal Chim Acta 607(1):1-14.

*Chillrud SN, Bopp RF, Simpson HJ, et al. 1999. Twentieth century atmospheric metal fluxes into Central Park Lake, New York City. Environ Sci Technol 33(5):657-662.

Chiu NH, Moilanen LH. 2003. Evaluation of the oral reference dose for vanadium. Toxicol Sci 72(S-1):29.

*Ciranni R, Antonetti M, Migliore L. 1995. Vanadium salts induce cytogenetic effects in in vivo treated mice. Mutat Res 343(1):53-60.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

CLPSD. 1988. Contract laboratory program statistical database. Washington, DC: U.S. Environmental Protection Agency, Contract Laboratory Program.

Cohen MD, Becker S, Devlin R, et al. 1997. Effects of vanadium upon polyI-C: Induced responses in rat lung and alveolar macrophages. J Toxicol Environ Health 51(6):591-608.

Cohen MD, Fukayama MY, Wei CI. 1991. Immunotoxicological studies of ammonium metavanadate in mice. In: Dillon HK, Ho MH, eds. Biological monitoring of exposure to chemicals: Metals. New York, NY: John Wiley and Sons, 127-144.

*Cohen MD, Klein CB, Costa M. 1992. Forward mutations and DNA-protein crosslinks induced by ammonium metavanadate in cultured mammalian cells. Mutat Res 269(1):141-148.

Cohen MD, McManus TP, Yang Z, et al. 1996a. Vanadium affects macrophage interferon-gamma-binding and -inducible responses. Toxicol Appl Pharmacol 138(1):110-120.

*+Cohen MD, Wei C, Tan H, et al. 1986. Effect of ammonium metavanadate on the murine immune response. J Toxicol Environ Health 19:279-298.

Cohen MD, Yang Z, Zelikoff JT, et al. 1996b. Pulmonary immunotoxicity of inhaled ammonium metavanadate in Fisher 344 rats. Fundam Appl Toxicol 33(2):254-263.

Colin-Barenque L, Avila-Costa M, Delgado V, et al. 2004. Mice olfactory bulb neuronal death after V2O5 inhalation. Toxicologist 78(1-S):233.

*Cong Z, Kang S, Dong S, et al. 2008. Elemental and individual particle analysis of atmospheric aerosols from high Himalayas. Environ Monit Assess [Dec 13; Epub ahead of print.]

*Conklin AW, Skinner CS, Felten TL, et al. 1982. Clearance and distribution of intratracheally instilled vanadium-48 compounds in the rat. Toxicol Lett 11:199-203.

*Crampton EW, Lloyd LE. 1954. The effect of water restriction on the food intake and food efficiency of growing rats. J Nutr 54(2):221-224.

*Crans DC, Amin SS, Keramidas AD. 1998. Chemistry of relevance to vanadium in the environment. In: Nriagu JO, ed. Vanadium in the environment. Vol. 30. New York, NY: John Wiley & Sons, Inc., 73-95.

Cui CT, Uriu-Adams JY, Tchaparian EH, et al. 2004. Metavanadate causes cellular accumulation of copper and decreased lysyl oxidase activity. Toxicol Appl Pharmacol 199(1):35-43.

*+Cusi K, Cukier S, DeFronzo RA, et al. 2001. Vanadyl sulfate improves hepatic and muscle insulin sensitivity in type 2 diabetes. J Clin Endocrinol Metab 86(3):1410-1417.

*+Dai S, McNeill JH. 1994. One-year treatment of non-diabetic and streptozotocin-diabetic rats with vanadyl sulphate did not alter blood pressure or haematological indices. Pharmacol Toxicol 74(2):110-115.

*+Dai S, Thompson KH, McNeill JH. 1994a. One-year treatment of streptozotocin-induced diabetic rats with vanadyl sulphate. Pharmacol Toxicol 74(2):101-109.

*+Dai S, Thompson KH, Vera E, et al. 1994b. Toxicity studies on one-year treatment of non-diabetic and streptozotocin-diabetic rats with vanadyl sulphate. Pharmacol Toxicol 75(5):265-273.

*+Dai S, Vera E, McNeill JH. 1995. Lack of haematological effect of oral vanadium treatment in rats. Pharmacol Toxicol 76(4):263-268.

*Dannecker W, Schroeder B, Stechmann H. 1990. Organic and inorganic substances in highway tunnel exhaust air. Sci Total Environ 93:293-300.

De Cremer K, Cornelis R, Strijckmans K, et al. 2002. Fractionation of vanadium in urine of Wistar rats as a function of time after intraperitoneal injection. J Inorg Biochem 90(1-2):71-77.

*de la Torre A, Granero S, Mayayo E, et al. 1999. Effect of age on vanadium nephrotoxicity in rats. Toxicol Lett 105(1):75-82.

Dill JA, Lee KM, Mellinger KH, et al. 2004. Lung deposition and clearance of inhaled vanadium pentoxide in chronically exposed F344 rats and B6C3F1 mice. Toxicol Sci 77(1):6-18.

*+Dimond EG, Caravaca J, Benchimol A. 1963. Excretion, toxicity, lipid effect in man. Am J Clin Nutr 12:49-53.

*DOE. 2008. Fuel oil and kerosene sales 2007. Washington, DC: U.S. Department of Energy, Energy Information Administration, Office of Oil and Gas.

Domingo JL. 1996. Vanadium: A review of the reproductive and developmental toxicity. Reprod Toxicol 10(3):175-182.

Domingo JL. 2000. Vanadium and diabetes. What about vanadium toxicity? Mol Cell Biochem 203(1-2):185-187.

Domingo JL. 2002. Vanadium and tungsten derivatives as antidiabetic agents: A review of their toxic effects. Biol Trace Elem Res 88(2):97-112.

Domingo JL, Bosque MA, Luna M, et al. 1993a. Prevention by Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) of vanadate-induced developmental toxicity in mice. Teratology 48(2):133-138.

*Domingo JL, Gomez M, Llobet JM, et al. 1990. Chelating agents in the treatment of acute vanadyl sulphate intoxication in mice. Toxicology 62(2):203-211.

Domingo JL, Gomez M, Sanchez DJ, et al. 1992a. Tiron administration minimizes the toxicity of vanadate but not its insulin mimetic properties in diabetic rats. Life Sci 50(18):1311-1317.

Domingo JL, Gomez M, Sanchez DJ, et al. 1995. Toxicology of vanadium compounds in diabetic rats: The action of chelating agents on vanadium accumulation. Mol Cell Biochem 153(1-2):233-240.

*+Domingo JL, Llobet JM, Tomas JM, et al. 1985. Short-term toxicity studies of vanadium in rats. J Appl Toxicol 5(6):418-420.

*+Domingo JL, Paternan JM, Llobet JM, et al. 1986. Effects of vanadium on reproduction, gestation, parturition and lactation in rats upon oral administration. Life Sci 39:819-824.

Domingo JL, Sanchez DJ, Gomez M, et al. 1992b. Administration of vanadyl sulfate by gavage does not normalize blood glucose levels in streptozotocin-induced diabetic rats. Res Commun Chem Pathol Pharmacol 75(3):369-372.

Domingo JL, Sanchez DJ, Gomez M, et al. 1993b. Oral vanadate and tiron in treatment of diabetes mellitus in rats: Improvement of glucose homeostasis and negative side-effects. Vet Hum Toxicol 35(6):495-500.

Domingo JL, Schuhmacher M, Agramunt MC, et al. 2001. Levels of metals and organic substances in blood and urine of workers at a new hazardous waste incinerator. Int Arch Occup Environ Health 74(4):263-269.

+Donaldson J, Hemming R, LaBella F. 1985. Vanadium exposure enhances lipid peroxidation in the kidney of rats and mice. Can J Physiol Pharmacol 63:196-199.

*Duce RA, Hoffman GL. 1976. Atmospheric vanadium transport to the ocean. Atmos Environ 10:989-996.

Duffus JH. 2007. Carcinogenicity classification of vanadium pentoxide and inorganic vanadium compounds, the NTP study of carcinogenicity of inhaled vanadium pentoxide, and vanadium chemistry. Regul Toxicol Pharmacol 47(1):110-114.

*Dundar MS. 2006. Vanadium concentrations in settled outdoor dust particles. Environ Monit Assess 123(1-3):345-350.

Dutch Safety Institute. 1980. Vanadium tetrachloride. 2nd ed. Amsterdam, Holland: Dutch Association of Safety Exposure, Dutch Chemical Industry Association, 952.

*Edel J, Sabbioni E. 1988. Retention of intratracheally instilled and ingested tetravalent and pentavalent vanadium in the rat. J Trace Elem Electrolytes Health Dis 2:23-30.

*Edel J, Pietra R, Sabbioni E, et al. 1984. Disposition of vanadium in rat tissues at different age. Chemosphere 13:87-93.

*Ehrlich VA, Nersesyan AK, Atefie K, et al. 2008. Inhalative exposure to vanadium pentoxide causes DNA damage in workers: Results of a multiple end point study. Environ Health Perspect 116(12):1689-1693.

*+Elfant M, Keen CL. 1987. Sodium vanadate toxicity in adult and developing rats. Biol Trace Elem Res 14:193-208.

*Engler RM. 1979. Bioaccumulation of toxic substances from contaminated sediments by fish and benthic organisms. In: Management of bottom sediments containing toxic substances. Washington, DC: U.S. Environmental Protection Agency, 325-354.

*EPA. 1982. Management of hazardous waste leachate. Washington, D.C.: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. PB91181578.

*EPA. 1983a. Methods for chemical analysis of water and wastes. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600479020.

*EPA. 1983b. Method 286.1. In: Methods for chemical analysis of water and wastes. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600479020.

*EPA. 1983c. Method 286.2. In: Methods for chemical analysis of water and wastes. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600479020.

EPA. 1983d. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 122, Appendix D, Table V.

*EPA. 1985a. Health and environmental effects profile for vanadium pentoxide. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA600x85114.

EPA. 1985b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.

EPA. 1985c. U.S. Environmental Protection Agency. Fed Regist 50:50225-50228.

EPA. 1985d. Vanadium pentoxide. Washington, DC: U.S. Environmental Protection Agency. EPA chemical profiles.

EPA. 1986c. Reference values for risk assessment. Final draft. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. ECAOC1N477.

EPA. 1986a. Test methods for evaluating solid waste. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Wasted and Emergency Response. Laboratory manual physical/chemical methods. Vol. 1A.

EPA. 1986b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

EPA. 1987a. Emergency planning and notification. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355, Appendix A.

EPA. 1987b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix 1x.

EPA. 1987c. U.S. Environmental Protection Agency. Fed Regist 52:21152-21208.

EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. EPA600687008.

EPA. 1989. Interim methods for development of inhalation reference doses. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. EPA600888066F.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development. EPA600890066A. PB90238890.

*EPA. 1994a. Determination of metals and trace elements in water and wastes by inductively coupled plasma-atomic emission spectrometry. Method 200.7. In: Methods for the determination of metals in environmental samples, Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=300036HL.txt. May 22, 2009.

*EPA. 1994b. Determination of trace elements in waters and wastes by inductively coupled plasma - mass spectrometry. Method 200.8. In: Methods for the determination of metals in environmental samples, Supplement 1. Cincinnati, OH: U.S. Environmental Protection Agency. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=300036HL.txt. May 22, 2009.

*EPA. 1994c. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, Washington DC. EPA600890066F.

EPA. 1995. Determination of background concentrations of inorganics in soils and sediments at hazardous waste sites. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA540S96500.

*EPA. 1997a. Determination of trace elements in marine waters by on-line chelation preconcentration and inductively coupled plasma - mass spectrometry. Method 200.10. In: Methods for the determination of chemical substances in marine and estuarine environmental matrices. 2nd ed. Cincinnati, OH: National Exposure Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency. EPA600R97072. http://www.epa.gov/microbes/marinmet.pdf. May 22, 2009.

EPA. 1997b. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum.

EPA. 1998a. Automated Form R for Windows: User's guide (RY97). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.

*EPA. 1998b. The drinking water contaminant candidate list. U.S. Environmental Protection Agency. Fed Regist 63:10274. http://www.gpoaccess.gov/fr/index.html. May 11, 2009.

*EPA. 2003a. Method 200.5: Determination of trace elements in drinking water by axially viewed inductively coupled plasma - atomic emission spectrometry Cincinnati, OH: U.S. Environmental Protection Agency, National Exposure Research Laboratory, Office of Research and Development. http://www.epa.gov/nerlcwww/m_200_5.pdf. May 23, 2009.

*EPA. 2003b. National primary drinking water regulations. Washington, DC: Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. http://www.epa.gov/safewater/contaminants/index.html. May 19, 2009.

*EPA. 2005a. Partition coefficients for metals in surface water, soil, and waste. Washington DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600R05074.

*EPA. 2005b. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2006a. Drinking water standards and health advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency. http://epa.gov/waterscience/criteria/drinking/. May 19, 2009.

*EPA. 2006b. National recommended water quality criteria. Washington, DC: Office of Water, Office of Science and Technology, U.S. Environmental Protection Agency. http://www.epa.gov/waterscience/criteria/wqcriteria.html. May 11, 2009.

*EPA. 2007. Method 6010C: Inductively coupled plasma-atomic emission spectrometry. In: Test methods for evaluating solid waste, physical/chemical methods. U.S. Environmental Protection Agency, http://www.epa.gov/osw/hazard/testmethods/sw846/pdfs/6010c.pdf. August 10, 2009.

*EPA. 2008a. Acute exposure guideline levels (AEGLs). Second AEGL Chemical Priority List. Washington, DC: Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. http://www.epa.gov/oppt/aegl/pubs/priority_2.htm. May 19, 2009.

*EPA. 2008b. Drinking water contaminant candidate list and regulatory determinations. U.S. Environmental Protection Agency. http://www.epa.gov/OGWDW/ccl/basicinformation.html. August 13, 2009.

*EPA. 2009a. Vanadium and vanadium compounds. Modernized STORET system: Regular results by project (stormodb): Characteristic search by CAS number. U.S. Environmental Protection Agency. http://www.epa.gov/storet/dbtop.html. April 23, 2009.

*EPA. 2009b. Hazardous air pollutants. Clean Air Act. U.S. Environmental Protection Agency. United States Code. 42 USC 7412. http://www.epa.gov/ttn/atw/orig189.html. May 19, 2009.

*EPA. 2009c. Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3. http://www.epa.gov/lawsregs/search/40cfr.html. May 20, 2009.

*EPA. 2009d. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notifications. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. http://www.epa.gov/lawsregs/search/40cfr.html. May 20, 2009.

*EPA. 2009e. Superfund, emergency planning, and community right-to-know programs. Extremely hazardous substances and their threshold planning quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355, Appendix A. http://www.epa.gov/lawsregs/search/40cfr.html. May 20, 2009.

EPA. 2009f. Superfund, Emergency Planning, And Community Right-To-Know Programs. Toxic Chemical Release Reporting. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. http://www.epa.gov/lawsregs/search/40cfr.html. May 11, 2009.

*EPA. 2009g. Toxic substances control act. Chemical lists and reporting periods. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 712.30. http://www.epa.gov/lawsregs/search/40cfr.html. May 20, 2009.

*EPA. 2009h. Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4. http://www.epa.gov/lawsregs/search/40cfr.html. May 20, 2009.

*Etcheverry SB, Cortizo AM. 1998. Bioactivity of vanadium compounds on cells in culture. In: Nriagu JO, ed. Vanadium in the environment. Part I: Chemistry and biochemistry. John Wiley & Sons, Inc., 359-394.

Faria de Rodriguez C, Gallo M, Marcano M, et al. 1998a. [Toxic effects of ammonium metavanadate on the growth and number of the offspring of Swiss albino mice.] Invest Clin 39(suppl 1):87-97. (Spanish)

Faria de Rodriguez C, Villalobos H, Nava de Leal C. 1998b. [Teratogenic effects of ammonium metavanadate on the CNS of the offspring of albino rats. A histological and histochemical study]. Invest Clin 39(suppl 1):55-85. (Spanish)

Fassett JD, Kingston HM. 1985. Determination of nanogram quantities of vanadium in biological material by isotope dilution thermal ionization mass spectrometry with ion counting detection. Anal Chem 57:2474-2478.

*+Fawcett JP, Farquhar SJ, Thou T, et al. 1997. Oral vanadyl sulphate does not affect blood cells, viscosity or biochemistry in humans. Pharmacol Toxicol 80:202-206.

*FDA. 2008. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://vm.cfsan.fda.gov/~dms/eafus.html. May 19, 2009.

*FEDRIP. 2009. Vanadium. Federal Research in Progress database. Springfield, VA: National Technical Information Service.

Feng X, Melander AP, Klaue B. 2000. Contribution of municipal waste incineration to trace metal deposition on the vicinity. Water Air Soil Pollut 119:295-316.

*Fernandes KG, Nogueira AR, Neto JA, et al. 2007. Determination of vanadium in human hair slurries by electrothermal atomic absorption spectrometry. Talanta 71(3):1118-1123.

*Figueroa DA, Rodriguez-Sierra CJ, Jimenez-Velez BD. 2006. Concentrations of Ni and V, other heavy metals, arsenic, elemental and organic carbon in atmospheric fine particles (PM2.5) from Puerto Rico. Toxicol Ind Health 22(2):87-99.

*Fiorentino CE, Paoloni JD, Sequeira ME, et al. 2007. The presence of vanadium in groundwater of southeastern extreme the Pampean region Argentina relationship with other chemicals. J Contam Hydrol 93(1-4):122-129.

*Fomon SJ. 1966. Body composition of the infant: Part 1: The male reference infant. In: Faulkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35(suppl 5):1169-1175.

*Foresti M, Scippa S, Mele F, et al. 2001. A short low-level exposure to metavanadate during a cell cycle-specific interval of time is sufficient to permanently derange the differentiative properties of Mel cells. Mutagenesis 16(5):395-400.

Fortoul TI, Bizarro-Nevares P, Acevedo-Nava S, et al. 2007. Ultrastructural findings in murine seminiferous tubules as a consequence of subchronic vanadium pentoxide inhalation. Reprod Toxicol 23(4):588-592.

Fortoul TI, Pinon-Zarate G, Diaz-Bech ME, et al. 2008. Spleen and bone marrow megakaryocytes as targets for inhaled vanadium. Histol Histopathol 23(11):1321-1326.

Fortoul TI, Pinon-Zarate G, Gonzalez-Villalva A, et al. 2005. Spleen repercussions after chronic inhalation of vanadium pentoxide (V2O5) evaluated In mice. Toxicol Sci 84(1-S):236.

Fortoul TI, Quan-Torres A, Sanchez I, et al. 2002. Vanadium in ambient air: Concentrations in lung tissue from autopsies of Mexico City residents in the 1960s and 1990s. Arch Environ Health 57(5):446-449.

*Fox MR. 1987. Assessment of cadmium, lead and vanadium status of large animals as related to the human food chain. J Anim Sci 65:1744-1752.

Fox PM, Doner HE. 2003. Accumulation, release, and solubility of arsenic, molybdenum, and vanadium in wetland sediments. J Environ Qual 32(6):2428-2435.

*+Franke KW, Moxon AL. 1937. The toxicity of orally ingested arsenic, selenium, tellurium, vanadium and molybdenum. J Pharmacol Exp Ther 61:89-102.

French RJ, Jones PJ. 1993. Role of vanadium in nutrition: Metabolism, essentiality and dietary considerations. Life Sci 52(4):339-346.

*Gallagher FJ, Pechmann I, Bogden JD, et al. 2008. Soil metal concentrations and vegetative assemblage structure in an urban brownfield. Environ Pollut 153(2):351-361.

Galli A, Giromini L, Del Carratore R, et al. 1990. Genotoxicity and effect of microsomal enzymes of vanadium compounds. Mutat Res 234:427-428.

+Ganguli S, Reuland DJ, Franklin LA, et al. 1994a. Effects of maternal vanadate treatment of fetal development. Life Sci 55(16):1267-1276.

*+Ganguli S, Reuland DJ, Franklin LA, et al. 1994b. Effect of vanadate on reproductive efficiency in normal and streptozocin-treated diabetic rats. Metabolism 43(11):1384-1388.

Geyikoglu F, Turkez H. 2008. Boron compounds reduce vanadium tetraoxide genotoxicity in human lymphocytes. Environ Toxicol Pharmacol 26(3):342-347.

*Gibson DP, Brauninger R, Shaffi HS, et al. 1997. Induction of micronuclei in Syrian hamster embryo cells: Comparison of results in the SHE cell transformation assay for national toxicology program test chemicals. Mutat Res 392(1-2):61-70.

Gichner T, Cabrera Lopez G, Wagner ED, et al. 1994. Induction of somatic mutations in Tradescantia clone 4430 by three phenylenediamine isomers and the antimutagenic mechanisms of diethyldithiocarbamate and ammonium meta-vanadate. Mutat Res 306(2):165-172.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect 101(supp 2):65-71.

*+Goldfine AB, Simonson DC, Folli F, et al. 1995. Metabolic effects of sodium metavanadate in humans with insulin-dependent and noninsulin-dependent diabetes mellitus in vivo and in vitro studies. J Clin Endocrinol Metab 80(11):3311-3320.

*Gomez M, Domingo JL, Llobet JM, et al. 1988. Effectiveness of chelation therapy with time after acute vanadium intoxication. J Appl Toxicol 8:439-444.

*Gomez M, Domingo JL, Llobet JM, et al. 1991. Effectiveness of some chelating agents on distribution and excretion of vanadium in rats after prolonged oral administration. J Appl Toxicol 11(3):195-198.

Gonzalez-Villalva A, Fortoul TI, Avila-Costa MR, et al. 2006. Thrombocytosis induced in mice after subacute and subchronic V2O5 inhalation. Toxicol Ind Health 22(3):113-116.

Goswami A, Singh AK, Venkataramani B. 2004. Erratum to "8-hydroxyquinoline anchored to silica gel via new moderate size linker: Synthesis and applications as a metal ion collector for their flame atomic absorption spectrometric determination" [Erratum to: Talanta 60(2003) 1141-1154]. Talanta 62:863.

*Grayson M. 1983. Kirk-Othmer encyclopedia of chemical technology. 3rd ed. New York, NY: John Wiley & Sons, 688-704.

Gregurek D, Reimann C, Stumpfl EF. 1998. Trace elements and precious metals in snow samples from the immediate vicinity of nickel processing plants, Kola Peninsula, northwest Russia. Environ Pollut 102(2-3):221-232.

Gummow B, Bastianello SS, Botha CJ, et al. 1994. Vanadium air pollution: A cause of malabsorption and immunosuppression in cattle. Onderstepoort J Vet Res 61(4):303-316.

*Gummow B, Botha CJ, Noordhuizen JP, et al. 2005. The public health implications of farming cattle in areas with high background concentrations of vanadium. Prev Vet Med 72(3-4):281-290.

*Gummow B, Botha CJ, Williams MC. 2006. Chronic vanadium poisoning in calves and its treatment with calcium disodium ethylenediaminetetraacetate. Vet Res Commun 30(7):807-822.

Gupta VK, Tandon SG. 1973. N-arylhydroxamic acids as reagents for vanadium (V). Spectrophotometric determination of vanadium (V) with n-m-tolyl-p-methoxybenzohydroxamic acid. Anal Chim Acta 66:39-48.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences and Press Institute Press.

*Gylseth B, Leira HL, Steinnes E, et al. 1979. Vanadium in the blood and urine of workers in a ferroalloy plant. Scand J Work Environ Health 5:188-194.

*Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Company, 163, 332, 335-336, 524, 542-551, 964-965, 1029-1033, 1058-1059, 1076-1087, 1128-1129, 1209, 1214-1215, 1221, 1224, 1226-1227, 1235-1243, 1250-1252, 1290-1292, 1477-1451, 1481.

+Haider SS, Kashyap SK. 1989. Vanadium intoxication inhibits sulfhydryl-groups and glutathione in the rat brain. Ind Health 27:23-25.

Haider SS, Abdel-Gayoum AA, el-Fakhri M, et al. 1998. Effect of selenium on vanadium toxicity in different regions of rat brain. Hum Exp Toxicol 17(1):23-28.

*Hamel FG, Duckworth WC. 1995. The relationship between insulin and vanadium metabolism in insulin target tissues. Mol Cell Biochem 153(1-2):95-102.

Hamel FG, Solomon SS, Jespersen AS, et al. 1993. Alteration of tissue vanadium content in diabetes. Metabolism 42(12):1503-1505.

*Hanauske U, Hanauske A, Marshall MH, et al. 1987. Biphasic effect of vanadium salts on in vitro tumor colony growth. Int J Cell Cloning 5:170-178.

+Hansard SL, Ammerman CB, Henry RR, et al. 1982. Vanadium metabolism in sheep. I. Comparative and acute toxicity of vanadium compounds in sheep. J Anim Sci 55:344-349.

Hansen TV, Aaseth J, Skaug V. 1986. Hemolytic activity of vanadylsulphate and sodium vanadate. Acta Pharmacol Toxicol (Copenh) 59(suppl 7):562-565.

*Harland BF, Harden-Williams BA. 1994. Is vanadium of human nutritional importance yet? J Am Diet Assoc 94(8):891-894.

*Harris WR, Carrano CJ. 1984. Binding of vanadate to human serum transferrin. J Inorg Biochem 22:201-218.

*Harris WR, Friedman SB, Silberman D. 1984. Behavior of vanadate and vanadyl ion in canine blood. J Inorg Biochem 20:157-169.

*Harrison RM, Smith DJ, Luhana L. 1996. Source apportionment of atmospheric polycyclic aromatic hydrocarbons collected from an urban location in Birmingham, U.K. Environ Sci Technol 30(3):825-832.

Hauser R, Elreedy S, Hoppin JA, et al. 1995. Airway obstruction in boilermakers exposed to fuel oil ash. A prospective investigation. Am J Respir Crit Care Med 152:1478-1484.

*HazDat. 2009. Vanadium. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Heaton RW, Rahn KA, Lowenthal DH. 1990. Determination of trace elements, including regional tracers, in Rhode Island (USA) precipitation. Atmos Environ 24(1):147-154.

*Heit M, Klusek C, Baron J. 1984. Evidence of deposition of anthropogenic pollutants in remote Rocky Mountain lakes. Water Air Soil Pollut 22:403-416.

Higashino H, Bogden JD, Lavenhar MA, et al. 1983. Vanadium, Na-K-ATPase, and potassium adaptation in the rat. Am J Physiol 244:F105-F111.

Hilliard HE. 1987. Vanadium. In: The minerals yearbook - minerals and metals, 917-927.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

Hogan GR. 1990. Peripheral erythrocyte levels, hemolysis and three vanadium compounds. Experientia 46(5):444-446.

Hope BK. 1997. An assessment of the global impact of anthropogenic vanadium. Biogeochem 37(1):1-13.

*Hoshishima K, Shimai KS, Kano K. 1983. The combined administration of certain metals in trace dose upon the post natal development of behavior in mice. Dev Toxicol Environ Sci 11:529-532.

*Hovmand MF, Kemp K, Kystol J, et al. 2008. Atmospheric heavy metal deposition accumulated in rural forest soils of southern Scandinavia. Environ Pollut 155(3):537-541.

HSDB. 1992. Vanadim and vanadium compounds. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov.

*HSDB. 2009. Vanadium and vanadium compounds. Hazardous Substances Data Bank, National Library of Medicine. http://toxnet.nlm.nih.gov. May 21, 2009.

*IARC. 2006. Vanadium Pentoxide. In: IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 86: Cobalt in hard metals and cobalt sulfate gallium arsenide, indium phosphide and vanadium pentoxide. Lyon, France: International Agency for Research on Cancer, 227-292.

*IARC. 2009. Agents Reviewed by the IARC Monographs. Volumes 1-99. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/index.php. May 19, 2009.

ICRP. 1975. Report of the task group on reference man. In: International commission on radiological protection. Vol. 23. New York, NY: Pergamon Press, 416.

*Ikem A, Nwankwoala A, Odueyungbo S, et al. 2002. Levels of 26 elements in infant formula from USA, UK, and Nigeria by microwave digestion and ICP-OES. Food Chem 77:439-447.

*International Joint Commission. 1978. Great Lakes water quality board - appendix E Status report on organic and heavy metal contaminants in the lakes Erie, Michigan, Huron and Superior basins. Windsor, Ontario: International Joint Commission, Great Lakes Water Quality Board.

*IOM. 2001. Arsenic, boron, nickel, silicon, and vanadium. In: Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Acadamy Press, Food and Nutrition Board, Institute of Medicine. http://books.nap.edu/openbook.php?record_id=10026&page=502. May 27, 2009.

*IRIS. 2009. Vanadium pentoxide. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/index.html. May 11, 2009.

*Irsigler GB, Visser PJ, Spangenberg PA. 1999. Asthma and chemical bronchitis in vanadium plant workers. Am J Ind Med 35(4):366-374.

*Ishida O, Kihira K, Tsukamoto Y, et al. 1989. Improved determination of vanadium in biological fluids by electrothermal atomic absorption spectrometry. Clin Chem 35:127-130.

*Ivancsits S, Pilger A, Diem E, et al. 2002. Vanadate induces DNA strand breaks in cultured human fibroblasts at doses relevant to occupational exposure. Mutat Res 519(1-2):25-35.

*+Jain GC, Pareek H, Sharma S, et al. 2007. Reproductive toxicity of vanadyl sulphate in male rats. J Health Sci 53(1):137-141.

Jha AR, et al. 1979. A sensitive and selective spot test method for the detection of vanadium (V) in a water sample. Int J Environ Stud 14:235-236.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs. cerebral cortex. Brain Res 190(1):3-16.

*Jones MM, Basinger MA. 1983. Chelate antidotes for sodium vanadate and vanadyl sulfate intoxication in mice. J Toxicol Environ Health 12:749-756.

*Kada T, Koichi H, Shirasu Y. 1980. Screening of environmental chemical mutagens by the rec-assay system with Bacillus subtilis. In: De Serres FJ, Hollaender A, eds. Chemcial mutagens: Principles and methods for their detection. Vol. 6. New York, NY: Plenum Press, 149-173.

*Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat Res 77:109-116.

Kanisawa M, Schroeder HA. 1967. Life term studies on the effects of arsenic, germanium, tin, and vanadium on spontaneous tumors in mice. Cancer Res 27:1192-1195.

Kasibhatla U, Rai V. 1993a. Changes in the plasma levels of phosphatases and transaminases in rabbits following vanadium exposure. Pollut Res 12(1):19-27.

*+Kasibhatla U, Rai V. 1993b. Haematological changes following vanadium exposure. Geobios 20(2):85-95.

Kawai T, Seijji K, Watanabe T, et al. 1989. Urinary vanadium as a biological indicator of exposure to vanadium. Int Arch Occup Environ Health 61:283-287.

Keller RJ, Sharma RP. 1985. In vitro and in vivo effects of vanadate on K+-dependent phosphatase activities from subcellular fractions of brain, kidney, and liver. Toxicol Lett 26:9-14.

Kellett RJ, Barker ED. 1989. The effect of vanadate on glucose transport and metabolism in rat small intestine. Biochim Biophys Acta 979:311-315.

*Kennish MJ. 1998. Trace metal-sediment dynamics in estuaries: Pollution assessment. Rev Environ Contam Toxicol 155:69-110.

*Kingsnorth AN, LaMuraglia GM, Ross JS, et al. 1986. Vanadate supplements and 1,2-dimethyl-hydrazine induced colon cancer in mice: Increased thymidine incorporation without enhanced carcinogenesis. Br J Cancer 53:683-686.

*Kinney PL, Chillrud SN, Ramstrom S, et al. 2002. Exposures to multiple air toxics in New York City. Environ Health Perspect 110(suppl 4):539-546.

*+Kiviluoto M. 1980. Observations on the lungs of vanadium workers. Br J Ind Med 37:363-366.

Kiviluoto M, Pyy L, Pakarinen A. 1979a. Serum and urinary vanadium of vanadium-exposed workers. Scand J Work Environ Health 5:362-367.

*Kiviluoto M, Pyy L, Pakarinen A. 1981a. Clinical laboratory results of vanadium-exposed workers. Arch Environ Health 36:109-113.

*+Kiviluoto M, Pyy L, Pakarinen A. 1981b. Serum and urinary vanadium of workers processing vanadium pentoxide. Int Arch Occup Environ Health 48:251-256.

*+Kiviluoto M, Rasanen O, Rinne A, et al. 1979b. Effects of vanadium on the upper respiratory tract of workers in a vanadium factory: A macroscopic and microscopic study. Scand J Work Environ Health 5:50-58.

+Kiviluoto M, Rasanen O, Rinne A, et al. 1981c. Intracellular immunoglobulins in plasma cells of nasal biopsies taken from vanadium-exposed workers: A retrospective case control study by the peroxidase-antiperoxidase (PAP) method. Anat Anz 149:446-450.

*Klein CB, Kargacin B, Su L, et al. 1994. Metal mutagenesis in transgenic Chinese hamster cell lines. Environ Health Perspect 102(suppl 3):63-67.

*Kleinsasser N, Dirschedl P, Staudenmaier R, et al. 2003. Genotoxic effects of vanadium pentoxide on human peripheral lymphocytes and mucosal cells of the upper aerodigestive tract. Int J Environ Health Res 13(4):373-379.

*+Knecht EA, Moorman WJ, Clark JC, et al. 1992. Pulmonary reactivity to vanadium pentoxide following subchronic inhalation exposure in a non-human primate animal model. J Appl Toxicol 12(6):427-434.

*+Knecht EA, Moorman WJ, Clark JC, et al. 1985. Pulmonary effects of acute vanadium pentoxide inhalation in monkeys. Am Rev Respir Dis 132:1181-1185.

Kobayashi K, Himeno S, Satoh M, et al. 2006. Pentavalent vanadium induces hepatic metallothionein through interleukin-6-dependent and -independent mechanisms. Toxicology 228(2-3):162-170.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29(18):4430-4433.

Kordowiak AM, Goc A, Drozdowska E, et al. 2005. Sodium orthovanadate exerts influence on liver golgi complexes from control and streptozotocin-diabetic rats. J Inorg Biochem 99(5):1083-1089.

Korn MG, Santos DS, Welz B, et al. 2007. Atomic spectrometric methods for the determination of metals and metalloids in automotive fuels - a review. Talanta 73(1):1-11.

*Koutrakis P, Briggs SLK, Leaderer BP. 1992. Source apportionment of indoor aerosols in Suffolk and Onondaga counties, New York. Environ Sci Technol 26:521-527.

Kovacs-Huber G. 1982. Pesticide monitoring in Lake Balaton between 1978-1980. Hung J Ind Chem 10:57-75.

*+Kowalska M. 1988. The effect of vanadium on lung collagen content and composition in two successive generations of rats. Toxicol Lett 41:203-208.

Krachler M, Mohl C, Emons H, et al. 2003. Atmospheric deposition of V, Cr, and Ni since the late glacial: Effects of climatic cycles, human impacts, and comparison with crustal abundances. Environ Sci Technol 37(12):2658-2667.

*Krishna AK, Govil PK. 2007. Soil contamination due to heavy metals from an industrial area of Surat, Gujarat, Western India. Environ Monit Assess 124(1-3):263-275.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Krishnan SS, Quittkat S, Crapper DR. 1976. Atomic absorption analysis for traces of aluminum and vanadium in biological tissue. A critical evaluation of the graphite furnace atomizer. Can J Spectrosc 21:25-30.

*Kučera J, Byrne AR, Mravcova A, et al. 1992. Vanadium levels in hair and blood of normal and exposed persons. Sci Total Environ 115(3):191-205.

*Kučera J, Lener J, Mnukova J, et al. 1998. Vanadium exposure tests in human: Hair, nails, blood. In: Nriagu JO, ed. Vanadium in the environment, part 2: Health effects. New York, NY: John Wiley & Sons, Inc., 55-74.

*Kučera J, Sabbioni E. 1998. Baseline vanadium levels in human blood, serum, and urine. In: Nriagu JO, ed. Vanadium in the environment, part 2: Health effects. New York, NY: John Wiley & Sons, Inc., 75-90.

*Lagerkvist B, Nordberg GF, Vouk V. 1986. Vanadium. In: Friberg L, Nordberg GR, Vouk VB, et al., eds. Handbook on the toxicology of metals. Vol. II: Specific metals. Amsterdam: Elsevier, 638-663.

*Lavi N, Alfassi ZB. 1988. Determination of trace amounts of titanium and vanadium in human blood serum by neutron activation analysis: Coprecipitation with Pb/PDC/2 or Be/PDC/3. J Radioanal Chem 126:361-374.

+Lee KP, Gillies PJ. 1986. Pulmonary response and intrapulmonary lipids in rats exposed to bismuth orthovanadate dust by inhalation. Environ Res 40:115-135.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

Lener J, Kucera J, Kodl M, et al. 1998. Health effects of environmental exposure to vanadium. In: Nriagu JO, ed. Vanadium in the environment, part 2: Health effects. New York, NY: John Wiley & Sons, Inc., 1-20.

*Léonard A, Gerber GB. 1994. Mutagenicity, carcinogenicity and teratogenicity of vanadium compounds. Mutat Res 317(1):81-88.

Leopardi P, Villani P, Cordelli E, et al. 2005. Assessment of the in vivo genotoxicity of vanadate: Analysis of micronuclei and DNA damage induced in mice by oral exposure. Toxicol Lett 158(1):39-49.

*Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantyne B, Marrs T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*+Levy BS, Hoffman L, Gottsegan S. 1984. Boilermakers' bronchitis. J Occup Med 26:567-570.

*+Lewis CE. 1959. The biological effects of vanadium. II. The signs and symptoms of occupational vanadium exposure. AMA Arch Ind Health 19:497-503.

*Lewis RJ. 2007. Hawley's condensed chemical dictionary. 15th ed. Hoboken, NJ: John Wiley & Sons, Inc., 71, 1149, 1151.

*Lide DR. 2008. CRC handbook of chemistry and physics. 88th ed. Boca Raton, FL: CRC Press, 4-40, 4-90, 4-92, 4-98.

*Lin TS, Chang CL, Shen FM. 2004. Whole blood vanadium in Taiwanese college students. Bull Environ Contam Toxicol 73(5):781-786.

*Liu Y, Woodin MA, Smith TJ, et al. 2005. Exposure to fuel-oil ash and welding emissions during the overhaul of an oil-fired boiler. J Occup Environ Hyg 2(9):435-443.

*Livingston AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4(2-3):301-324.

*+Llobet JM, Domingo JL. 1984. Acute toxicity of vanadium compounds in rats and mice. Toxicol Lett 23:227-231.

*+Llobet JM, Colomina MT, Sirvent JJ, et al. 1993. Reproductive toxicity evaluation of vanadium in male mice. Toxicology 80(2-3):199-206.

Llobet JM, Granero S, Torres A, et al. 1998. Biological monitoring of environmental pollution and human exposure to metals in Tarragona, Spain: III. Blood levels. Trace Elem Electrolytes 15(2):76-80.

Loring DH. 1979. Geochemistry of cobalt, nickel, chromium, and vanadium in the sediments of the estuary and open gulf of St. Lawrence. Can J Earth Sci 16:1196-1209.

Lough GC, Schauer JJ, Park J, et al. 2005. Emissions of metals associated with motor vehicle roadways. Environ Sci Technol 39:826-836.

Lowe TP, Day DD. 2002. Metal concentrations in zebra mussels and sediments from embayments and riverine environments of eastern Lake Erie, southern Lake Ontario, and the Niagara River. Arch Environ Contam Toxicol 43:301-308.

*Lusky LM, Braun HA, Laug EP. 1949. The effect of BAL on experimental lead, tungsten, vanadium, uranium, copper and copper-arsenic poisoning. J Ind Hyg Toxicol 31:301-305.

*Macias-Zamora JV, Villaescusa-Celaya JA, Munoz-Barbosa A, et al. 1999. Trace metals in sediment cores from the Campeche shelf, Gulf of Mexico. Environ Pollut 104(1):69-77.

Mackinson FW, Stricoff RS, Partridge LJ. 1978. NIOSH/OSHA-occupational health guidelines for chemical hazards. DHHS (NIOSH) Publication.

*Mamane Y, Pirrone N. 1998. Vanadium in the atmosphere. In: Nriagu JO, ed. Advances in environmental science and technology. Vanadium in the environment, Part 1: Chemistry and biochemistry. Vol. 30. New York, NY: John Wiley and Sons, 37-71.

*Martin DM, Chasteen ND. 1988. Vanadium. Methods Enzymol 158:402-421.

*Martin HW, Kaplan DI. 1998. Temporal changes in cadmium, thallium and vanadium mobility in soil and phytoavailability under field conditions. Water Air Soil Pollut 101(1-4):399-410.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two in vitro test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74(2-3):135-149.

McCrindle CM, Mokantla E, Duncan N. 2001. Peracute vanadium toxicity in cattle grazing near a vanadium mine. J Environ Monit 3(6):580-582.

*Mermut AR, Jain JC, Song L, et al. 1996. Trace element concentrations of selected soils and fertilizers in Saskatchewan, Canada. J Environ Qual 25(4):845-853.

*Mielke HW, Gonzales CR, Smith MK, et al. 2000. Quantities and associations of lead, zinc, cadmium, manganese, chromium, nickel, vanadium, and copper in fresh Mississippi Delta alluvium and New Orleans alluvial soils. Sci Total Environ 246:249-259.

*Migliore L, Bocciardi R, Macri C, et al. 1993. Cytogenetic damage induced in human lymphocytes by four vanadium compounds and micronucleus analysis by fluorescence in situ hybridization with a centromeric probe. Mutat Res 319(3):205-213.

Migliore L, Cocchi L, Macri C, et al. 1992. Cytogenetic effects induced in vitro and in vivo by vanadium compounds. Mutat Res 271(2):175-176.

*Migliore L, Scarpato R, Falco P. 1995. The use of fluorescence in situ hybridization with a beta-satellite DNA probe for the detection of acrocentric chromosomes in vanadium-induced micronuclei. Cytogenet Cell Genet 69(3-4):215-219.

Migliore L, Zotti-Martelli L, Scarpato R. 1999. Detection of chromosome loss and gain induced by griseofulvin, estramustine, and vanadate in binucleated lymphocytes using FISH analysis. Environ Mol Mutagen 34(1):64-68.

*Miguel AH, De Aquino Neto FR, Cardoso JN, et al. 1995. Characterization of indoor air quality in the cities of Sao Paulo and Rio de Janeiro, Brazil. Environ Sci Technol 29:338-345.

Miramand P, Fowler SW. 1998. Bioaccumulation and transfer of vanadium in marine organisms. In: Nriagu JO, ed. Advances in environmental science and technology. Vanadium in the environment, Part 1: Chemistry and biochemistry. Vol. 30. New York, NY: John Wiley and Sons, 167-197.

*Mitchell WG, Floyd EP. 1954. Ascorbic acid and ethylene diamine tetraacetate as antidotes in experimental vanadium poisoning. Proc Soc Exp Biol Med 85:206-208.

*+Morgan AM, El-Tawil OS. 2003. Effects of ammonium metavanadate on fertility and reproductive performance of adult male and female rats. Pharmacol Res 47(1):75-85.

*Morrison RJ, Gangaiya P, Naqasima MR, et al. 1997. Trace metal studies in the Great Astrolabe Lagoon, Fiji, a pristine marine environment. Mar Pollut Bull 34(5):353-356.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokinet 5(6):485-527.

Morton-Bermea O, Carrillo-Chavez A, Hernandez E, et al. 2004. Determination of metals for leaching experiments of mine tailings: Evaluation of the potential environmental hazard in the Guanajuato Mining District, Mexico. Bull Environ Contam Toxicol 73:770-776.

*Mosher BW, Winkler P, Jaffrezo JL. 1993. Seasonal aerosol chemistry at dye 3 greenland. Atmospheric Environment Part a General Topics 27(17-18):2761-2772.

*+Mountain JT, Delker LL, Stokinger HE. 1953. Studies in vanadium toxicology. Reduction in the cystine content of rat hair. AMA Arch Ind Hyg Occup Med 8:406-411.

Mountain JT, Stockell FR, Stokinger HE. 1955. Studies in vanadium toxicology: III. Fingernail cystine as an early indicator of metabolic changes in vanadium workers. AMA Arch Ind Health 12:494-502.

*Mousty F, Omenetto N, Pietra R, et al. 1984. Atomic-absorption spectrometric, neutron-activation and radioanalytical techniques for the determination of trace metals in environmental, biochemical and toxicological research. Part I. Vanadium. Analyst 109:1451-1454.

Mravcova A, Jirova D, Janci H, et al. 1993. Effects of orally administered vanadium on the immune system and bone metabolism in experimental animals. Sci Total Environ Suppl Pt 1:663-669.

*Mukherjee B, Patra B, Mahapatra S, et al. 2004. Vanadium-an element of atypical biological significance. Toxicol Lett 150(2):135-143.

*+Musk AW, Tees JG. 1982. Asthma caused by occupational exposure to vanadium compounds. Med J Aust 1:183-184.

Mussali-Galante P, Rodriguez-Lara V, Avila-Costa MR, et al. 2007. Mechanisms of vanadium toxicity. In: Fortoul TI, Avila-Costa MR, eds. Vanadium: Its impact on health. New York, NY: Nova Science Publishers, 7-19.

Mussali-Galante P, Rodriguez-Lara V, Hernandez-Tellez B, et al. 2005. Inhaled vanadium pentoxide decrease gamma-tubulin of mouse testes at different exposure times. Toxicol Ind Health 21(9):215-222.

*NAS/NRC. 1989. Report of the oversight committee. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press. Biologic markers in reproductive toxicology.

Nava de Leal CA, Villalobos H, Faria de Rodriguez C. 1998. [Changes in female reproduction induced by ammonium metavanadate in Swiss albino mice]. Invest Clin 39(supp l):99-122. (Spanish)

+Naylor GJ, Smith AH, Bryce-Smith D, et al. 1984. Elevated vanadium content of hair and mania. Biol Psychiatry 19:759-764.

Nechay BR, Saunders JP. 1978. Inhibition by vanadium of sodium and potassium dependent adenosinetriphosphatase derived from animal and human tissues. J Environ Pathol Toxicol 2:247-262.

Nielsen FH. 1995. Vanadium in mammalian physiology and nutrition. In: Sigel H, Sigel A, eds. Metal ions in biological systems. Vol. 31. New York, NY: Marcel Dekker, Inc., 543-573.

Nielsen T. 1996. Traffic contribution of polycyclic aromatic hydrocarbons in the center of a large city. Atmos Environ 30(20):3481-3490.

NIOSH. 1976. National occupational hazard survey (1970) database. Cincinnati, OH: U.S. department of Health and Human Services, National Institute of Occupational Safety and Health.

*+NIOSH. 1983. Health hazard evaluation report HETA 80-096-1359, Eureka Company, Bloomington, IL. Washington, DC: U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health. PB85163574.

NIOSH. 1984a. National occupational exposure survey (1980-1983) database. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health.

NIOSH. 1984b. NIOSH manual of analytical methods. Washington, DC: U.S. Department of Health and Human Services, National Institute of Occupational Safety and Health.

*NIOSH. 1994. Vanadium oxides. Method 7504. In: NIOSH manual of analytical methods. Centers for Disease Control, National Institute for Occupational Safety and Health, http://www.cdc.gov/niosh/nmam/pdfs/7504.pdf. May 26, 2009.

*NIOSH. 2003a. Elements by ICP (nitric/perchloric acid ashing). Method 7300. In: NIOSH manual of analytical methods. 4th ed. Centers for Disease Control, National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7300.pdf. May 26, 2009.

*NIOSH. 2003b. Elements by ICP (aqua regia ashing). Method 7301. In: NIOSH manual of analytical methods. 4th ed. Centers for Disease Control, National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7301.pdf. May 26, 2009.

*NIOSH. 2003c. Elements by ICP (hot block/HCl/HNO3 digestion). Method 7303. In: NIOSH manual of analytical methods. 4th ed. Centers for Disease Control, National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7303.pdf. May 26, 2009.

*NIOSH. 2003d. Elements on wipes. Method 9102. In: NIOSH manual of analytical methods. 4th ed. Centers for Disease Control, National Institute for Occupational Safety and Health, http://www.cdc.gov/niosh/nmam/pdfs/9102.pdf. May 26, 2009.

*NIOSH. 2004. NIOSH Health Hazard Evaluation Report: HETA No. 2003-0171-2925, PCC Schlosser, Redmond, Oregon. Cincinnati, OH: National Institute for Occupational Safety and Health.

*NIOSH. 2005. Vanadium pentoxide. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/. May 19, 2009.

*Nixon DE, Neubauer KR, Eckdahl SJ, et al. 2002. Evaluation of a tunable bandpass reaction cell for an inductively coupled plasma mass spectrometer for the determination of chromium and vanadium in serum and urine. Spectrochim Acta Part B 57:951-966.

*NLM. 2009. Vanadium. Bethesda, MD: U.S. National Library of Medicine, National Institutes of Health, Department of Health and Human Services. http://dietarysupplements.nlm.nih.gov/dietary/ingredDetail.jsp?contain=Vanadium&id=1280. June 17, 2009.

Novelli M, De Tata V, Fierabracci V, et al. 2005. Comparative study on the preventing effects of oral vanadyl sulfate and dietary restriction on the age-related glucose intolerance in rats. Aging Clin Exp Res 17(5):351-357.

*NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Research Council. National Academy Press.

*Nriagu JO. 1992. Review: Toxic metal pollution in Africa. Sci Total Environ 121:1-37.

Nriagu JO, Pirrone N. 1998. Emissions of vanadium into the atmosphere. In: Nriagu JO, ed. Advances in environmental science and technology. Vanadium in the environment, Part 1: Chemistry and biochemistry. Vol. 30. New York, NY: John Wiley and Sons, 25-36.

*+NTP. 2002. NTP toxicology and carcinogenesis studies of vanadium pentoxide (CAS No. 1314-62-1) in F344/N rats and B6C3F1 mice (inhalation). Natl Toxicol Program Tech Rep Ser (507):1-343.

*NTP. 2005. Report on carcinogens, 11th edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. May 11, 2009.

*NTP. 2008. Chemical information review document for oral exposure to tetravalent and pentavalent vanadium compounds. National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health,. http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/NIEHS_Vanadium_compounds_508.pdf. August 3, 2009.

*Oberg SG, Parker R, Sharma RP. 1978. Distribution and elimination of an intratracheally administered vanadium compound in the rat. Toxicology 11:315-323.

*O'Neil MJ, Heckelman PE, Koch CB, eds. 2006. The merck index. 14th ed. Whitehouse Station, NJ: Merck & Co., Inc., 90, 4192, 1705-1706.

*Ordóñez A, Loredo J, Demiguel E, et al. 2003. Distribution of heavy metals in the street dusts and soils of an industrial city in northern Spain. Arch Environ Contam Toxicol 44:160-170.

*OSHA. 1991. Confirmation of vanadium pentoxide in workplace atmospheres. Occupational Safety and Health Administration. http://www.osha.gov/dts/sltc/methods/inorganic/id185/id185.html. April 7, 2009.

*OSHA. 2002. Metal and metalloid particulates in workplace atmospheres (ICP analysis). Occupational Safety and Health Administration. Division of Physical Measurements and Inorganic Analyses, OSHA Technical Center. http://www.osha.gov/dts/sltc/methods/inorganic/id125g/id125g.pdf. May 23, 2009.

*OSHA. 2009. Toxic and Hazardous Substances. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000, Table Z 1. http://www.osha.gov/comp-links.html. May 19, 2009.

Oster MH, Llobet JM, Domingo JL, et al. 1993. Vanadium treatment of diabetic Sprague-Dawley rats results in tissue vanadium accumulation and pro-oxidant effects. Toxicology 83(1-3):115-130.

OTA. 1990. Neurotoxicity: Identifying and controlling poisons of the nervous system. Washington, DC: Office of Technology Assessment.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

*Owusu-Yaw J, Cohen MD, Fernando SY, et al. 1990. An assessment of the genotoxicity of vanadium. Toxicol Lett 50(2-3):327-336.

Pantelica A, Salagean M, Schreiber H. 1998. Comparative evaluation of some pollutants in the airborne particulate matter in Eastern and Western Europe: Two-city study, Bucharest-Stuttgart. AU - CERCASOV V. Environ Pollut 101(3):331-337.

Parkash P, Gupta A. 1991. Cardiotoxic effects of vanadium as revealed through electrocardiogram. Indian J Ind Med 37(1):32-36.

*Parker RD, Sharma RP. 1978. Accumulation and depletion of vanadium in selected tissues of rats treated with vanadyl sulfate and sodium orthovanadate. J Environ Pathol Toxicol 2:235-245.

Parr RM, Aras NK, Iyengar GV. 2006. Dietary intakes of essential trace elements: Results from total diet studies supported by the IAEA. J Radioanal Nucl Chem 270(1):155-161.

*+Paternain JL, Domingo JL, Gomez M, et al. 1990. Developmental toxicity of vanadium in mice after oral administration. J Appl Toxicol 10(3):181-186.

*+Paternain JL, Domingo JL, Llobet JM, et al. 1987. Embryotoxic effects of sodium metavanadate administered to rats during organogenesis. Rev Esp Fisiol 43(2):223-228.

*Patterson BW, Hansard SL, Ammerman CB, et al. 1986. Kinetic model of whole-body vanadium metabolism: Studies in sheep. Am J Physiol 251:R325-R332.

Paul KR, Gupta VK. 1982. Toxicology, solvent extraction and spectrophotometric determination of vanadium in complex materials. Am Ind Hyg Assoc J 43:529-532.

*Pennington JA, Jones JW. 1987. Molybdenum, nickel, cobalt, vanadium, and strontium in total diets. J Am Diet Assoc 12:1644-1650.

Phillips T, Nechay BR, Heidelbaugh D. 1983. Vanadium: Chemistry and the kidney. Fed Proc 42:2969-2973.

Pierce LM, Alessandrini F, Godleski JJ, et al. 1996. Vanadium-induced chemokine mRNA expression and pulmonary inflammation. Toxicol Appl Pharmacol 138(1):1-11.

Pinon-Zarate G, Rodriguez-Lara V, Rojas-Lemus M, et al. 2005. Gender differences in spleen megakaryocyte features after chronic inhalation of vanadium [Abstract]. Toxicol Lett 158(suppl 1):S161.

Pinon-Zarate G, Rodriguez-Lara V, Rojas-Lemus M, et al. 2008. Vanadium pentoxide inhalation provokes germinal center hyperplasia and suppressed humoral immune responses. J Immunotoxicol 5(2):115-122.

*+Poggioli R, Arletti R, Bertolini A, et al. 2001. Behavioral and developmental outcomes of prenatal and postnatal vanadium exposure in the rat. Pharmacol Res 43(4):341-347.

*Polissar AV, Hopke PK, Poirot RL. 2001. Atmospheric aerosol over Vermont: Chemical composition and sources. Environ Sci Technol 35:4604-4621.

*Poucheret P, Verma S, Grynpas MD, et al. 1998. Vanadium and diabetes. Mol Cell Biochem 188:73-80.

Poulsen OM, Christensen JM, Sabbioni E, et al. 1994. Trace element reference values in tissues from inhabitants of the European community. V. Review of trace elements in blood, serum and urine and critical evaluation of reference values for the Danish population. Sci Total Environ 141:197-215.

Poykio R, Maenpaa A, Peramaki P, et al. 2005. Heavy metals (Cr, Zn, Ni, V, Pb, Cd) in ligonberries (*Vaccinium vitis-idaea L.*) and assessment of human exposure in two industrial areas in the Kemi-Tornio Region, Northern Finland. Arch Environ Contam Toxicol 48:338-343.

Presley BJ. 1997. A review of arctic trace metal data with implications for biological effects. Mar Pollut Bull 35(7-12):226-234.

Pugazhenthi S, Khandelwal RL. 1990. Insulin like effects of vanadate on hepatic glycogen metabolism in nondiabetic and streptozocin-induced diabetic rats. Diabetes 39(7):821-827.

*Pyrzyńska K, Wierzbicki T. 2004. Determination of vanadium species in environmental samples. Talanta 64:823-829.

Pytkowski B, Jagodzinska-Hamann L. 1996. Effects of in vivo vanadate administration on calcium exchange and contractile force of rat ventricular myocardium. Toxicol Lett 84(3):167-173.

Pyy L, Lajunen LH, Hakala E. 1983. Determination of vanadium in workplace air by DCP emission spectrometry. Am Ind Hyg Assoc J 44:609-614.

Quickert N, Zdrojewski A, Dubois L. 1974. The accurate measurement of vanadium in airborne particulates. Int J Environ Anal Chem 3:229-238.

*Ramanadham S, Heyliger C, Gresser MJ, et al. 1991. The distribution and half-life for retention of vanadium in the organs of normal and diabetic rats orally fed vanadium(IV) and vanadium(V). Biol Trace Elem Res 30(2):119-124.

Rawal SB, Singh MV, Salhan A, et al. 1997. Influence of vanadium on acclimatization of humans to high altitude. Int J Biometeorol 40(2):95-98.

Reimann C, De Caritat P, Halleraker JH, et al. 1997. Rainwater composition in eight arctic catchments in northern Europe (Finland, Norway and Russia). Atmos Environ 31(2):159-170.

Ress NB, Chou BJ, Renne RA, et al. 2003a. Carcinogenicity of inhaled vanadium pentoxide in F344/N rats and B6C3F1 mice. Toxicol Sci 74(2):287-296.

Ress NB, Roycroft JH, Hailey JR, et al. 2003b. Toxic and carcinogenic effects in the lungs of rats and mice exposed to vanadium pentoxide by whole-body inhalation. Toxicol Sci 72(S-1):85.

*Rhoads K, Samders CL. 1985. Lung clearance, translocation, and acute toxicity of arsenic, beryllium, cadmium, cobalt, lead, selenium, vanadium and ytterbium oxides following deposition in rat lung. Environ Res 36:359-378.

*Riediker M, Williams R, Devlin R, et al. 2003. Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. Environ Sci Technol 37:2084-2093.

Ringelband U, Hehl O. 2000. Kinetics of Vanadium Bioaccumulation by the brackish water hydroid *Cordylophora caspia* (Pallas). Bull Environ Contam Toxicol 65(4):486-493.

Rodriguez-Mercado JJ, Roldan-Reyes E, Altamirano-Lozano M. 2003. Genotoxic effects of vanadium(IV) in human peripheral blood cells. Toxicol Lett 144(3):359-369.

*Rojas E, Valverde M, Herrera LA, et al. 1996. Genotoxicity of vanadium pentoxide evaluate by the single cell gel electrophoresis assay in human lymphocytes. Mutat Res 359(2):77-84.

*Roldán RE, Altamirano LM. 1990. Chromosomal aberrations, sister-chromatid exchanges, cell-cycle kinetics and satellite associations in human lymphocyte cultures exposed to vanadium pentoxide. Mutat Res 245(2):61-66.

+Roschin IV. 1967. [Vanadium]. In: Izrael'son ZI, ed. [Toxicology of the rare metals]. Jerusalem: Israel Program for Scientific Translations, 52-60. (Russian)

*+Roshchin AV, Ordzhonikidze EK, Shalganova IV. 1980. [Vanadium-toxicity, metabolism, carrier state]. J Hyg Epidemiol Microbiol Immunol 24:377-383. (Russian)

*RTECS. 2009. Vanadium and vanadium compounds. Registry of Toxic Effects on Chemical Substances. National Institute of Occupational Safety and Health. MDL Information Systems, Inc. May 26, 2009.

Rutzke MA, Gutenmann WH, Lisk DJ, et al. 2000. Toxic and nutrient element concentrations in soft tissues of zebra and guagga mussels from Lakes Erie and Ontario. Chemosphere 40:1353-1356.

*Rydzynski K. 2001. Vanadium, Niobium, and Tantalum. In: Bingham E, Cohrssen B, Powell CH, eds. Patty's toxicology. Vol. 3. 5th ed. New York, NY: John Wiley & Sons, Inc., 1-38.

*Sabbioni E, Marafante E. 1978. Metabolic patterns of vanadium in the rat. Bioinorg Chem 9:389-408.

*Sabbioni E, Kueera J, Pietra R, et al. 1996. A critical review on normal concentrations of vanadium in human blood, serum, and urine. Sci Total Environ 188(1):49-58.

*Sadiq M, Alam I. 1997. Metal concentrations in a shallow groundwater aquifer underneath petrochemical complex. Water Res 31(12):3089-3097.

*Sadiq M, Mian AA. 1994. Nickel and vanadium in air particulates at Dhahran (Saudi Arabia) during and after the Kuwait oil fires. Atmos Environ 28(13):2249-2253.

Sadiq M, Alam IA, Al-Mohanna H. 1992b. Bioaccumulation of nickel and vanadium by clams (*Meretrix meretrix*) living in different salinities along the Saudi coast of the Arabian Gulf. Environ Pollut 76(3):225-231.

Sadiq M, AlThagafi KM, Mian AA. 1992a. Preliminary evaluation of metal contamination of soils from the Gulf War activities. Bull Environ Contam Toxicol 46:633-639.

*Salazar-Coria L, Amezcua-Allieri MA, Tenorio-Torres M, et al. 2007. Polyaromatic hydrocarbons (PAHs) and metal evaluation after a diesel spill in Oaxaca, Mexico. Bull Environ Contam Toxicol 79(4):462-467.

Saldivar L, Espejel G, Sanchez I, et al. 2004. Study of vanadium, an experimental model in mice. Toxicol Appl Pharmacol 197(3):274-275.

*Saleh MA, Wilson BL. 1999. Analysis of metal pollutants in the Houston Ship Channel by inductively coupled plasma/mass spectrometry. Ecotoxicol Environ Saf 44:113-117.

*+Sanchez D, Ortega A, Domingo JL, et al. 1991. Developmental toxicity evaluation of orthovanadate in the mouse. Biol Trace Elem Res 30(3):219-226.

*+Sanchez DJ, Colomina MT, Domingo JL. 1998. Effects of vanadium on activity and learning in rats. Physiol Behav 63(3):345-350.

*Sanchez DJ, Colomina MT, Domingo JL, et al. 1999. Prevention by sodium 4,5-dihydroxybenzene-1,3-disulfonate (tiron) of vanadium-induced behavioral toxicity in rats. Biol Trace Elem Res 69(3):249-259.

Sanchez DJ, Gomez M, Domingo JL, et al. 1992. Maternal and developmental toxicity of metavanadate in mice. In: Anastassopoulou J, Collery P, Etienne JC, eds. Metal ions in biology and medicine. Vol. 2. Paris: John Libbey Eurotext, 319-320.

*+Schroeder HA, Balassa JJ. 1967. Arsenic, germanium, tin and vanadium in mice: Effects on growth, survival and tissue levels. J Nutr 92(2):245-252.

*+Schroeder HA, Mitchener M. 1975. Life-term effects of mercury, methyl mercury, and nine other trace metals on mice. J Nutr 105(4):452-458.

*Schroeder HA, Balassa JJ, Tipton IH. 1963. Abnormal trace metals in man - vanadium. J Chronic Dis 16:1047-1071.

*+Schroeder HA, Mitchener M, Nason AP. 1970. Zirconium, niobium, antimony, vanadium and lead in rats: Life term studies. J Nutr 100(1):59-68.

*Schroeder WH, Dobson M, Kane DM, et al. 1987. Toxic trace elements associated with airborne particulate matter: A review. JAPCA 37(11):1267-1285.

*Schuhmacher M, Bocio A, Agramunt MC, et al. 2002. PCDD/F and metal concentrations in soil and herbage samples collected in the vicinity of a cement plant. Chemosphere 48:209-217.

*+Scibior A. 2005. Some selected blood parameters in rats exposed to vanadium and chromium via drinking water. Trace Elem Electrolytes 22(1):40-46.

*+Scibior A, Zaporowska H, Ostrowski J. 2006. Selected haematological and biochemical parameters of blood in rats after subchronic administration of vanadium and/or magnesium in drinking water. Arch Environ Contam Toxicol 51(2):287-295.

*Seiler HG. 1995. Analytical procedures for the determination of vanadium in biological materials. In: Sigel H, Sigel A, eds. Metal ions in biological systems. New York, NY: Marcel Dekker, Inc., 671-688.

Sella SM, Pereiranetto AD, Delestal LM. 2001. Trace metals in the atmosphere of Niteroi City, RJ, Brazil. Bull Environ Contam Toxicol 67:271-275.

Senesi GS, Baldassarre G, Senesi N, et al. 1999. Trace element inputs into soils by anthropogenic activities and implications for human health. Chemosphere 39(2):343-377.

*Sepe A, Ciaralli L, Ciprotti M, et al. 2003. Determination of cadmium, chromium, lead and vanadium in six fish species from the Adriatic Sea. Food Addit Contam 20(6):543-552.

*Setchell BP, Waites GMH. 1975. The blood testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society, 143-172.

Shahin U, Yi SM, Paode RD, et al. 2000. Long-term elemental dry deposition fluxes measured around Lake Michigan with an automated dry deposition sampler. Environ Sci Technol 34:1887-1892.

*+Sharma RP, Bourcier DR, Brinkerhoff CR, et al. 1981. Effects of vanadium on immunologic functions. Am J Ind Med 2(2):91-99.

*Sharma RP, Oberg SG, Parker RD. 1980. Vanadium retention in rat tissues following acute exposures to different dose levels. J Toxicol Environ Health 6:45-54.

*Sheridan CJ, Pfleger RC, McClellan RO. 1978. Cytotoxicity of vanadium pentoxide on pulmonary alveolar macrophages from dog, rabbit, and rat: Effect on viability and effect on lipid metabolism. Ann Resp Inhalation Toxicol:294-298.

Sheu CW, Rodriguez I, Lee JK. 1992. Proliferation and morphological transformation of BALB/3T3 cells by a prolonged treatment with sodium orthovanadate. Food Chem Toxicol 30(4):307-311.

Shimy TM. 1997. Distribution of selected trace metals and its relation with environmental pollution. Energy Sources 19(8):851-860.

Shrivastava S, Jadon A, Shukla S. 2007. Effect of tiron and its combination with nutritional supplements against vanadium intoxication in female albino rats. J Toxicol Sci 32(2):185-192.

Shrivastava S, Jadon A, Shukla S, et al. 2007. Chelation therapy and vanadium: Effect on reproductive organs in rats. Indian J Exp Biol 45(6):515-523.

Siemon H, Schneider H, Fuhrmann GF. 1982. Vanadium increases selective K+-permeability in human erythrocytes. Toxicology 22:271-278.

Singh PP, Junnarkar AY. 1991. Behavioural and toxic profile of some essential trace metal salts in mice and rats. Indian J Pharmacol 23(3):153-159.

Sitprija V, Tungsanga K, Tosukhowong P, et al. 1993. Metabolic problems in northeastern Thailand: Possible role of vanadium. Miner Electrolyte Metab 19(1):51-56.

*+Sjöberg SG. 1950. Vanadium pentoxide dust: A clinical and experimental investigation on its effect after inhalation. Stockholm: Esselte AB, 6-188.

*+Sjöberg SG. 1956. Vanadium dust, chronic bronchitis and possible risk of emphysema. Acta Med Scand 154:381-386.

*Smith DJ, Harrison RM, Luhana L, et al. 1996. Concentrations of particulate airborne polycyclic aromatic hydrocarbons and metals collected in Lahore, Pakistan. Atmos Environ 30(23):4031-4040.

*Smith JB. 1983. Vanadium ions stimulated DNA synthesis in Swill mouse 3T3 and 3T6 cells. Proc Natl Acad Sci USA 80:6162-6166.

*Smith DM, Pickering RM, Lewith GT. 2008. A systematic review of vanadium oral supplements for glycaemic control in type 2 diabetes mellitus. Q J Med 101(5):351-358.

Soldi T, Riolo C, Alberti G, et al. 1996. Environmental vanadium distribution from an industrial settlement. Sci Total Environ 181(1):45-50.

*Sora S, Carbone MLA, Pacciarini M, et al. 1986. Disomic and diploid meiotic products induced in *Saccharomyuces cerevisiae* by the salts of 27 elements. Mutagenesis 1(1):21-28.

*SRI. 2008. Directory of chemical producers: United States. Menlo Park, CA: SRI Consulting, 912.

*+Steffen RP, Pamnani MB, Clough DL, et al. 1981. Effect of prolonged dietary administration of vanadate on blood pressure in the rat. Hypertension 3(3 Pt 2):I-173 to I-178.

*+Stokinger HE, Wagner WD, Mountain JT, et al. 1953. Unpublished results. Cincinnati, OH: Division of Occupational Health. (As cited in IRIS 2009).

*Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 406-407.

*+Susic D, Kentera D. 1986. Effect of chronic vanadate administration on pulmonary circulation in the rat. Respiration 49:68-72.

*Susic D, Kentera D. 1988. Dependence of the hypertensive effect of chronic vanadate administration on renal excretory function in the rat. J Hypertens 6(3):199-204.

*Sweet CW, Vermette SJ, Landsberger S. 1993. Sources of toxic trace elements in urban air in Illinois. Environ Sci Technol 27(12):2502-2510.

Symanski HJ. 1983. Vanadium, alloys and compounds. In: Encyclopedia of occupational health and safety. Vol. II. Geneva, Switzerland: International Labour Office, 2240-2241.

Szakmary E, Naray M, Tatrai E, et al. 2003. Embryotoxic and teratogenic effect of vanadium pentoxide on rats and rabbits. Egeszsegtudomany 47(1-2):45-57.

*Taylor HE, Antweiler RC, Roth DA, et al. 2001. The occurrence and distribution of selected trace elements in the upper Rio Grande and tributaries in Colorado and northern New Mexico. Arch Environ Contam Toxicol 41:410-426.

*+Thomas DL, Stiebris K. 1956. Vanadium poisoning in industry. Med J Aust 1:607-609.

*Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing, 365-394.

*Thomas KW, Pellizzari ED, Berry MR. 1999. Population-based dietary intakes and tap water concentrations for selected elements in the EPA region V national human exposure assessment survey (NHEXAS). J Expo Anal Environ Epidemiol 9:402-413.

*Thompson KH, Orvig C. 2006. Vanadium in diabetes: 100 years from Phase 0 to Phase I. J Inorg Biochem 100(12):1925-1935.

*Thompson HJ, Chasteen ND, Meeker LD. 1984. Dietary vanadyl (IV) sulfate inhibits chemically-induced mammary carcinogenesis. Carcinogenesis 5:849-851.

Thompson KH, Leichter J, McNeill JH. 1993. Studies of vanadyl sulfate as a glucose-lowering agent in STZ-diabetic rats. Biochem Biophys Res Commun 197(3):1549-1555.

*Thompson KH, Tsukada Y, Xu Z, et al. 2002. Influence of chelation and oxidation state on vanadium bioavailability, and their effects on tissue concentrations of zinc, copper, and iron. Biol Trace Elem Res 86(1):31-44.

Toya T, Fukuda K, Takaya M, et al. 2001. Lung lesions induced by intratracheal instillation of vanadium pentoxide powder in rats. Ind Health 39(1):8-15.

*TRI07. 2009. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. April 7, 2009.

Trumbo P, Yates AA, Schlicker S, et al. 2001. Dietary reference intakes: Vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. J Am Diet Assoc 101(3):294-301.

Tunali S, Yanardag R. 2006. Effect of vanadyl sulfate on the status of lipid parameters and on stomach and spleen tissues of streptozotocin-induced diabetic rats. Pharmacol Res 53(3):271-277.

*USGS. 1987. Metals, atomic emission spectrometry, inductively coupled plasma (ICP). In: Methods for the determination of inorganic substances in water and fluvial sediments, techniques of water-resources investigations of the United States Geological Survey. Denver, CO: U.S. Geological Survey. http://infotrek.er.usgs.gov/pls/htmldb/f?p=119:38:8660777138310287:::P38_METHOD_ID:8896. May 23, 2009.

*USGS. 1993. Vanadium, colorimetry, catalytic oxidation, automated-segmented flow. U.S. Geological Survey. http://pubs.er.usgs.gov/djvu/OFR/1993/ofr_93_125.djvu. May 26, 2009.

*USGS. 1996. Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory - preparation procedure for aquatic biological material determined for trace metals. Denver, CO: U.S. Geological Survey, Department of the Interior. Open-File Report 96-362. http://nwql.usgs.gov/Public/pubs/OFR96-362/OFR96-362.pdf. May 22, 2009.

*USGS. 1998. Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory - determination of elements in whole-water digests using inductively coupled plasma-optical emission spectrometry and inductively coupled plasma-optical emission spectrometry and inductively coupled plasma-mass spectrometry. Denver, CO: U. S. Geological Survey. Open-File Report 98-165. http://pubs.er.usgs.gov/usgspubs/ofr/ofr98165. May 22, 2009.

*USGS. 1999. Methods of analysis by the U.S. Geological Survey National Water Quality Laboratory - determination of dissolved arsenic, boron, lithium, selenium, strontium, thallium, and vanadium using inductively. Denver, CO: U.S. Geological Survey. Open-file report 99-093. http://nwql.usgs.gov/Public/pubs/OFR99-093/OFR99-093.pdf. May 23, 2009.

*USGS. 2006. Determination of elements in natural-water, biota, sediment, and soil samples using collision/reaction cell inductively - coupled plasma - mass spectrometry. U.S. Department of the Interior, U.S. Geological Survey. http://pubs.usgs.gov/tm/2006/tm5b1/PDF/TM5-B1.pdf. May 22, 2009.

USGS. 2008. Vanadium. Mineral commodity summaries. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/vanadium/mcs-2008-vanad.pdf. May 21, 2009.

*USGS. 2009a. Vanadium. Mineral commodity summaries. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/vanadium/mcs-2009-vanad.pdf. May 21, 2009.

*USGS. 2009b. 2007 Minerals yearbook. U.S. Department of the Interior, U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/vanadium/myb1-2007-vanad.pdf. May 27, 2009.

*USGS. 2009c. Quality of water from domestic wells in principal aquifers of the United States, 1991-2004. Reston, VA: U.S. Department of the Interior, U.S. Geological Survey. Scientific Investigations Report 2008-5227. http://pubs.usgs.gov/sir/2008/5227. August 3, 2009.

Vannetten C, Cann SAH, Morley DR, et al. 2000. Elemental and radioactive analysis of commercially available seaweed. Sci Total Environ 255:169-175.

*Van Zinderen Bakker, Jaworski JF. 1980. Effects of vanadium in the Canadian environment. Ottawa, Canada: National Research Council Canada, Associate Committee Scientific Criteria for Environmental Quality, 1-94.

Verma S, Cam MC, McNeill JH. 1998. Nutritional factors that can favorably influence the glucose/insulin system: Vanadium. J Am Coll Nutr 17(1):11-18.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238(2):476-483.

*Villani P, Cordelli E, Leopardi P, et al. 2007. Evaluation of genotoxicity of oral exposure to tetravalent vanadium in vivo. Toxicol Lett 170(1):11-18.

*+Vintinner FJ, Vallenas R, Carlin CE, et al. 1955. Study of the health of workers employed in mining and processing of vanadium ore. AMA Arch Ind Health 12:635-642.

*Vouk VB. 1979. Vanadium. In: Friberg L, Nordberg GR, Vouk VB, eds. Handbook on the toxicology of metals. New York, NY: Elsevier North Holland, 659-674.

*Waters MD. 1977. Toxicology of vanadium. In: Mehlam MA, Marzulli FN, Maibach HI, eds. Advances in Modern Toxicology. Vol. 2. New York, NY: Wiley, 147-189.

*Waters MD, Gardner DE, Coffin DL. 1974. Cytotoxic effects of vanadium on rabbit alveolar macrophages in vitro. Toxicol Appl Pharmacol 28:253-263.

Weast RC. 1969. Chemical rubber company handbook of chemistry and physics. 50th ed. Cleveland, OH: CRC Press, Inc., B-144-B-145, 261.

*Wehrli B, Stumm W. 1989. Vanadyl in natural waters: Adsorption and hydrolysis promote oxygenation. Geochim Cosmochim Acta 53:69-77.

*Wei C, Misra HP. 1982. Cytotoxicity of ammonium metavanadate to cultured bovine alveolar macrophages. J Toxicol Environ Health 9:995-1006.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

+Westenfelder C, Hamburger RK, Garcia ME. 1981. Effect of vanadate on renal tubular function in rats. Am J Physiol Renal Physiol 240(6):F522-F529.

WHO. 1987. Air quality guidelines for Europe. Copenhagen, Denmark: World Health Organization, Regional Office of Europe.

*WHO. 1988. Vanadium. In: Environmental health criteria 81. Geneva, Switzerland: World Health Organization,

*WHO. 2000. Air quality guidelines. 2nd edition. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/air/activities/20050223_4. May 11, 2009.

WHO. 2001. Vanadium pentoxide and other inorganic vanadium compounds. Concise International Chemical Assessment Document 29.

*WHO. 2006. Guidelines for drinking-water quality. 3rd edition. Geneva, Switzerland: World Health Organization.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advance treatise. Vol. II. New York, NY: Academic Press, 1-247.

+Wide M. 1984. Effect of short-term exposure to five industrial metals on the embryonic and fetal development of the mouse. Environ Res 33(1):47-53.

Windholz M. 1983. The Merck index. Rahway, NJ: Merck & Co., Inc., 82, 1417-1419.

*Witkowska D, Oledzka R, Markowska B. 1988. Effect of intoxication with vanadium compounds on copper metabolism in the rat. Bull Environ Contam Toxicol 40:309-316.

Woodin MA, Liu Y, Hauser R, et al. 1999. Pulmonary function in workers exposed to low levels of fuel-oil ash. J Occup Environ Med 41(11):973-980.

Woodin MA, Liu Y, Neuberg D, et al. 2000. Acute respiratory symptoms in workers exposed to vanadium-rich fuel-oil ash. Am J Ind Med 37(4):353-363.

*Woolery M. 2005. Vanadium compounds. In: Kirk-Othmer encyclopedia of chemical technology. John Wiley & Sons, Inc. http://mrw.interscience.wiley.com/emrw/9780471238966/kirk/article/vanawool.a01/current/pdf. May 27, 2009.

*Wozniak K, Blasiak J. 2004. Vanadyl sulfate can differentially damage DNA in human lymphocytes and HeLa cells. Arch Toxicol 78(1):7-15.

*+Wyers H. 1946. Some toxic effects of vanadium pentoxide. Br J Ind Med 3:177-182.

*+Yao J, Battell ML, McNeill JH. 1997. Acute and chronic response to vanadium following two methods of streptozotocin-diabetes induction. Can J Physiol Pharmacol 75(2):83-90.

*+Zaporowska H, Wasilewski W. 1989. Some selected peripheral blood and haemopoietic system indices in Wistar rats with chronic vanadium intoxication. Comp Biochem Physiol C Comp Pharmacol Toxicol 93C(1):175-180.

*+Zaporowska H, Wasilewski W. 1990. Some selected hematological indices in Wistar rats in the vanadium-ethanol interaction. Comp Biochem Physiol C Comp Pharmacol Toxicol 96(1):33-38.

*+Zaporowska H, Wasilewski W. 1991. Significance of reduced food and water consumption in rats intoxicated with vanadium. Comp Biochem Physiol C 99(3):349-352.

*+Zaporowska H, Wasilewski W. 1992a. Combined effect of vanadium and zinc on certain selected haematological indices in rats. Comp Biochem Physiol C 103(1):143-147.

*+Zaporowska H, Wasilewski W. 1992b. Haematological results of vanadium intoxication in Wistar rats. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 101C(1):57-61.

*+Zaporowska H, Wasilewski W, Slotwinska M. 1993. Effect of chronic vanadium administration in drinking water to rats. Biometals 6(1):3-10.

*+Zenz C, Berg BA. 1967. Human responses to controlled vanadium pentoxide exposure. Arch Environ Health 14:709-712.

*+Zenz C, Bartlett JP, Thiede WM, et al. 1962. Acute vanadium pentoxide intoxication. Arch Environ Health 5:542-546.

*Zhong BZ, Gu ZW, Wallace WE, et al. 1994. Genotoxicity of vanadium pentoxide in Chinese hamster V79 cells. Mutat Res 321(1-2):35-42.

Zhou D, Feng C, Lan Y, et al. 2007. Paired-control study on the effect of vanadium on neurobehavioral functions. Sichuan Da Xue Xue Bao Yi Xue Ban 38(3):468-470.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12(1):29-34.

*Zoller WH, Gordon GE, Cladney ES, et al. 1973. The sources and distribution of vanadium in the atmosphere. In: Advances in chemistry series no. 123. Trace elements in the environment. Washington DC: American Chemical Society, 31-47.

Zychlinski L, Byczkowski JZ, Kulkarni AP. 1991. Toxic effects of long-term intratracheal administration of vanadium pentoxide in rats. Arch Environ Contam Toxicol 20(3):295-298.

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.

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 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 that 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.

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 of people that 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.

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.

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.

***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 that 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 that 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.

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) that 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

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 dynamic behavior of a material in the body, used to predict 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, whereas 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 that 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) concentration 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 group.

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 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

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/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 100-fold 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 and Environmental Medicine, 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 and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vanadium compounds
CAS Numbers: 7440-62-2
Date: August 2009
Profile Status: Pre-Public Comment, Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 0.0008 [ ] mg/kg/day [X] mg vanadium/m^3

Reference: NTP. 2002. NTP toxicology and carcinogenesis studies of vanadium pentoxide (CAS No. 1314-62-1) in F344/N rats and B6C3F1 mice (inhalation). Natl Toxicol Program Tech Rep Ser (507):1-343.

Experimental design: Groups of 40–60 female F344 rats were exposed to 0, 1, 2, or 4 mg vanadium pentoxide/m^3 (0, 0.56, 1.1, and 2.2 mg vanadium/m^3) 6 hours/day, 5 days/week for 16 days. On days 6 and 13, 10 rats/group were killed and a histopathological examination of the lungs was conducted. Four animals per group were killed for examination of onset and extent of lung lesions on days 1, 2, 5, 10, and 16. The remaining animals were used to measure blood and lung concentrations of vanadium, lung clearance half-times, and cell proliferation rates.

Effect noted in study and corresponding doses: Hyperplasia of alveolar epithelium and bronchiole epithelium were observed in 100% of the female rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days. Significant increases in the incidence of histiocytic infiltrate and inflammation were observed in rats exposed to 1.1 or 2.2 mg vanadium/m^3 for 6 or 13 days and in rats exposed to 0.56 mg vanadium/m^3 for 13 days. A significant increase in fibrosis was observed in rats exposed to 2.2 mg vanadium/m^3 for 13 days. No histopathological alterations were observed in the four female rats killed after 1 day of exposure; by day 2, inflammation and histiocytic infiltrates (increased number of alveolar macrophages) were observed in the rats exposed to 2.2 mg vanadium/m^3. Hyperplasia of the alveolar and bronchiolar epidthelium was first observed on day 5 in rats exposed to 1.1 or 2.2 mg vanadium/m^3.

Dose and end point used for MRL derivation: Increase in the incidence of lung inflammation in rats exposed to 0.56 mg vanadium/m^3 as vanadium pentoxide for 13 days.

[ ] NOAEL [X] LOAEL

A BMD analysis was considered for determining the point of departure for the inflammation in female rats exposed to vanadium pentoxide for 13 days. All available dichotomous models in the EPA benchmark dose software ([BMDS] version 2.1) were fit to the incidence data for lung inflammation (0/10, 8/10, 10/10, and 10/10 in rats exposed to 0, 0.56, 1.1, or 2.2 mg vanadium/m^3) using the extra risk option. The multistage model was run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all the models providing adequate fit to the data, the lowest lower bound on the BMC (BMCL) is selected as the point of departure when the difference between the BMDLs estimated from these models are more three-fold; otherwise, the BMCL from the model with the lowest AIC is chosen. In accordance with U.S. EPA (2000) guidance,

benchmark concentrations (BMCs) and BMCLs associated with an extra risk of 10% are calculated for all models.

Table A-1. Model Predictions for the Incidence of Inflammation in Female Rats Exposed to Vanadium Pentoxide 6 Hours/Day, 5 Days/Week for 13 Days

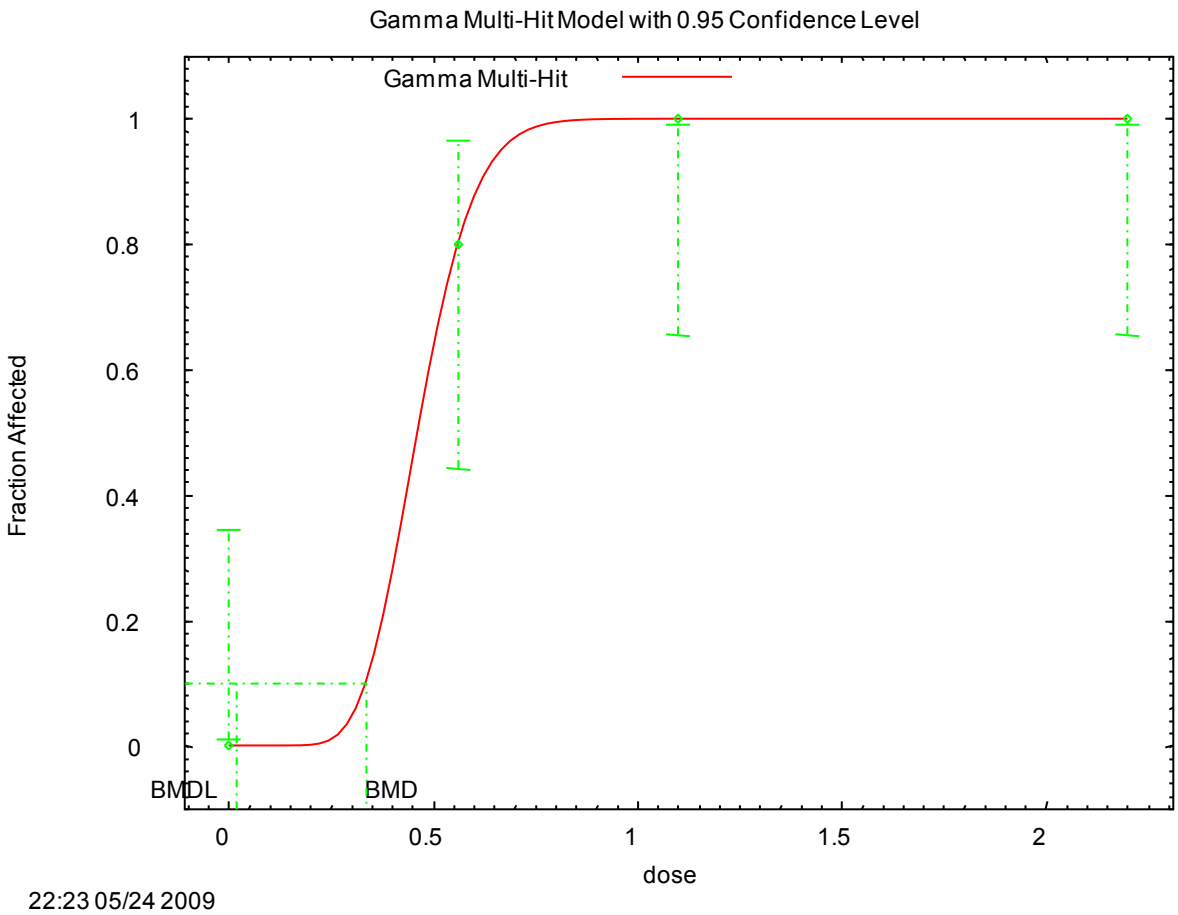
Model	χ^2 Goodness of fit p-value[a]	AIC	BMC_{10} (mg V/m^3)	$BMCL_{10}$ (mg V/m^3)
Gamma[b]	**1.00**	**12.01**	**0.33**	**0.02**
Logistic	1.00	14.01	0.46	0.10
LogLogistic	1.00	12.01	0.46	0.01
LogProbit	1.00	14.01	0.42	0.03
Multistage[c]	0.93	12.69	0.03	0.02
Probit	1.00	14.01	0.38	0.09
Weibull[b]	1.00	14.01	0.25	0.02
Quantal-linear	0.93	12.69	0.03	0.02

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]Power restricted to ≥1
[c]Betas restricted to ≥0; 1-degree polynomial

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC

Source: NTP 2002

Figure A-1. Fit of Gamma Model to Data on the Incidence of Inflammation in Female Rats Exposed to Vanadium Pentoxide for 13 Days



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

Although the data provide an adequate statistical fit, the estimated $BMCL_{10}$ of 0.02 mg vanadium/m^3 appears to be an overly conservative estimate of a no-adverse-effect level, which may be a reflection of the limited amount of information from the study on the shape of the exposure-response relationship (incidences of lung inflammation were 0/10 in controls and 8/10 at the lowest vanadium concentration). In a chronic-duration study conducted by NTP (2002), no significant alterations in the incidence of lung inflammation were observed in male and female rats exposed to 0.28 mg vanadium/m^3; the LOAEL for lung inflammation was 0.56 mg vanadium/m^3 in males and 1.1 mg vanadium/m^3 in females.

Due to the low confidence in the $BMCL_{10}$, a NOAEL/LOAEL approach was used to determine the point of departure for the acute MRL.

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The duration-adjusted LOAEL of 0.1 mg vanadium/m^3 was converted to a human equivalent concentration ($LOAEL_{HEC}$) using the following equation:

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR_{TH}$$
$$LOAEL_{HEC} = 0.1 \text{ mg vanadium/m}^3 \times 0.732$$
$$LOAEL_{HEC} = 0.073 \text{ mg vanadium/m}^3$$

where:
The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR program (EPA 1990) was used to calculate a multiplier of 0.732 for the thoracic region was determined using a default body weight of 0.124 kg (EPA 1994c) and a particle size MMAD of 1.2 µm with a geometric standard deviation of 1.9

Was a conversion used from intermittent to continuous exposure? The LOAEL was adjusted for intermittent exposure as follows:

$$LOAEL_{ADJ} = LOAEL \times 6 \text{ hours/day} \times 5 \text{ days/week}$$
$$LOAEL_{ADJ} = 0.56 \text{ mg vanadium/m}^3 \times 6 \text{ hours/24 hours} \times 5 \text{ days/7 days}$$
$$LOAEL_{ADJ} = 0.1 \text{ mg vanadium/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: Data on acute toxicity of vanadium in humans are limited to an experimental study in which a small number of subjects were exposed to vanadium pentoxide dust for 8 hours (Zenz and Berg 1967). A persistent cough lasting for 8 days developed in two subjects exposed to 0.6 mg vanadium/m^3; at 0.1 mg vanadium/m^3, a productive cough without any subjective complaints or impact on work or home activities were observed in 5 subjects. The available studies in laboratory animals focused on potential respiratory tract effects. Impaired lung function characterized as airway obstructive changes (increased resistance and decreased airflow) were observed in monkeys exposed to 2.5 or 1.7 mg vanadium/m^3 as vanadium pentoxide for 6 hours (Knecht et al. 1985, 1992); the highest NOAEL for this effect was 0.34 mg vanadium/m^3. Alveolar and bronchiolar epithelial hyperplasia and inflammation were observed in the lungs of mice exposed to 1.1 mg vanadium/m^3 6 hours/day, 5 days/week for 13 days (NTP 2002). Although the Knecht et al. (1985, 1992) or NTP (2002) studies did not include examination of potential end points outside of the respiratory tract, longer-duration studies have identified the respiratory tract as the most sensitive target of toxicity (NTP 2002).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Sam Keith, Larry Cseh

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vanadium compounds
CAS Numbers: 7440-62-2
Date: August 2009
Profile Status: Pre-Public Comment, Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 19
Species: Rat

Minimal Risk Level: 0.0001 [ ] mg/kg/day [X] mg vanadium/m^3

Reference: NTP. 2002. NTP toxicology and carcinogenesis studies of vanadium pentoxide (CAS No. 1314-62-1) in F344/N rats and B6C3F1 mice (inhalation). Natl Toxicol Program Tech Rep Ser (507):1-343.

Experimental design: Groups of 50 male and 50 female F344 rats were exposed to 0, 0.5, 1, or 2 mg vanadium pentoxide/m^3 (0, 0.28, 0.56, and 1.1 mg vanadium/m^3) 6 hours/day, 5 days/week for 104 weeks. The following parameters were used to assess toxicity: clinical observations, body weights (every 4 weeks from week 5 to 89 and every 2 weeks from week 92 to 104), complete necropsy, and microscopic examination of major tissues and organs.

Effect noted in study and corresponding doses: No significant alterations in survival or body weight gain were observed in the vanadium-exposed rats. A summary of selected non-neoplastic respiratory tract lesions is presented in Table A-2. Alveolar histiocytic infiltrates were observed in males and females exposed to ≥0.28 mg vanadium/m^3. Significant increases in the incidence of hyperplasia of the alveolar and bronchiolar epithelium were observed in males exposed to ≥0.28 mg vanadium/m^3 and females exposed to ≥0.56 mg vanadium/m^3. Squamous metaplasia was observed in alveolar epithelium of males and females exposed to 1.1 mg vanadium/m^3 and in the bronchiolar epithelium of males exposed to 1.1 mg vanadium/m^3. Chronic inflammation was observed in males exposed to 0.56 or 1.1 mg vanadium/m^3 and females exposed to 1.1 mg vanadium/m^3 and interstitial fibrosis was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.28 or 1.1 mg vanadium/m^3. An increased incidence of brownish pigment in alveolar macrophages was observed in males exposed to 1.1 mg vanadium/m^3 and females exposed to 0.56 or 1.1 mg vanadium/m^3; this effect was considered to be of little biological relevance. Chronic inflammation, degeneration, and hyperplasia of the epiglottis were observed in the larynx of males and females exposed to ≥0.28 mg vanadium/m^3; squamous metaplasia of the epiglottis respiratory epithelium was also observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3. Goblet cell hyperplasia of the nasal respiratory epithelium was observed in males exposed to ≥0.28 mg vanadium/m^3 and in females exposed to 1.1 mg vanadium/m^3. A positive trend for increased incidences of uterine stromal polyp was observed; NTP did not consider it to be related to vanadium pentoxide exposure. An increased incidence of nephropathy was observed in male rats exposed to 0.56 or 1.1 mg vanadium/m^3; NTP considered the finding to be of marginal biological significance because there was a lack of increase in severity, as compared to controls, and significant findings in female rats. No significant increases in the incidence of lung neoplasms were observed; however, the incidence of alveolar/bronchiolar adenoma in males exposed to 0.28 mg vanadium/m^3 and alveolar/bronchiolar carcinoma or combined incidence of adenoma and carcinoma in males exposed to 0.28 or 1.1 mg vanadium/m^3 were higher than historical controls. These increases in lung tumors were considered to be related to vanadium pentoxide exposure.

Table A-2. Selected Respiratory Tract Effects Observed in Rats Exposed to Vanadium Pentoxide 6 Hours/Day, 5 Days/Week for 2 Years

Air concentration (mg vanadium/m^3)	0	0.28	0.56	1.1
Males				
Lungs				
Alveolar hyperplasia	7/50 (2.3)	24/49[b] (2.0)	34/48[b] (2.0)	49/50[b] (3.3)
Bronchiole hyperplasia	3/50 (2.3)	17/49[b] (2.2)	31/48[b] (1.8)	49/50[b] (3.3)
Inflammation	5/50 (1.6)	8/49 (1.8)	24/48[b] (1.3)	42/50[b] (2.4)
Fibrosis	7/50 (1.4)	7/49 (2.0)	16/48[c] (1.6)	38/50[b] (2.1)
Histiocyte infiltration	22/50 (1.3)	40/49[b] (2.0)	45/48[b] (2.3)	50/50[b] (3.3)
Larynx				
Chronic inflammation	3/49 (1.0)	20/50[b] (1.1)	17/50[b] (1.5)	28/49[b] (1.6)
Degeneration of epiglottis respiratory epithelium	0/49	22/50[b] (1.1)	23/50[b] (1.1)	33/50[b] (1.5)
Hyperplasia of epiglottis respiratory epithelium	0/49	22/50[b] (1.1)	23/50[b] (1.1)	33/49[b] (1.5)
Squamous metaplasia of epiglottis respiratory epithelium	0/49	18/50[b] (1.5)	34/50[b] (1.5)	32/49[b] (1.9)
Nose				
Hyperplasia of respiratory epithelium goblet cell	4/49 (1.8)	15/50[b] (1.8)	12/49[c] (2.0)	17/48[b] (2.1)
Female				
Lung				
Alveolar hyperplasia	4/49 (1.0)	8/49 (1.8)	21/50[b] (1.2)	50/50[b] (3.1)
Bronchiole hyperplasia	6/49 (1.5)	5/49 (1.6)	14/50[c] (1.3)	48/50[b] (3.0)
Inflammation	10/49 (1.5)	10/49 (1.1)	14/50 (1.2)	40/50[c] (1.7)
Fibrosis	19/49 (1.4)	7/49 (1.3)	12/50 (1.6)	32/50[b] (1.4)
Histiocyte infiltration	26/49 (1.4)	35/49[c] (1.3)	44/50[b] (2.0)	50/50[b] (1.9)
Larynx				
Chronic inflammation	8/50 (1.8)	26/49[b] (1.5)	27/49[b] (1.3)	37/50[b] (1.4)
Degeneration of epiglottis respiratory epithelium	2/50 (1.0)	33/49[b] (1.2)	26/49[b] (1.2)	40/50[b] (1.5)
Hyperplasia of epiglottis respiratory epithelium	0/50	25/49[b] (1.4)	26/49[b] (1.3)	33/50[b] (1.5)
Squamous metaplasia of epiglottis respiratory epithelium	2/50 (2.0)	7/49 (1.9)	7/40 (1/7)	16/50[b] (1.4)
Nose				
Hyperplasia of respiratory epithelium goblet cell	13/50 (2.0)	18/50 (2.0)	16/50 (1.9)	30/50[b] (2.0)

[a]Average severity grade of lesions in affected animals: 1=minimal; 2=mild, 3=moderate; 4=marked
[b]$p \leq 0.01$
[c]$p \leq 0.05$

Source: NTP 2002

Dose and end point used for MRL derivation: The human equivalent concentration of the $BMCL_{10}$ for degeneration of respiratory epithelium of the epiglottis, 0.003 mg vanadium/m^3, was used as the point of departure for the chronic-duration inhalation MRL.

[ ] NOAEL [ ] LOAEL [X] $BMCL_{10}$

BMD analysis was used to determine the point of departure for select respiratory tract lesions in rats exposed to vanadium pentoxide for 2 years. A number of lesions were observed in male and female rats exposed to 0.28 mg vanadium/m^3 including hyperplasia of the alveolar and bronchiolar epithelium, chronic inflammation of the larynx, degeneration of the epiglottis, and hyperplasia of respiratory epithelial goblet cells. The incidence of these lesions in male rats were modeled using all available dichotomous models in the EPA BMDS (version 2.1) that were fit to the incidence data for alveolar hyperplasia, bronchial hyperplasia, using the extra risk option. The multistage model was run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: goodness-of-fit p-value (p>0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL is selected as the point of departure when the difference between the BMCLs estimated from these models are more three-fold; otherwise, the BMCL from the model with the lowest AIC is chosen. In accordance with U.S. EPA (2000) guidance, BMCs and BMCLs associated with an extra risk of 10% are calculated for all models.

The results of the BMD analyses are presented in Table A-3 and Figures A-2 through A-6.

Table A-3. Model Predictions for Respiratory Effects in Rats Exposed to Vanadium Pentoxide for 2 Years

Model	χ^2 Goodness of fit p-value[a]	AIC	BMC_{10} (mg V/m^3)	$BMCL_{10}$ (mg V/m^3)
Alveolar hyperplasia in male rats				
Gamma[b]	0.25	183.50	0.12	0.04
Logistic	0.52	181.44	0.11	0.09
Log-Logistic	0.08	185.40	NA	NA
Log-Probit	0.13	184.60	0.15	0.08
Multistage[c]	0.21	184.00	0.05	0.04
Probit	**0.57**	**181.29**	**0.10**	**0.09**
Weibull[b]	0.33	183.11	0.10	0.05
Quantal-Linear	0.21	184.00	0.05	0.04
Bronchiolar hyperplasia in male rats				
Gamma[b]	0.28	165.38	0.17	0.10
Logistic	0.60	163.19	0.15	0.12
Log-Logistic	0.08	167.58	NA	NA
Log-Probit	0.12	166.67	0.19	0.13
Multistage[c]	0.56	164.51	0.13	0.07
Probit	**0.71**	**162.87**	**0.14**	**0.12**
Weibull[b]	0.45	164.73	0.15	0.09
Quantal-linear	0.03	170.74		

Table A-3. Model Predictions for Respiratory Effects in Rats Exposed to Vanadium Pentoxide for 2 Years

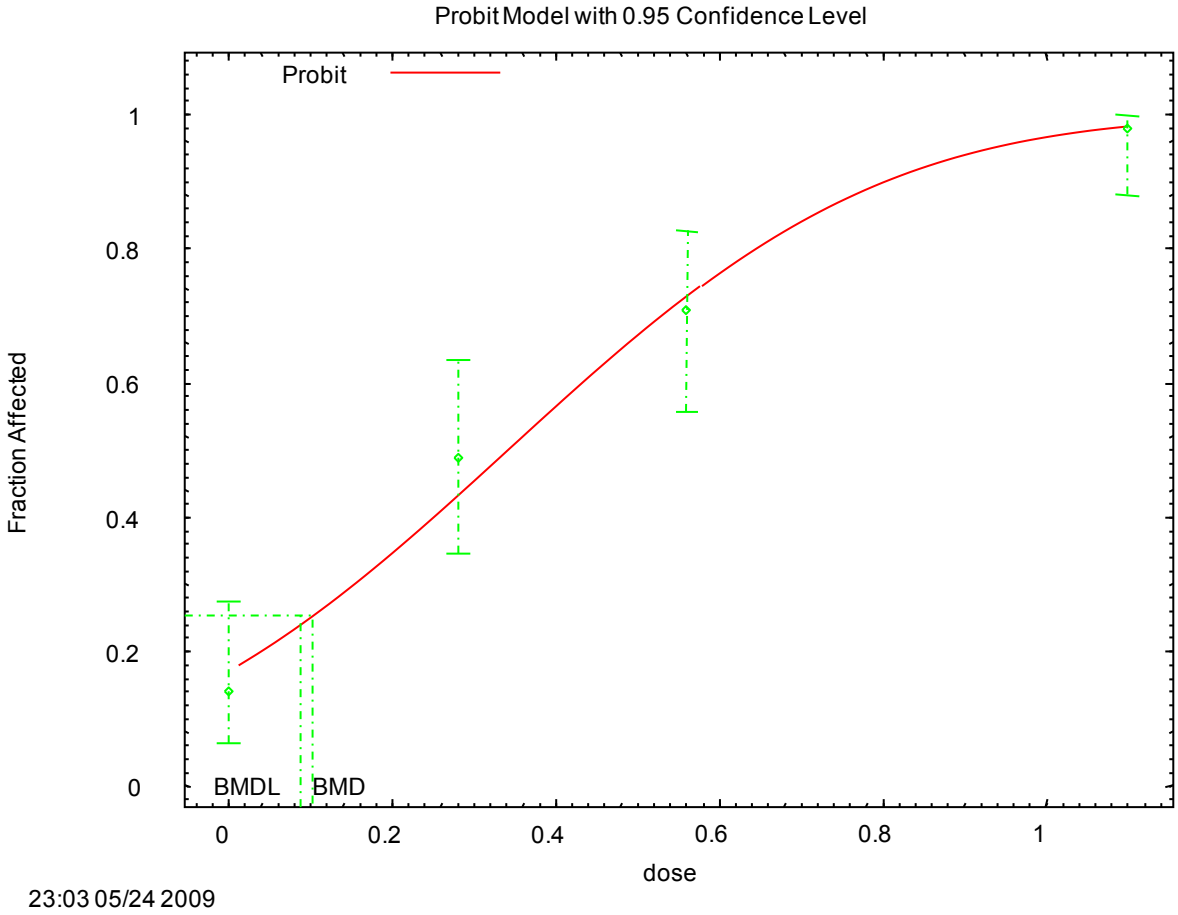
Model	χ^2 Goodness of fit p-value[a]	AIC	BMC_{10} (mg V/m^3)	$BMCL_{10}$ (mg V/m^3)
Chronic inflammation in larynx of male rats				
Gamma[b]	0.04	230.93	NA	NA
Logistic	0.01	235.47	NA	NA
Log-Logistic	**0.11**	**229.28**	**0.10**	**0.07**
Log-Probit	0.00	235.73	NA	NA
Multistage[c]	0.04	230.93	NA	NA
Probit	0.01	235.09	NA	NA
Weibull[b]	0.04	230.93	NA	NA
Quantal-linear	0.04	230.93	NA	NA
Degeneration of epiglottis respiratory epithelium in male rats				
Gamma[b]	0.06	210.55	NA	NA
Logistic	0.00	230.64	NA	NA
Log-Logistic	**0.47**	**206.17**	**0.06**	**0.04**
Log-Probit	0.01	214.79	NA	NA
Multistage[c]	0.06	210.55	NA	NA
Probit	0.00	229.81	NA	NA
Weibull[b]	0.06	210.55	NA	NA
Quantal-linear	0.06	210.55	NA	NA
Hyperplasia of nasal respiratory epithelial goblet cells in male rats				
Gamma[b]	0.12	213.84	0.32	0.20
Logistic	0.07	215.11	NA	NA
Log-Logistic	**0.15**	**213.35**	**0.27**	**0.16**
Log-Probit	0.03	216.79	NA	NA
Multistage[c]	0.12	213.84	0.32	0.20
Probit	0.07	214.97	NA	NA
Weibull[b]	0.12	213.84	0.32	0.20
Quantal-linear	0.12	213.84	0.32	0.20

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]Power restricted to ≥1
[c]Betas restricted to ≥0; 1-degree polynomial

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD; NA = not applicable

Source: NTP 2002

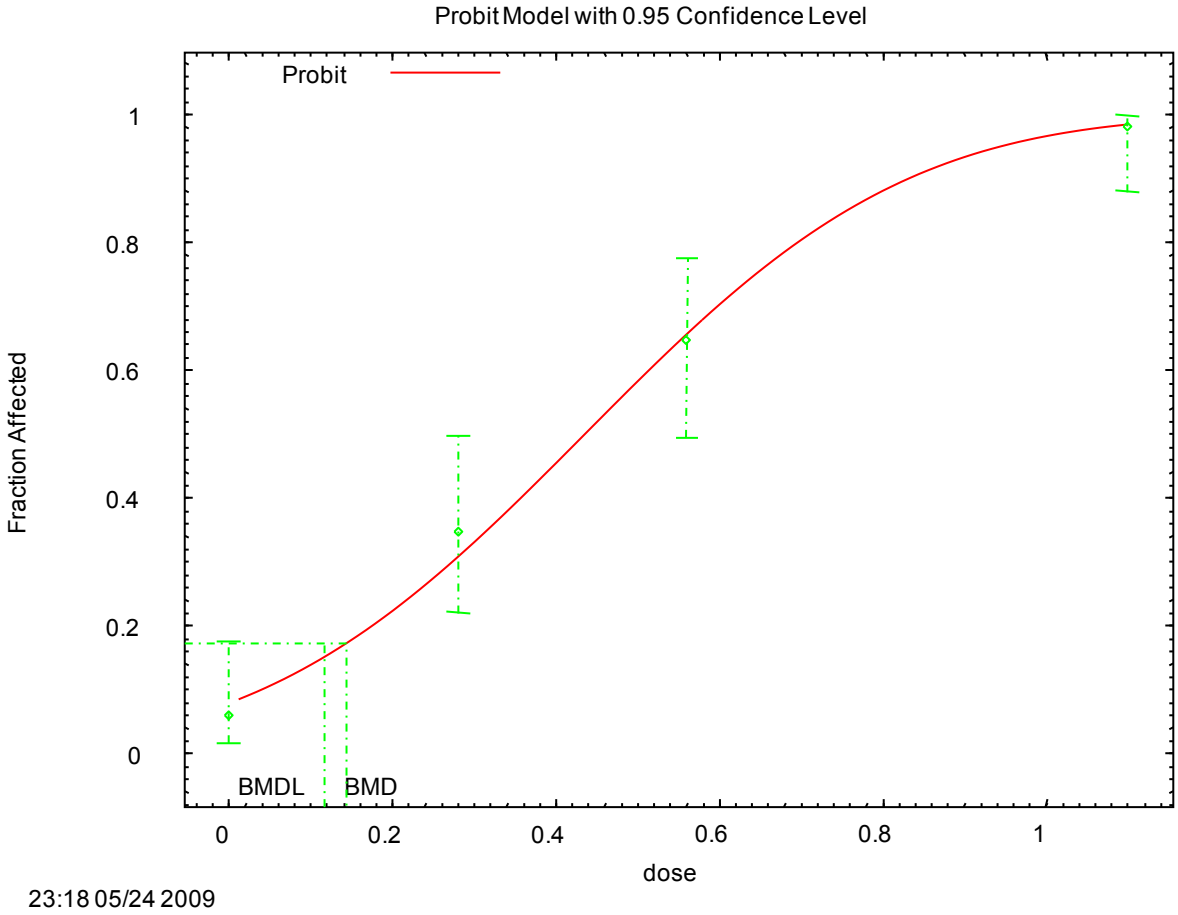
Figure A-2. Fit of Probit Model to Data on the Incidence of Alveolar Hyperplasia in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

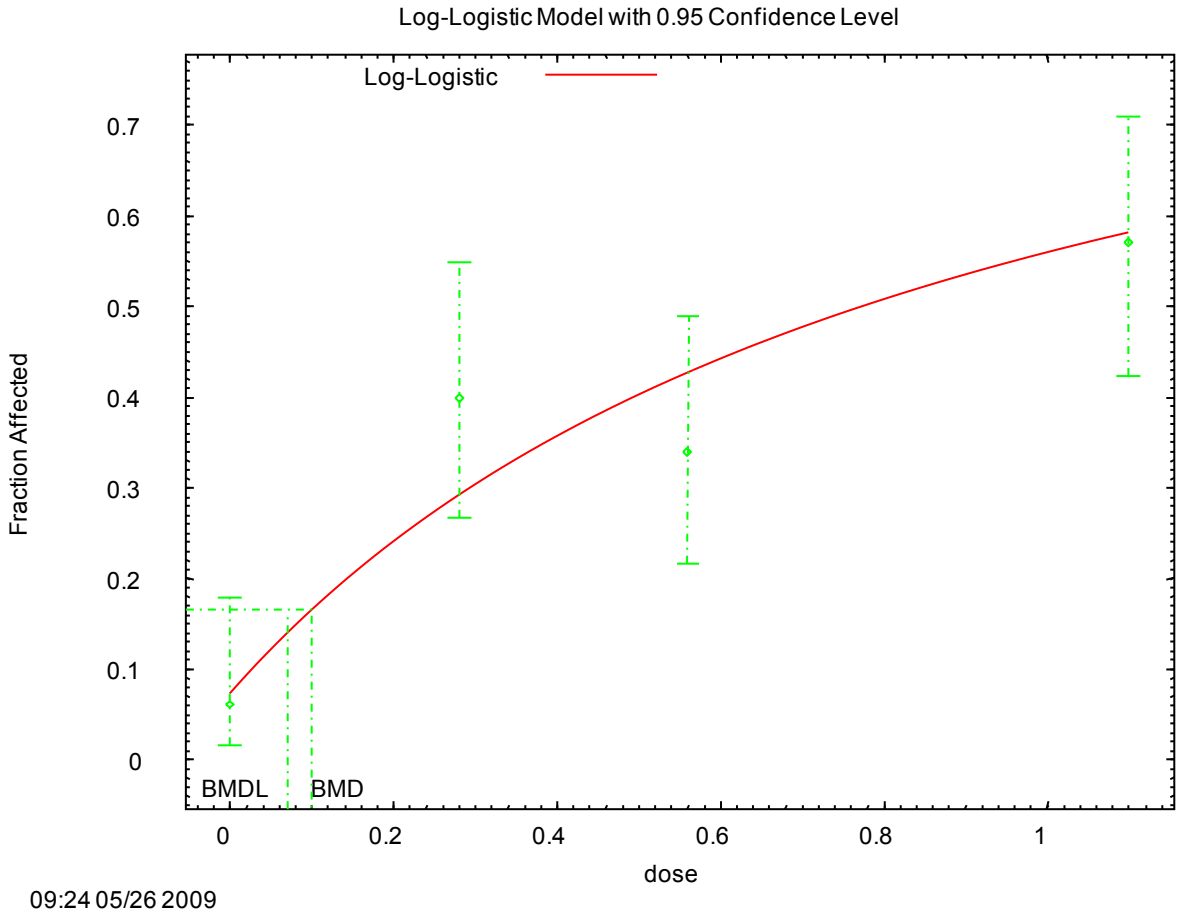
Figure A-3. Fit of Probit Model to Data on the Incidence of Bronchiolar Hyperplasia in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

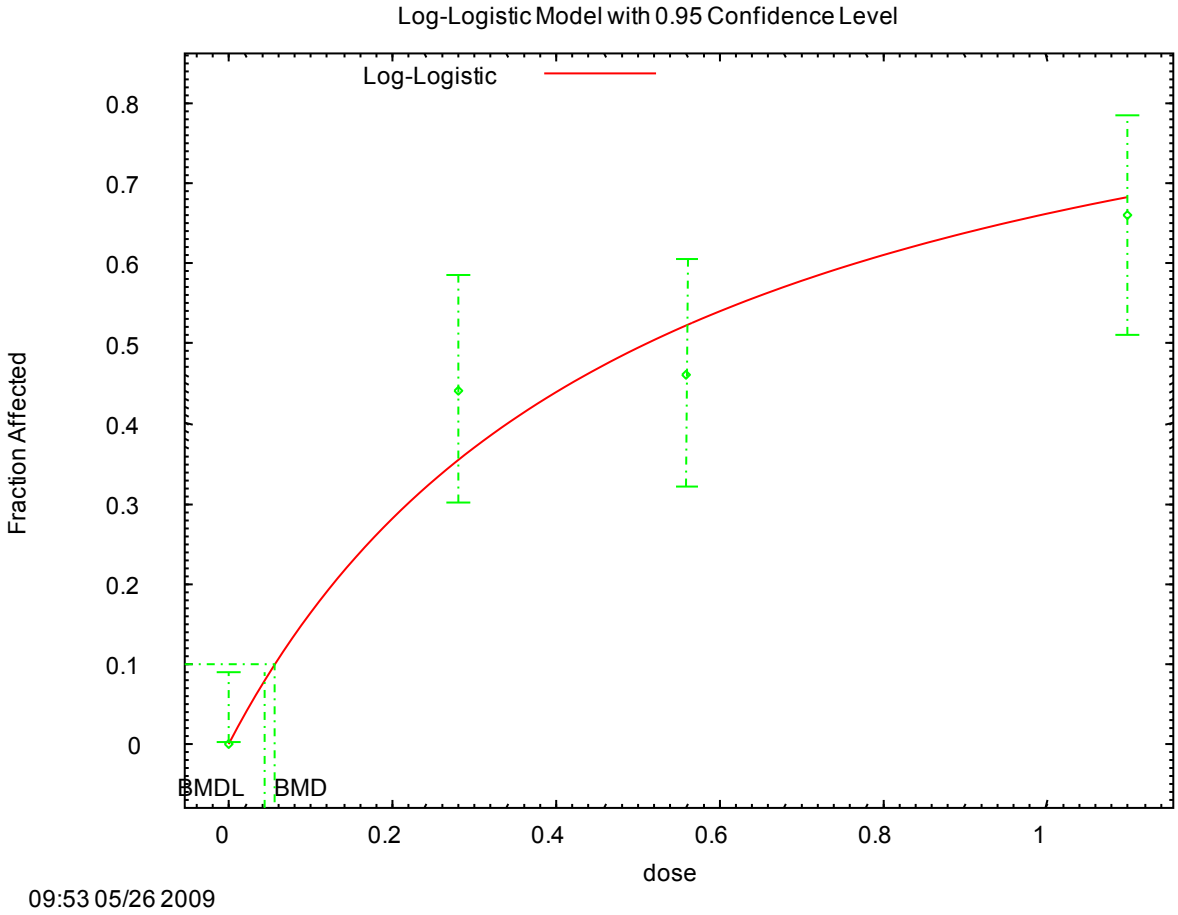
Figure A-4. Fit of Log-logistic Model to Data on the Incidence Chronic Inflammation in Larynx of Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

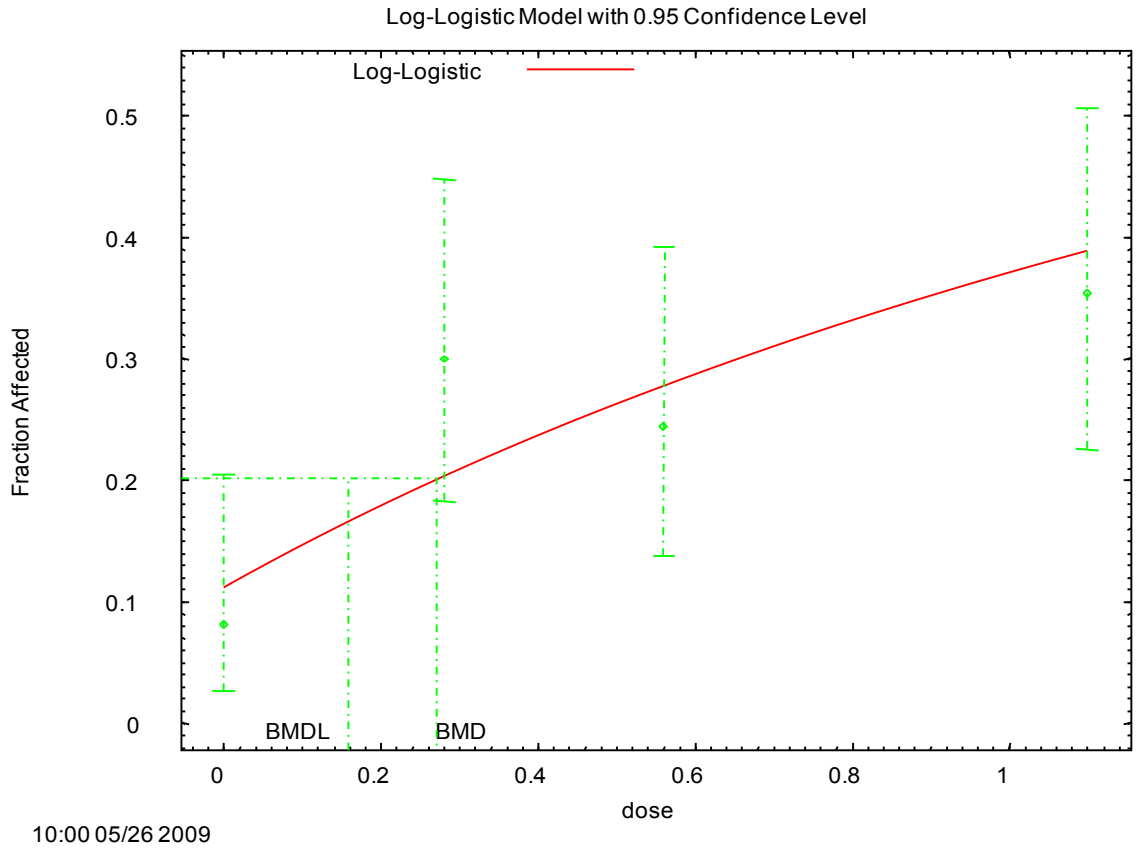
Figure A-5. Fit of Log-logistic Model to Data on the Incidence of Degeneration of Epiglottis Respiratory Epithelium in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

Figure A-6. Fit of Log-logistic Model to Data on the Incidence of Hyperplasia of Nasal Respiratory Epithelial Goblet Cells in Male Rats Exposed to Vanadium Pentoxide for 2 Years



BMCs and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg vanadium/m^3

Source: NTP 2002

In summary, the lowest $BMCL_{10}$ values for alveolar epithelial hyperplasia, bronchiolar epithelial hyperplasia, laryngeal chronic inflammation, degeneration of epiglottis epithelium, and hyperplasia of nasal goblet cells were 0.09, 0.10, 0.07, 0.04, 0.16 mg vanadium/m^3, respectively.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Human equivalent concentrations were calculated for each $BMCL_{10}$ using the following equation:

$$BMCL_{HEC} = BMCL_{ADJ} \times RDDR$$

where:
The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR program (EPA 1994c) was used to calculate a multiplier for the different regions of the respiratory tract was determined using a default body weight of 0.380 kg (EPA 1994c) and a particle size MMAD of 1.2 µm with a geometric standard deviation of 1.9. The $BMDL_{HEC}$ values are presented in Table A-4

Table A-4. Summary of Human Equivalent Concentrations of BMCL Values for Rats Exposed to Vanadium Pentoxide for 2 Years

Effect	$BMCL_{10}$ (mg vanadium/m^3)	$BMCL_{ADJ}$[a] (mg vanadium/m^3)	RDDR	$BMCL_{HEC}$ (mg vanadium/m^3)
Alveolar epithelial hyperplasia	0.09	0.016	0.502[b]	0.008
Bronchiolar epithelial hyperplasia	0.10	0.018	0.971[c]	0.017
Laryngeal chronic inflammation	0.07	0.012	0.423[d]	0.005
Degeneration of epiglottis epithelium	0.04	0.0071	0.423[d]	0.003
Hyperplasia of nasal goblet cells	0.16	0.029	0.423[d]	0.012

[a]$BMCL_{ADJ}$= $BMCL_{10}$ x 6 hours/24 hours x 5 days/7 days
[b]Pulmonary region
[c]Thoracic region
[d]Extrathoracic region

BMCL = benchmark concentration, lower confidence limit RDDR = regional deposited dose ratio

Source: NTP 2002

Was a conversion used from intermittent to continuous exposure? The $BMCL_{10}$ was adjusted for intermittent exposure, as noted in Table A-4.

Other additional studies or pertinent information that lend support to this MRL: An increased combined incidence of alveolar/bronchiolar adenoma or carcinoma was observed in male rats (NTP 2002). Although the incidence was not significantly higher than concurrent controls, it was higher than historical controls and NTP considered it to be a vanadium-related effect.

In mice exposed to ≥0.56 mg vanadium/m^3 for 6 hours/day, 5 days/week for 2 years, significant increases in the incidence of alveolar and bronchiolar hyperplasia, chronic lung inflammation, squamous metaplasia of the respiratory epithelium of the epiglottis, goblet cell hyperplasia in the nasal respiratory epithelium and nasal olfactory epithelial atrophy, and hyaline degeneration were observed (NTP 2002). In addition to these effects, a significant increase in alveolar/bronchiolar carcinoma incidence was also observed in mice exposed to ≥0.56 mg vanadium/m^3.

Agency Contacts (Chemical Managers): Jessilynn Taylor, Sam Keith, Larry Cseh

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Vanadium compounds
CAS Numbers: 7440-62-6
Date: August 2009
Profile Status: Pre-Public Comment, Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 12
Species: Human

Minimal Risk Level: 0.01 [X] mg vanadium/kg/day [ ] mg vanadium/m^3

Reference: Fawcett JP, Farquhar SJ, Thou T, et al. 1997. Oral vanadyl sulphate does not affect blood cells, viscosity or biochemistry in humans. Pharmacol Toxicol 80:202-206.

Experimental design: Groups of men and women enrolled in a weight training program for at least 1 year were administered capsules containing 0 (11 men and 4 women) or 0.5 mg/kg/day vanadyl sulfate trihydrate (0.12 mg vanadium/kg/day) (12 men and 4 women) for 12 weeks. Fasting blood samples were collected at 0 and 12 weeks and analyzed for hematological (erthyroctye count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, platelet count, and total and differential leukocyte count) and serum chemistry (cholesterol, high density lipoprotein, triglycerides, albumin, total protein, total and direct bilirubin, alkaline phosphatase, ALT) parameters. Body weight and blood pressure were measured at weeks 4, 8, and 12.

Effect noted in study and corresponding doses: No significant alterations in blood pressure, body weight, or hematological or clinical chemistry parameters were found.

Dose and end point used for MRL derivation: NOAEL of 0.12 mg vanadium/kg/day for hematological alterations and blood pressure.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Studies in laboratory animals have identified several sensitive effects including alterations in erythrocyte and reticulocyte levels, increased blood pressure, neurobehavioral alterations, and developmental toxicity. Significant increases in blood pressure have been observed in rats exposed to 0.12 mg vanadium/kg/day for 210 days (Boscolo et al. 1994); increases in blood pressure have been observed at higher doses in several other

studies by these investigators (Carmagnani et al. 1991, 1992). In general, other studies have not found increases in blood pressure in rats exposed to doses as high as 31 mg vanadium/kg/day (Bursztyn and Mekler 1993; Sušić and Kentera 1986, 1988). Decreases in erythrocyte levels have been observed in rats exposed to 1.18 mg vanadium/kg/day as ammonium metavanadate in drinking water for 4 weeks (Zaporowska et al. 1993); at higher concentrations, decreases in hemoglobin and increases in reticulocyte levels have been observed (Ścibior 2005; Ścibior et al. 2006; Zaporowska and Wasilewski 1990, 1991, 1992a, 1992b; Zaporowska et al. 1993). Decreases in pup body weight and length have been observed in the offspring of rats administered 2.1 mg vanadium/kg/day as sodium metavanadate for 14 days prior to mating and throughout gestation and lactation (Domingo et al. 1986). At higher doses (6, 10, or 12 mg vanadium/kg/day), decreases in pup survival, and increases in the occurrence of gross, visceral, or skeletal malformations and anomalies were observed (Elfant and Keen 1987; Morgan and El-Tawil 2003; Poggioli et al. 2001).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Sam Keith, Larry Cseh

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 that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

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, ATSDR has derived 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.

MRLs 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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 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 (less than 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 two "18r" data points in sample 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 regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one 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 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL 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

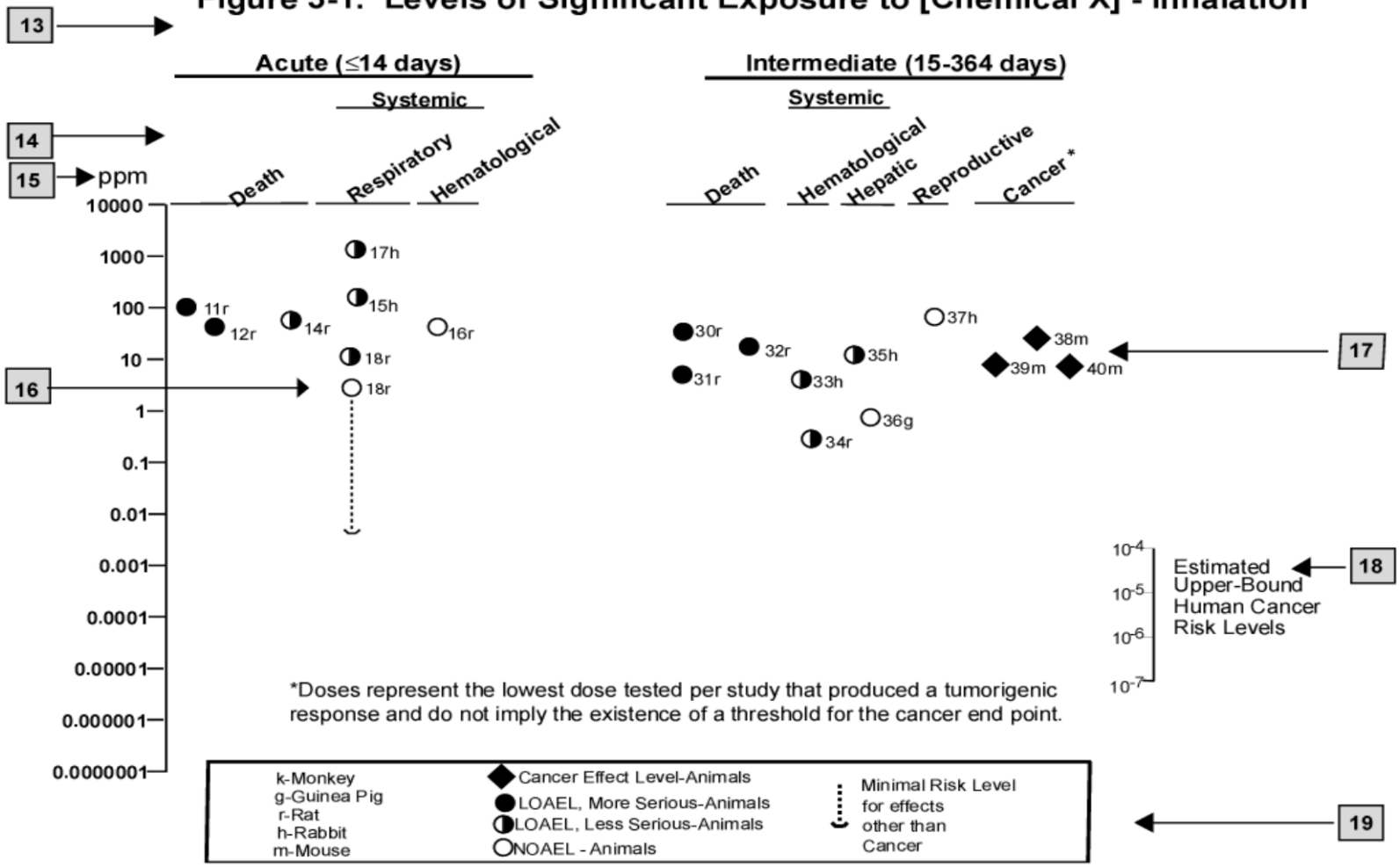
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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



This page is intentionally blank.

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
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
AOEC	Association of Occupational and Environmental Clinics
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
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
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/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental 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
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
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
NHANES	National Health and Nutrition Examination Survey
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
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

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
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
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

>	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

This page is intentionally blank.

APPENDIX D. INDEX

absorbed dose 74, 86
adsorbed....125, 126
adsorption 124, 125, 126
alanine aminotransferase (see ALT) 39
ALT (see alanine aminotransferase) 39, 40, 61
ambient air 4, 129, 130, 144, 147
aspartate aminotransferase (see AST)....39
AST (see aspartate aminotransferase)....39, 61
bioavailability 85
bioconcentration 126
biomarker....85, 86, 97, 149, 157
body weight effects....41, 62
breast milk 85, 142, 143
cancer....5, 11, 13, 25, 65, 68, 84, 161
carcinogen....87, 163
carcinogenic....5, 13, 25, 42, 66, 163
carcinogenicity 13, 42, 66, 94
carcinoma 13, 16, 42, 43, 94
cardiovascular....38, 60, 94
cardiovascular effects 38, 59, 94
chromosomal aberrations....66, 68, 71
clearance 40, 72, 74, 77, 81
death 25, 26, 44, 61, 85, 90, 126
deoxyribonucleic acid (see DNA)....66
dermal effects 40
developmental effects 13, 20, 42, 65, 66, 85, 92, 95, 98
diabetes....5, 11, 20, 25, 60, 92, 113, 136, 141
DNA (see deoxyribonucleic acid) 66, 67, 68, 69, 70, 71, 86, 87, 95
elimination half-time 75, 78
elimination rate....85
endocrine 82, 83
fetus 83
gastrointestinal effects 20, 39, 60, 92
general population 4, 11, 12, 117, 141, 147, 148
genotoxic 25, 71
genotoxicity 66, 71, 95
groundwater....123, 132
half-life 86, 151
hematological effects....23, 39, 60, 92
hepatic effects....39, 61
immunological....25, 41, 64, 90, 96
immunological effects 64
K_{ow} 104, 105
LD_{50} 44
metabolic effects....63
micronuclei 66, 71
milk....11, 73, 77, 88, 136, 138, 139, 141, 143, 146
musculoskeletal effects....39
neurobehavioral 21, 83, 89, 93, 96
neurological effects....5, 41, 64, 66
nuclear 151
ocular effects 40, 44
pharmacodynamic....78

pharmacokinetic....78, 79, 80, 84
renal effects....40, 62
reproductive effects....41, 64, 66, 92, 95
respiratory effects....12, 27, 44, 93, 96
retention....74, 75, 85
solubility....73, 146
systemic effects....27, 44, 66
toxicokinetic....11, 25, 82, 98, 99
tremors....41, 96
tumors....42, 44, 87, 94